Multiple Sclerosis Therapeutics

Second edition
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Preface to first edition

A little over 20 years ago it was thought by many that research into experimental therapies in multiple sclerosis (MS) was, at best, unlikely to provide valid or reproducible information relating to the treatment of the disease. This pessimistic opinion was reflected at the First International Conference on Therapeutics in Multiple Sclerosis, held in 1982. The concerns were based on many unsubstantial claims for efficacy for treatments that could not be confirmed and on the failure to identify a significant treatment effect in the many trials that had been done prior to the meeting. While the failures were due in part to a highly variable and unpredictable clinical course, which is the clinical hallmark of the disease, there was also concern that a higher level of scientific quality was needed in experimental therapeutic research in MS. Today, research on new therapies in MS has become increasingly efficient and effective in identifying the effect of these therapies on the course of the disease. In fact, research into the treatment of MS can be considered an example of excellence in experimental therapeutics in neurological disease. The change is evidenced by the approval in the USA of three therapies for the relapsing-remitting phase of the disease.

The change can be related to several factors. Certainly, demonstration that magnetic resonance imaging (MRI) can provide an objective means for monitoring MS, at least in some phases of the disease course, has provided a very powerful tool in experimental therapeutics in MS. Most important, however, has been the growth of expertise in clinical research in MS. Impressive advances in the attention given to the design of clinical trials in MS ranging from early phase 1 or 2 studies to pivotal phase 3 studies are now evident. Examples of clinical trials with severe or fatal flaws in trials design, common in the past, are now unusual. These advances reflect the growing importance given to clinical research in MS.

Despite these advances, many unresolved questions relating to the study of new therapies in MS persist. Beginning with an important meeting focusing on clinical outcomes in MS research sponsored by the National Multiple Sclerosis Society and held in 1994, use of both clinical and MRI outcomes has been carefully studied. New approaches to the assessment of clinical disease progression have been described and are now beginning to be used in clinical trials. Further, use of MRI as an outcome measure has been and continues to be carefully evaluated. Thus, summary of the advances in MS experimental therapeutics, including detailed assessment of clinical and MRI outcomes, is especially timely.

Early in the use of MRI as an outcome measure, many investigators were convinced that measure of disease activity on MRI could replace clinical outcome measures completely. It was hoped that MRI was a direct measure of the disease activity occurring in MS and that monitoring changes in disease activity as seen on MRI during the use of a new treatment could establish the effectiveness of that treatment. It is now clear that, although MRI is a very powerful tool, the ability to translate changes in disease activity
seen using conventional MR imaging directly to clinical outcomes is not perfect. It is becoming increasingly evident that the evolution of the MS lesion is complex and probably variable among patients. Further, the evolution of the pathological processes involved in the disease probably does not represent a continuum of a single process, but, instead, various components each contributing in different ways to damage of the myelin sheath and the axon. Thus, it is likely that the correlation between various MRI modalities differs during various stages of the disease process. For example, the level of disease activity as measured on T2-weighted images or on post-contrast T1-weighted images early in the course of the disease may be helpful in predicting the severity of future disease. These same measures of disease activity, when examined later in the course of the disease, may have little relationship to the level of disability existing at the time of study or to the future progression of the disease. It is likely that progression is closely related to irreversible damage to the myelin sheath and to axonal damage, neither of which are specifically reflected on T2-weighted images. Further, the level of new activity seen in contrast-enhanced T1-weighted images may only have a small impact on the overall level of disease once a large degree of diseased brain exists. Thus, it is hoped that imaging sequences, which have greater pathological specificity for the events contributing most directly to progression, will provide a more useful tool for monitoring new therapies in clinical trials.

The chapters incorporated in the first section of this book, written by individuals with particular expertise in their respective areas, will provide an up-to-date review of the assessment of clinical and MRI outcomes measures that are and that will be used in clinical trials in MS. Overall, the reader will develop an understanding of the problems in experimental therapeutics that are unique to MS, knowledge about clinical outcomes that form the heart of clinical trials, and a solid foundation regarding the strengths and weaknesses of imaging as an outcome measure in clinical trials in MS. The interest in experimental therapeutics in MS is growing rapidly as advances in immunology and genetics point to therapies that may have potential for modifying the disease process. The issues discussed will provide the reader with the information necessary to assess and to participate in this exciting area of clinical research.

Following this basic foundation, subsequent chapters examine the results of the most important symptomatic and disease-modifying therapies in MS. As one reviews current understanding of many of these therapies, one can understand the importance of well-designed clinical studies. Unfortunately, in many cases, the effectiveness of these therapies is incompletely resolved. More importantly, the ability of many of the therapies to have a truly modifying effect on the course of the disease is uncertain. As implied above, it is likely that the effect of some of these therapies will differ among patients and with respect to the stage of the disease process when they are administered. As the reader evaluates the results obtained with therapies that have been tested in MS, the need for continued improvement in trial design will become apparent. The decision as to whether and when to treat is dependent upon both the physician and the patient having a complete understanding of the effect of the therapy in relation to the stage of the disease and in relation to side effects. In many cases, considerable uncertainty still exists and assessment by both physician and patient of the risks in relation to the benefit is difficult.
It is hoped that careful attention to future trial design and the use of new imaging modalities to define better the effect of the therapies will lead not only to new, effective treatments but also to improved understanding of the disease process.

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Preface to second edition

Progress in our understanding of multiple sclerosis or in our ability to treat the disease was remarkably small until the beginning of the 1990s. In contrast, during the 1990s progress both in the identification of therapies and in the understanding of the pathophysiology of the illness progressed rapidly. The first edition of *Multiple Sclerosis Therapeutics* presented an excellent state-of-the-art review of the results of advances in the understanding of the mechanisms and treatment of the disease. Fortunately, progress in MS research seen during the early 1990s has continued and over the past 3 years important new findings have emerged and observations made in previous years have been refined and focused.

With respect to our understanding of the biology of the disease, the past 3 years have seen a continued focus on the events occurring in the MS lesion and important new information on the heterogeneity of the pathological processes leading to myelin destruction has been described. The importance of damage to the axon, even early in the disease process, has been further defined and new information on repair processes or, more accurately, the failure of repair processes has been studied.

The implications of heterogeneity in the pathological processes producing myelin damage are great with respect to the probable impact of therapies; therapies that target an inflammatory component to the disease may have limited value in patients in whom myelin damage occurs in the absence of an important inflammatory component. Although the ability to determine which patient will or will not benefit from a particular therapy is not yet known, progress has been made over the past 3 years in understanding some of the mechanisms of the approved therapies and, slowly, the longer term value of these treatments is becoming better understood. Probably most important the results of recent clinical trials have made the value of treatment early in the disease course clearer.

Imaging continues to be an important tool for helping to establish the benefit of new therapies and for understanding the disease process. Formal guidelines for the use of MRI as a diagnostic tool have been developed and the value of MRI in selecting patients for early therapy is now generally accepted. The application of functional imaging to MS has increased, as has the focus on the cognitive changes caused by the disease.

Finally, a new emphasis is being placed on the management of the disease using approaches that can be an adjunct to disease modifying therapies. The role of rehabilitative strategies is being actively studied, as are other symptomatic therapies designed to improve the quality of life for individuals with the illness.

This new edition of *Multiple Sclerosis Therapeutics* has both updated prior chapters and added new chapters to reflect advances over the past few years. Because of the importance of new information which has appeared over the past three years on both approved and emerging therapies, chapters dealing with approved therapies such as beta interferon, glatiramer acetate and mitoxantrone, non-approved therapies used clinically such as IVIg and plasma exchange and new or evolving strategies such as stem cell
transplantation and the combination of multiple therapies have been extensively revised. Further, new chapters have been added to review topics that have received attention since the publication of the first edition. These include chapters on sex hormones and pregnancy-related factors as well as a discussion of complementary and alternative therapies. Finally, a discussion on cost-benefit analyses has been included.

It is fortunate that a second edition is needed as it reflects the continued progress in helping to alleviate disease activity and the resulting symptoms of MS. Hopefully a third edition will be needed within a few years.

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Acknowledgements

Our thanks are due to the many authors who contributed towards this book. The publishers have been a pleasure to work with: our thanks to Martin Dunitz for providing early advice, and to Alan Burgess and Charlotte Mossop for all their efforts in coordinating the project and ensuring the expeditious publication of this book. Dr Bruce Trapp generously provided the beautiful micrograph on the cover. Finally, this book is dedicated to Sally, Jennifer, Joshua, Marilyn, Brian and Jamie.
I

Introduction
INTRODUCTION

The past decade has witnessed substantial progress in our understanding of the pathogenesis of multiple sclerosis (MS), improvement in our ability to diagnose the disease and monitor its course, and the emergence of MS as a treatable neurologic disease. Nevertheless, the development of effective treatments for MS has been impeded by several characteristics of the disease. The purpose of this chapter is to discuss the aspects of MS that have an impact on the design of clinical trials, the development of new disease therapies, and patient care. These aspects include heterogeneity in disease course, in severity, and in manifestations; the presence of subclinical disease activity early in the disease; and the complexity of pathogenic mechanisms.

HETEROGENEITY IN MS

Disease course

The clinical course of MS presents challenges because the disease has strikingly heterogeneous clinical manifestations that evolve over decades in most patients. A classification of disease course has been developed by consensus (Table 1.1)\[1\]. During the relapsing-remitting stage, periodic relapses occur at irregular and unpredictable intervals, averaging approximately one per year. The episodic attacks of neurologic dysfunction are followed by partial or complete recovery, and individual relapses are separated by a clinically stable phase. Relapses tend to become less conspicuous over the years, and the majority of patients (approximately 75%) ultimately evolve into a pattern of gradual neurologic deterioration, termed secondary progression. During this stage, physical, cognitive, emotional, social, and economic decline is the rule, and the illness seems more refractory to treatment. This stage of the disease is also difficult to study, because deterioration typically occurs slowly over the course of years, and the significant individual variability persists. The transition from relapsing-remitting MS to secondary progressive MS does not occur at a precise point in time. Rather, clinical relapses become less distinct episodes, recovery becomes less robust, and the relapsing-remitting stage blends into the secondary progressive stage, typically 10–20 years after the onset of symptoms. The transition to the secondary progressive stage can be dated only in retrospect, once it is clear that the patient has continuously worsened for months or years.
Eighty-five percent of patients have relapsing-remitting MS. Table 1.1 Clinical categories of multiple sclerosis

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Relapsing-remitting MS</td>
<td>Episodic relapses with recovery and a stable phase between relapses. MS begins as relapsing-remitting MS in approximately 85% of cases. Clinical relapses imply that the disease is active, but clinical remission does not mean the disease is quiescent. MRI studies have shown that the disease may be active when the disease is clinically inactive.</td>
</tr>
<tr>
<td>Secondary progressive MS</td>
<td>Gradual neurologic deterioration with or without superimposed acute relapses in a patient who previously had relapsing-remitting MS. Over 75% of patients with relapsing-remitting MS will develop secondary progressive MS. A major goal of disease therapy in relapsing-remitting MS patients is to prevent evolution to secondary progressive MS.</td>
</tr>
<tr>
<td>Primary progressive MS</td>
<td>Gradual, nearly continuous neurologic deterioration from the onset of symptoms. Some patients with primary progressive MS have onset in middle age and MRI and CSF findings identical to patients with secondary progressive MS. These patients probably have secondary progressive MS, but without evident clinical relapses during the early stage of disease. Other primary progressive MS patients appear to have a degenerative process with minimal evidence of inflammation. These patients present with a gradually worsening gait disorder and often have minimal cranial disease by MRI scans.</td>
</tr>
<tr>
<td>Progressive relapsing MS</td>
<td>Gradual neurologic deterioration from onset but with subsequent superimposed relapses. This is an unusual clinical pattern that may also be analogous to secondary progressive MS without an initial relapsing-remitting course.</td>
</tr>
</tbody>
</table>

Adapted from Lublin and Reingold[1]

forms of MS, either relapsing-remitting MS or secondary progressive MS. Approximately 10–15% of patients have so-called primary progressive MS, in which continuous clinical deterioration occurs from the onset of disease (see chapter 34). Patients with primary progressive MS tend to have symptom onset at a later age (typically between the ages of 40 and 60 years), and the female preponderance seen with relapsing forms of MS is not evident. Patients with primary progressive MS present clinically with insidiously progressive spastic weakness, imbalance, and sphincter dysfunction; diffuse and less nodular T2 lesions on magnetic resonance imaging (MRI); fewer or no gadolinium-enhancing lesions; and little inflammatory change in the cerebrospinal fluid (CSF).[2] These cases may represent a type of MS that is less dependent on inflammation and that may be primarily degenerative. A consensus has emerged that primary progressive MS should be considered separately from the other groups for the purpose of controlled clinical trials, in part because of uncertainty about the etiologic relationship between this...
form and the other categories. Some patients with primary progressive MS exhibit clinical features, MRI findings, and a CSF profile similar to those of patients with secondary progressive MS and probably have the same disease as secondary progressive MS, but without clinically distinct relapses during the early stage. This is probably also true of progressive relapsing MS. Thus, studies in primary progressive MS are problematic because these cases are relatively uncommon, and because the primary progressive MS category probably comprises a combination of secondary progressive MS patients who did not have a symptomatic relapsing-remitting stage and patients with a less inflammatory central nervous system (CNS) disease that is less responsive to immunomodulatory treatment approaches.

Common practice has been to attempt to select relatively homogeneous patient groups for inclusion in clinical trials, typically by defining disability limits using the Kurtzke Expanded Disability Status Scale (EDSS) and by entering patients within specified disease categories. This strategy aims at reducing between-patient variability and increasing the power to show therapeutic effects with a given sample size. This explains why separate trials have been conducted for patients with relapsing-remitting MS, secondary progressive MS, and primary progressive MS.

There are several caveats to restricting trials to certain types of patients. First, excessively narrow entry criteria may impede recruitment. Second, it may not be clear whether the results of a trial enrolling a selected cohort of patients can be extrapolated to other groups of MS patients. Third, the distinction between clinical disease categories is not precise, and the reliability of classifying patients into these categories has never been tested. In all likelihood, there is an admixture of patients in MS trials. This point is well illustrated by the European and North American trials of interferon beta-1b in secondary progressive MS, in which two trials with very similar entry criteria enrolled different patient populations and yielded different results with the same therapeutic agent. The problems of classifying patients are most intense at the interface between relapsing-remitting MS and secondary progressive MS. As disease duration and EDSS increase, the patient is more likely to be categorized as having secondary progressive MS, and the cut-off point appears to be around EDSS 4.0. At this level and above, the large majority of patients would be classified as secondary progressive MS. Finally, it must be recognized that clinical disease categories are defined empirically—biologic markers for the categories are not available.

Table 1.2 lists characteristics of patients entered into several large MS clinical trials. Despite overlap, disease duration and disability level are clearly different in trials in relapsing-remitting MS from trials in secondary progressive MS. Because the reliability and utility of restricting entry by disease category is unclear, some trials allowed entry of patients based only on disability criteria (e.g. the studies of sulfasalazine and linomide). Patients in these trials were intermediate between the populations in trials restricted to relapsing-remitting MS or secondary progressive MS in terms of disability score and disease duration.
Clinical manifestations

The potential clinical manifestations of MS are myriad and can include, among others, cognitive impairments of a variety of types, loss of vision or abnormalities of eye movements, weakness, spasticity, cerebellar dysfunction, sensory loss or positive sensory phenomena, bowel and bladder dysfunction, fatigue, and paroxysmal phenomena. Patients within a disease category exhibit a wide range of clinical manifestations in varying combinations, and manifestations typically change in individual patients over time. Even within multiply affected families, there is striking clinical heterogeneity between affected family members. Management of the wide variety of MS symptoms is a challenge to the clinician. However, with the increased emphasis on disease-modifying therapies, one needs to remember that identification and effective treatment of troublesome symptoms of MS can have a major beneficial effect on the patient’s ability to function and quality of life (see chapters 35–42).

The heterogeneity in potential clinical manifestations also presents significant challenges for the design of clinical trials. Separate trials and treatment arms within a given trial contain variable admixtures of clinical manifestations that are not necessarily

| Table 1.2 Patient characteristics in selected controlled clinical trials |
|--------------------------------|---------|----------------|---------------|
| Agent tested by clinical trial | n       | Age (years)    | Duration of disease (years) | EDSS |
| Trials with entry restricted to relapsing-remitting MS | | | | |
| Interferon beta-1b[^8] | 372 | 35 | 4.4 | 2.9 |
| Interferon beta-1a[^10] | 301 | 37 | 6.5 | 2.4 |
| Interferon beta-1a[^11] | 560 | 35* | 5.3* | 2.5 |
| Glatiramer acetate[^9] | 251 | 34 | 6.9 | 2.6 |
| **Mean** | 35.2 | 5.6 | | 2.6 |
| Trials with entry restricted to secondary progressive MS | | | | |
| Interferon beta-1b (European[^83]) | 718 | 41 | 13.1 | 5.1 |
| Interferon beta-1b (North American[^84]) | 939 | 47 | 14.7 | 5.1 |
| Interferon beta-1a (SPECTRIMS[^85]) | 618 | 43 | 13.3 | 5.4 |
| Interferon beta-1a (IMPACT[^27]) | 436 | 47 | 14.2 | 5.2 |
| **Mean** | 44.5 | 14.3 | | 5.2 |
| Trials with entry not restricted by disease category | | | | |
| Sulfasalazine[^4] | 199 | 28 | 5.5 | 2.5 |
| Linomide[^5] | 715 | 46 | 15.3 | 5.2 |
| **Mean** | 42.1 | 13.2 | | 4.6 |

*Median; all other values are mean.
evenly matched between studies. Outcome measures must be multidimensional to capture the ways in which MS affects patients. Traditional clinical outcome measures are heavily weighted towards motor impairment, particularly gait dysfunction. Common symptoms such as sphincter disturbances, pain, and fatigue may have significant effects on quality of life without affecting measures of physical impairment and disability. Finally, symptomatic and disease-modifying therapies may have differing effects on different disease manifestations (i.e. benefit for some with no effect on others, or even worsening).

**Disease severity and prognostic factors**

Because of pronounced variability, there is a need for accurate prognostic markers that could be used both for treatment decisions concerning individual patients and for selecting appropriate patients for clinical trials. Overall, 50% of patients are unable to carry out household and employment responsibilities 10 years after disease onset, 50% require an assistive device to walk after 15 years, and 50% are unable to walk after 25 years. However, about 10% of patients have unusually bad disease and deteriorate to severe irreversible disability in only a few years. Another 10% have benign disease, with intermittent neurologic symptoms but little disease progression and minimal disability decades after the initial symptoms.

Although the ultimate prognosis for MS is poor, it is a chronic disease that usually changes slowly. During the time frame of a clinical trial, typically 2–3 years, clinical evidence of disease activity is modest. For example, most patients in large-scale trials in relapsing-remitting MS experienced no relapses or only one relapse. Also, in these studies, one-third or fewer of the placebo patients demonstrated worsening on traditional measures of impairment or disability, such as the EDSS, over 2–3 years. Clinical stability in the majority of placebo-treated patients results in the need for large sample sizes. One approach to this problem has been to develop more sensitive outcome measures (see below).

Another approach has been to attempt to enroll patients at risk of disease activity and exclude patients who are not likely to change during the trial. In groups of patients, benign disease has been associated with sensory symptoms or optic neuritis at onset, good recovery from relapses, and infrequent relapses early in the disease course. Conversely, symptom onset at an older age, progressive disease from onset, or poor recovery from relapses mark a relatively worse prognosis. However, clinical features are only weak predictors of overall prognosis, and their value for assigning prognosis for the purpose of informative enrollment in clinical trials has not been successful. The presence of multicentric white matter lesions at the time of first MS symptoms has been associated with a higher risk of MRI and clinical disease progression in the subsequent 5 years. The presence of gadolinium-enhancing lesions at baseline in a clinical trial predicts the frequency of clinical relapses, increase in T2 lesion volume, and the risk of brain atrophy progression over the subsequent 2 years. Thus, most trials employ some entry criteria, either clinical (e.g. relapses or progression over a specified time period before the trial) or imaging (e.g. gadolinium-enhancing lesions on screening MRI scans), to identify patients with increased likelihood of exhibiting disease activity during the trial (so that they will be ‘informative’) and to exclude patients who are not likely to change during the trial period. However, these criteria are only partially effective. Also,
as discussed above, it must be remembered that overly restrictive entry criteria aimed at identifying active patients can make it difficult to find eligible patients and so impede recruitment.

CLINICAL OUTCOME MEASURES FOR MS TRIALS

Traditional clinical outcome measures

Traditional clinical outcome measures for MS trials include enumerating relapses and rating neurologic impairment or disability (see chapter 2). Relapses are defined as neurologic symptoms lasting at least 48 hours accompanied by a change in the neurologic examination that cannot be explained by infection or other intercurrent illness. Although seemingly straightforward, relapses can be difficult to identify precisely in clinical trials. Patients often report changes in their symptoms without clear-cut changes on neurologic examination, or have changes recorded on their neurologic examination that are not associated with a change in symptoms. Furthermore, different neurologists almost certainly define relapses differently despite using the same broad definition above.

To address this inconsistency, investigators have attempted to create operational definitions for relapses, including predefined changes on the examination or rating scales required to confirm a relapse, but this creates different types of problems. Other investigators have graded the severity of clinical relapses on the basis of the magnitude of change on clinical rating scales or the extent of interference with functioning. These definitions of severity are somewhat arbitrary, however, and have not been validated. The relapse rate remains useful as an outcome measure in controlled trials, but it is critical to mask the treatment from patients and evaluator effectively, because a relapse is in large part patient-defined. It is also absolutely mandatory that the relapse data be analysed in terms of impairment and disability data derived from the neurologic examination or quantitative tests of neurologic function. This is particularly important because patients typically experience fewer relapses while converting to steadily progressive neurologic deterioration.

A sizeable number of MS clinical rating scales of impairment and disability have been developed. Traditionally, the EDSS\[3\] has been the most frequently used scale in MS trials. The EDSS is an ordinal scale that comprises 19 steps between 0 and 10 in 0.5-point increments; increasing score represents increasing disability. Between 0 and 3.5, the composite score is based on the scores assigned to eight functional system scales. Between 4.0 and 5.5, the composite score represents the distance that the patient can ambulate; 6.0 represents the use of unilateral assistance such as a cane to walk; 6.5 represents the need for bilateral assistance, such as a walker. Scores from 7.0 to 9.5 represent increasing degrees of immobility and dependence. Groups of patients progress up the EDSS in a reasonably ordered and consistent way, and the EDSS has become well accepted as the standard method for categorizing patients by disease severity.

The EDSS has been criticized because of several shortcomings related to its use as an outcome measure for controlled clinical trials.\[19\] The main problems with the EDSS can be summarized as follows:
The standard neurologic examination is inherently subjective. In the lower range of the EDSS, the definitions for scoring the functional system scales based on the examination are vague and subjective. As a result, intra-rater and inter-rater reliability of the EDSS are poor even with formal training of evaluators.

In the middle range of the scale, the EDSS is almost entirely an ambulation instrument. Changes in other neurologic manifestations (e.g. arm function and vision) have no impact on the score. Furthermore, the information about ambulation is truncated into a small number of discrete categories, and so important information about change in walking ability is discarded. For example, an individual patient may remain at the 6.5 level for several years, during which walking becomes increasingly limited. The change may be apparent to both the patient and the evaluator, but the EDSS does not reflect it.

Because it is based on the standard neurologic examination, the EDSS is insensitive to cognitive impairment, a common and clinically important aspect of MS (see chapters 3 and 4). In the upper range, the EDSS steps are so vague and stable as to be almost useless as a rating scale for clinical trials.

The EDSS steps are non-linear, and so the rate at which patients progress through the scale varies at different points.

These attributes make the EDSS relatively insensitive to change in neurologic function and impair its ability to demonstrate treatment effects in clinical trials.

### The Multiple Sclerosis Functional Composite

In response to these concerns, a workshop was held in Charleston, South Carolina, USA, in 1994. The consensus from the workshop indicated that the majority of participants felt that an improved clinical outcome measure was required for future clinical trials. The new clinical outcome measure was to retain the best elements of the EDSS but include measure(s) of cognitive impairment and be quantitative, reproducible, and more useful in monitoring treatment effects in controlled clinical trials. The National Multiple Sclerosis Society’s Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis appointed the Clinical Outcomes Assessment Task Force and charged them with making specific recommendations for improved clinical outcome measures. The Task Force articulated desirable attributes of a clinical outcome measure for MS trials:

1. The measure should be quantitative, continuous, and linear to the extent possible.
2. The measure should have high intra-rater and inter-rater reliability or, for self-report measures, should have high test-retest reproducibility.
3. The measure should be sensitive to clinical change over a relatively short time interval, so that it could be reasonably expected to show therapeutic effects during a clinical trial.
4. The measure should be valid.
5. The measure should be easy to administer, well tolerated by subjects, economical, and time-efficient.

The need for increasingly sensitive clinical measures was considered of extreme importance to allow progress in the field. Table 1.3 shows sample size calculations for...
two clinical trials using EDSS worsening as the primary outcome. The first clinical trial is placebo-controlled. The sample size calculation assumes that 40% of placebo recipients will reach the clinical endpoint in 3 years. It is assumed that the active therapy will be 40% effective (i.e. only 24% of patients in the active treatment group will reach the clinical endpoint). Such a trial would require 132 subjects per arm, or a total of 264 subjects. Assuming a 20% drop-out rate, the study would require 317 patients to achieve a power of 80% to show the therapeutic effect at the required significance level of $p<0.05$. The second study in the table incorporates an active arm comparison. That is, treatment 1 was partially effective, and the second study compares treatment 2, a newer promising therapy, with the ‘standard’ treatment 1. For the active arm comparison study, 624 patients would be required to show a further 40% benefit of treatment 2 over treatment 1, assuming that the outcome measure and all other parameters remain unchanged. Thus, as partially effective therapies are developed, demonstrating effectiveness of better treatments will require longer trials, substantially increased sample sizes, more sensitive clinical measures, or some combination of these approaches.

To arrive at its recommendations, the Task Force analysed informative data sets from controlled clinical trials and natural history studies to assess potential measurement techniques against the favorable attributes listed above.\cite{21} Based on that analysis, the Task Force recommended a three-part composite, termed the Multiple Sclerosis Functional Composite (MSFC) for further testing and for use in controlled clinical trials.\cite{22} The MSFC includes quantitative functional tests of lower extremity function and ambulation (the timed 25-foot walk\cite{23}), upper extremity function (the nine-hole peg test\cite{24}), and cognitive function (the 3-second version of the Paced Auditory Serial Addition Test\cite{25}). Results from each of the component measured is transformed to a Z-score, representing the number of standard deviation units away from the mean of a reference population, and the individual Z-scores are averaged to create a single score.

The MSFC was used in the recently completed phase III study of interferon beta-1a in secondary progressive MS, demonstrating the feasibility of using the MSFC in a large-scale multinational study and confirming its excellent reproducibility.\cite{26} In this study, the MSFC was more sensitive to change in neurologic status over time than the EDSS and was able to show a beneficial treatment effect when the EDSS failed (see chapter 20).\cite{27} This study was the first to use the MSFC as the predefined primary clinical outcome measures. The MSFC is also being used as a secondary measure in a number of other ongoing trials.

Studies supporting the validity of the MSFC are rapidly accumulating. Validation of a new outcome measure is a complex process. Several aspects of validity are recognized. A number of studies support the validity of the MSFC, showing correlation with the EDSS,\cite{21,26,28,29} and disease course.\cite{28} The MSFC has been shown to correlate more strongly with T2-hyper-

<table>
<thead>
<tr>
<th>Table 1.3Number of study subjects required for a placebo-controlled trial and an active arm comparison trial</th>
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<tbody>
<tr>
<td><strong>Placebo-controlled trial</strong></td>
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<tr>
<td>Comparison</td>
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<td></td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Rate of worsening in control group</td>
</tr>
<tr>
<td>Rate of worsening in comparison group</td>
</tr>
<tr>
<td>Treatment effect size</td>
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<tr>
<td>Sample size for 3-year study*</td>
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</tbody>
</table>

*Assumes a 40% treatment effect; a two-tailed test of significance with $\alpha=0.05$ and $1-\beta=0.80$ and a 20% drop-out rate. Adapted from Rudick et al. [20]

intense lesion burden on cranial MRI [30–32] and whole brain atrophy [31,32] than the EDSS. The clinical relevance of the MSFC was supported by its correlation with patient self-reported MS symptoms and health-related quality of life. [29,33] In a long-term follow-up study, [32] subjects enrolled in the phase III study of interferon beta-1a in relapsing-remitting MS [10] were reassessed an average of 8.1 years after randomization. Baseline MSFC and MSFC worsening over 2 years in the original trial were highly correlated with requirement for assistance to walk, evolution from a relapsing-remitting to a secondary progressive course, and severe whole brain atrophy at follow-up. The MSFC correlated with these endpoints better than the EDSS did.

**SURROGATE MARKERS FOR USE IN MS TRIALS**

Ultimately, the goal of disease-modifying therapy in MS is to slow or prevent clinical deterioration. However, as discussed above, clinically meaningful disability develops over years in a typical patient with MS. Also, it has become increasingly clear that early in the disease clinical manifestations bear a loose relationship with the ongoing pathologic process. Thus, there is need for a surrogate marker that is sensitive (able to detect subclinical disease activity) and meaningful (able to predict the future clinical course). Although there have been reports of putative blood and CSF markers of immune activity or CNS tissue damage, most efforts to date have focused on the use of MRI for this purpose (see chapters 5–11).

**Subclinical disease activity in MS**

Although relapsing-remitting MS appears to have clinically active and quiescent periods, inflammatory lesions are developing or evolving almost continuously. Gadolinium enhancement represents the initial event (or at least a very early event) in the development of a new T2 lesion [34] and marks sites of active brain inflammation [35–37]. Approximately 50% of patients with relapsing-remitting MS have one or more gadolinium-enhancing lesions on a single cranial MRI scan obtained when the disease is clinically inactive [38,39] and over 70% have at least one gadolinium-enhancing lesion evident on three successive monthly MRI scans. Serial MRI studies have shown that MRI activity (the appearance of new or enlarging T2-hyperintense lesions, or gadolinium-
enhancing lesions) may exceed clinical relapses by 10–20 times.\textsuperscript{[40,41]} The vast majority of new gadolinium-enhancing lesions are clinically silent.\textsuperscript{[41]}

Approximately 60–70\% of patients have multiple brain lesions on MRI at the time of their initial clinical event,\textsuperscript{[42,43]} suggesting that subclinical inflammatory events predated the clinical presentation. Once relapsing-remitting MS has been established, residual clinical manifestations between relapses are often mild early in the disease, yet there is ongoing tissue damage, reflected in the accrual of T2-hyperintense MRI lesions.\textsuperscript{[40]} Atrophy probably also represents an end-stage effect of a variety of destructive processes in MS. Cerebral atrophy on MRI is a frequent finding in patients with severe, long-standing disease. With sufficiently sensitive techniques, atrophy can be detected in patients with early relapsing-remitting MS and only mild clinical disability.\textsuperscript{[18,44–46]} Thus, tissue damage is often accumulating in MS when the disease appears stable clinically.

Although accrual of T2-hyperintense lesions is the MRI hallmark of MS, the burden of T2-hyperintense lesions and their rate of accumulation over time correlate only very approximately with clinical disability. There are a number potential explanations for the dissociation. One explanation is that these lesions are pathologically heterogeneous—that is, inflammation, edema, demyelination, axonal damage, and gliosis all can have identical appearance on standard T2-weighted images. Hypointensity on T1-weighted images (so-called black holes),\textsuperscript{[47–49]} reduced magnetization transfer (measured by the magnetization transfer ratio),\textsuperscript{[47,50]} abnormal water diffusion,\textsuperscript{[51,52]} or decreased concentration of the neuronal marker \textit{N}-acetyl aspartate (NAA) on magnetic resonance spectroscopy\textsuperscript{[53–58]} are thought to represent lesions with more destructive pathology.

These techniques also suggest that recurrent brain inflammation damages axons. This was directly confirmed through histologic analysis of MS lesions\textsuperscript{[37,48]} in which axonal transection at sites of active inflammation was demonstrated, regardless of the duration of MS in the individual case. There is increasing evidence that accumulating axonal damage accounts, to a great extent, for disability progression. This hypothesis is supported by the finding that the burden of the more destructive MRI lesions with axonal damage tends to correlate somewhat better with clinical disability than the total T2 lesion burden does.

Another potential reason for the poor correlation between T2 lesion burden and disability may be the inability of standard T2-weighted MRI to detect significant pathology ‘between’ lesions. Pathologic studies have shown inflammation, demyelination, and axonal damage in areas outside visible plaques.\textsuperscript{[59,60]} Imaging at ultrahigh field strength (4.0–8.0 T) demonstrates lesions that are not visible at standard field strength (1.0–1.5 T).\textsuperscript{[61]} A variety of advanced imaging techniques have also shown widespread abnormalities in normal-appearing white matter. These techniques include T1 and T2 relaxation times,\textsuperscript{[62]} magnetic resonance spectroscopy,\textsuperscript{[55,63–67]} magnetization transfer imaging,\textsuperscript{[60,68,69]} and diffusion tensor imaging.\textsuperscript{[51,52]} The severity and extent of these abnormalities correlates reasonably well with disability. These observations suggest that imaging approaches that provide a global measure of pathology could be useful in monitoring individual patients over time, both in clinical practice and in clinical trials. Measures developed for this purpose include cerebral atrophy,\textsuperscript{[44,70]} whole-brain magnetization transfer ratio histograms,\textsuperscript{[71]} total brain NAA,\textsuperscript{[72]} and whole-brain diffusion magnetic resonance histograms.\textsuperscript{[73]} An alternative approach is the use of functional imaging techniques such as functional MRI and positron emission tomography,\textsuperscript{[75]} which can demonstrate neuronal dysfunction that is dissociated from
lesions either anatomically or temporally (see chapter 11). The functional disturbance may also identify regions that are compromised but not yet irreversibly damaged.

Thus, several lines of evidence indicate that active inflammation and resultant tissue damage during the relapsing-remitting stage of MS is not accurately reflected by clinical manifestations. One hypothesis holds that irreversible CNS tissue injury occurs repeatedly in the inflammatory lesions during the relapsing-remitting stage.\textsuperscript{[76]} This CNS injury accumulates over the years, leading to progressive clinical deterioration in patients with secondary progressive MS. Progressive disability develops only after the amount of tissue loss has exceeded a threshold, beyond which compensatory mechanisms are exhausted and functional decline ensues. MRI has the potential ability to provide a more accurate window on the ongoing pathology than clinical assessment does. Nevertheless, further studies are needed to confirm this putative advantage.

**MRI as a surrogate marker of the disease process**

The poor relationship between clinical manifestations and ongoing brain inflammation (and the resultant tissue damage) also implies that more accurate and sensitive markers of the pathologic process in relapsing-remitting MS will be required for use as a surrogate marker. The Food and Drug Administration (FDA) in the USA defines a ‘surrogate marker’ as any non-clinical measure that can reliably predict clinical changes ‘within a reasonable amount of time’. Although certain conventional MRI parameters (see chapters 5 and 6) correlate with disease activity, and although MRI can be used to predict the risk of conversion from clinically isolated syndromes suggestive of MS to clinically definite MS,\textsuperscript{[16]} no MRI measure has acceptable validity at present for predicting eventual disability in MS.

Nevertheless, it is generally agreed that MRI has the greatest potential for meeting the FDA definition of a surrogate marker. Neurologists already obtain cranial MRI scans periodically to assess MS disease activity and progression, to help to determine the need for disease-modifying therapy in patients with clinically mild disease, and to monitor the response to such therapy. The Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis of the United States National Multiple Sclerosis Society appointed a Task Force, which made recommendations about using MRI in clinical trials (Table 1.4).\textsuperscript{[77]} The Task Force report was generally optimistic about the potential for using MRI parameters as surrogate markers, made initial recommendations based primarily on analysing gadolinium-

<table>
<thead>
<tr>
<th>Table 1.4 Recommendations of the Task Force on Use of MRI in MS Clinical Trials</th>
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<tr>
<td>1 MRI is a highly sensitive marker of pathologic activity in relapsing-remitting and secondary progressive MS</td>
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<tr>
<td>2 There are significant correlations emerging between a number of magnetic resonance and clinical parameters, although in established MS the relationship between short-term MRI activity and long-term disability is uncertain</td>
</tr>
<tr>
<td>3 High sensitivity makes MRI an excellent tool for rapid screening of therapies aimed at suppressing new pathologic activity in relapsing-</td>
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remitting and secondary progressive MS. Because the long-term relationship between MRI and disability is still uncertain, MRI data should not be the definitive determinant of therapeutic efficacy. A clinically significant endpoint must be shown. MRI should be used to select appropriate patients with clinically isolated syndrome for trials of therapy aimed at delaying the evolution to definite MS.

4 There are evolving major improvements in the resolution and sensitivity of MRI and in new techniques to monitor demyelination and neuronal damage and to quantify lesion load. Further studies are needed in ongoing treatment trials to determine whether these new techniques (fluid-attenuated inversion recovery sequences, magnetization transfer imaging, magnetic resonance spectroscopic imaging, and diffusion-weighted imaging) will prove to be strongly predictive of clinical outcome.

enhancing lesions, and indicated the rapid developments in the field that can be expected to result in future more specific recommendations. The current status of MRI as a technique to monitor the MS disease process was recently reviewed.\textsuperscript{[78]}

Analysis of MRI lesions faces a number of important challenges as a surrogate marker for controlled clinical trials:

1 There are a number of candidate measures. For example, T2-hyperinten lesion lesion burden, T1-hypointense lesion burden, number or volume of gadolinium-enhancing lesions, number of new or enlarging T2-hyperintense lesions, lesion evolution are all potentially informative. However, these measures are interrelated, and it is not clear which should be used or how they should combined.

2 MRI lesions are highly dynamic with substantial variability within individual patients in longitudinal studies. This leads to potential for sampling error. For example, if a patient is tested during a burst of disease activity, lesion analysis may suggest that the pathology is increasing when the overall trend is actually decreasing. Also, there is substantial between-subject variability in MRI lesion burden. These two factors result in the need for large sample sizes or frequent MRI scans.

3 The processes that lead to loss of the blood-brain barrier resulting in increased permeability to gadolinium are not the cause of the accumulation of inflammatory cells in the CNS but rather the result of it. Furthermore, although the presence of gadolinium enhancement in MS is probably a marker of inflammation, inflammation and resultant tissue damage can probably proceed under some circumstances without gadolinium enhancement, at least as detected by conventional imaging techniques.

4 T2-hyperintense lesions comprise a variety of histopathologic substrates. Thus, T2-hyperintense lesions, although a characteristic finding in MS, are not a very specific one. Standard T2-weighted MRI is also not sensitive to all pathology in MS. Newer techniques such as magnetization transfer imaging, magnetic resonance spectroscopy, and diffusion tensor imaging demonstrate abnormalities extending beyond the lesions visualized with conventional MRI techniques and may be more sensitive to clinically relevant pathology. However, these techniques are difficult to standardize across institutions. Thus, their use in multicenter trials raises complex practical issues.
5 Global measures of the pathologic process, such as a whole-brain atrophy, whole-brain magnetization transfer ratio histograms, and total brain NAA, are appealing, since they are likely to reflect the net effect of various pathologic processes, and the outcome is likely to be meaningful. However, such global measures may not be sensitive to disease activity over short time intervals, and they do not provide insights into the mechanisms of tissue loss or the mechanisms of therapeutic responses.

6 Because therapeutic agents differ in their mechanisms of action, it is likely that they have differing effects on lesion formation, evolution, or repair. Thus, MRI endpoints need to be tailored to the agent under study.

7 Analysis of MRI lesions has not yet been shown to predict subsequent clinical deterioration reliably, although few studies so far have incorporated adequate methodology to establish predictive validity.

In summary, although MRI lesion analysis is promising, further studies are needed to define precisely how MRI should be used as a surrogate marker in clinical trials and to validate its use.

**FUTURE CONSIDERATIONS FOR THERAPEUTICS IN MS**

**Placebo control groups and active arm comparison studies**

Placebo-controlled trials in relapsing-remitting MS are now impractical, because effective therapies are available in most regions of the world. More importantly, placebo-controlled trials are ethically questionable (see chapter 12) given the convincing evidence for meaningful therapeutic benefits from the available treatments. The use of a placebo control group in studies of secondary progressive MS is also becoming increasingly problematic, with emerging reports of effective therapies (see chapters 20, 23, and 27). However, current therapies for both relapsing-remitting MS and secondary progressive MS are only partly effective; potentially better therapies need to be developed and tested. Therefore, it will be necessary to define a methodology for active arm comparison studies and for studies of drugs given in combination (see chapter 30). This will substantially increase the complexity and cost of controlled clinical trials unless more sensitive clinical measures or reliable surrogate markers can be identified.

**Early treatment**

There is an increasing consensus that disease-modifying therapy should be started early in patients with relapsing-remitting MS to delay or prevent subsequent neurologic disability, rather than withheld until after disability has become manifest (see chapter 33). The rationale for this recommendation is supported by the observation that subjects with relapsing-remitting MS in the placebo control arms in phase III studies who are then switched to active treatment during open-label follow-up studies continue to fare less well than subjects on active treatment from the beginning of the study. Once a specific neurologic impairment has persisted for longer than 6 months, spontaneous recovery is uncommon and no therapies are known that promote recovery. There also is a trend to increasing willingness to consider more aggressive therapies (see chapters 23, 27,
and 28) for patients who have continued disease activity despite standard treatments and for patients with worrying clinical or MRI features. These therapies have the potential for greater efficacy but carry the risk of greater toxicity.

**Quality of life and cost-benefit analyses**

With the trend in the direction of proactive preventive therapy designed to delay or prevent evolution to secondary progressive MS, the potential medical, economic, and societal benefits of effective therapy in the early disease stage may not be immediately evident. At early stages of the disease, many patients feel reasonably well and are working. How will we demonstrate the need for and the benefits of aggressive early treatment used to prevent the devastating later effects of MS? The use of more sensitive clinical endpoints that are able to detect smaller short-term changes in clinical status only exacerbates the issue of the clinical meaning of those changes. Increasingly, patient self-reports of health status and quality of life will be needed to address the clinical relevance of the results (see chapter 4). In addition, follow-up studies are needed to confirm that agents shown to be of benefit in the relatively short time period encompassed by controlled clinical trials continue to be effective and well tolerated and that the benefit shown in the short term translates into more clearly meaningful effects in the long term (see chapters 15 and 17). The methodologic issues in long-term studies are substantial. Finally, investigators and society at large are increasingly faced with the difficult issue of weighing the short- and long-term benefits of therapies against their cost (see chapter 12).

**Rationally designed interventions**

Most contemporary clinical trials are based on the concept that MS is caused by autoreactive T cells that injure the CNS. Interventions have ranged from highly specific inhibition of the trimolecular complex to global immune suppression. However, based on recent pathology studies, concepts of MS pathogenesis have substantially changed (see chapter 19). There is increased recognition that the pathogenic mechanisms in MS are more complex than was originally thought and involve not only cell-mediated mechanisms but also humoral mechanisms. Reports of benefit of therapeutic approaches likely to be directed to humoral mechanisms supports this concept (see chapters 25 and 26). There may also be a degenerative component, particularly at later stages of the disease. The pathologic process is probably heterogeneous; it may vary significantly between patients and in individual patients over time. The implication is that novel therapeutic approaches targeted at a variety of steps in the pathogenic process are needed (see chapters 30, 32, and 33).

The other implication is that individual patients may respond to different therapies. Once therapy is started, how do we distinguish responders from partial responders and non-responders? What are the most appropriate treatment options (switching agents or combination therapy) for patients demonstrating a suboptimal response? Is rational polypharmacy with agents aimed at different aspects of the disease process possible? Will we eventually develop adequate information related to pathogenic mechanisms, immunogenetics, and mechanisms of action of the therapies to design in a rational way
therapeutic interventions, or will development of MS therapeutics be predominantly a trial-and-error process?

**Neuronal pathology**

Axonal damage and neuronal pathology are now recognized to be prominent features of MS and major contributors to permanent disability, providing a rationale for neuroprotective factors in future clinical trials. However, understanding of the mechanisms leading to axonal degeneration, strategies to interrupt these processes, and methods to monitor this aspect of treatment in trials are lacking.

**Regenerative strategies**

Treatments aimed at augmenting repair processes, both remyelination and axonal regeneration, are greatly needed. Studies of these agents will require development of new methods to monitor repair and restoration of function.

**Application of clinical trial results to clinical practice**

Extrapolating from controlled clinical trials to clinical practice is an imprecise art. Neurologists are required to make decisions for individual patients based on limited data from clinical trials. By necessity, entry criteria for clinical trials are restricted to reduce heterogeneity and to focus the question for the trial. But in clinical practice only a tiny fraction of the patients have the same characteristics as the clinical trial population. Additionally, methods for monitoring individual patients during open-label therapy are lacking. Can we develop methods to address a common clinical question: ‘Is this drug working in this patient?’ This issue applies not only to disease-modifying therapies but also to symptomatic medications and non-pharmacologic therapeutic approaches. A valid definition of therapeutic response is needed for individual treatment decisions. Clinical studies at the interface between controlled clinical trials and clinical practice will be critical for optimizing therapy for individual MS patients.

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II
Clinical trial methodology
Measures of neurologic impairment and disability in multiple sclerosis

Gary R Cutter

INTRODUCTION

Measuring impairment and disability for the purpose of patient care differs from evaluating the impact of therapies in clinical trials. In the former, we are focused on the individual patient, with the goal of good care to prevent problems, alleviate suffering, and to have an impact on the course of disease. For these purposes, clinical assessments are needed to identify problems, document the course of the disease, provide etiological clues, and evaluate therapeutic efficacy. Because of complexity of the disease process in multiple sclerosis (MS) and the breadth of clinical consequences, clinical tools for MS can be effectively applied only by a skilled and experienced clinician. Good clinical care can be viewed as a series of informal clinical trials by an astute clinician using single patients as the study population. Individualized treatment is central to patient care, and successful response is the goal for each and every patient. This continual ongoing trial is appropriate at the individual level but is generally not appropriate for experimental studies. Rather, for the purpose of evaluating the impact of therapies on impairment and disability, clinical measurements derived from a population of patients under a common protocol are needed with predefined outcomes. This chapter describes the measurement of impairment and disability for use in MS clinical trials from a population, rather than from a patient care perspective. Many concepts discussed here are relevant at the patient level, but the reader should be cognizant that optimal measures for clinical trials may differ significantly from evaluative methods for individual patient care.

Many approaches to measuring impairment and disability exist, and the terminology often leads to confusion as to the concept being measured. The World Health Organization (WHO) developed the International Classification of Impairments, Disabilities, and Handicaps in 1980. In this framework, a patient is classified in terms of disease, impairment, disability, and handicap:

- disease represents the underlying diagnosis or pathologic process;
- impairment is the loss of physical or psychosocial capacities;
- disability refers to limitations in performing a usual activity of normal life;
- handicap is a disadvantage resulting from impairment or disability that inhibits or prevents a role that is normal for that person.

Nagi developed a functional limitation model, which described pathology, impairment, functional limitation, and disability. According to this model:
• pathology is the ‘interruption or interference of normal bodily processes or structures’;
• impairment is the ‘loss or abnormality of mental, emotional, physiological, or anatomical structure or function’;
• a functional limitation is ‘restriction or lack of ability to perform an action or activity in the manner or within the range considered normal’;
• disability is the ‘inability or limitation in performing socially defined activities and roles expected of individuals within a social or physical environment’.

There are marked similarities between these two formulations of impairment and disability, although the WHO framework equates handicap to what Nagi calls disability.

These related classifications seem to encompass the spectrum of impairment and disability, but at the measurement level another dimension needs to be considered. There is often great debate over the value of an outcome measure of disability in MS. For example, some believe extensive cognitive testing is essential to characterize a patient’s disability, while others are content with a more global assessment. Part of this debate stems from the perspective of the observer. Two general perspectives or models of disability drive measurement approaches. The first is the medical model of disability, which focuses on the individual patient, specifically on his or her impairment. This is the most familiar and common approach. The goal of treatment is to alleviate consequences of the impairment, to return the patient to normal (or as close to normal as possible). This model requires accurate diagnosis of the impairment and its pathology. It relies on a detailed understanding of normal function in order to develop the goals of intervention. In this model, patients are commonly labeled in terms of disability (e.g. wheelchairbound) rather than by level of impairment. The second perspective is the health psychology perspective. This vantage point is heavily focused on coping behaviors and developing strategies to minimize the effects of impairment. The view is that a person is disabled not only by his or her impairment, but also by the response to it. From this perspective, an assessment of daily living activities and how a patient plans to accomplish certain tasks make up the tools for assessing that patient. Both approaches are valid for a patientcentered approach to therapy, and both can lead to valid outcome measures in clinical trials. Interventions that seek to effect cure are best measured from the medical model perspective. Interventions that are designed to ameliorate symptoms can often be approached using the health psychology perspective.

In this chapter, the primary concern is with the measurement of impairment or disability from a medical model perspective. This is chosen because the evaluation of new therapies is usually focused from this perspective. While there are a wide range of measurement tools for application in MS encompassing everything from fatigue to sleep and to bowel and bladder functioning, this chapter focuses on global clinical trial outcome measures.
METHODOLOGIC ISSUES IN MEASURING IMPAIRMENT AND DISABILITY

Measures can be grouped into four classes:[3]

- biologic assays, which use laboratory methods, such as the amount of neutralizing antibodies, to assess a particular function or parameter;
- performance measures, which are standardized procedures for testing human function, such as the nine-hole peg test;[4]
- rating scales, which are ordered (ordinal) scales requiring human assessment, the most common in MS being Kurtzke’s Expanded Disability Status Scale (EDSS);[5] and
- self-report measures, which require individual patients to provide information about their condition from their own perspective; the Incapacity Status Scale[6] is an example of such a self-report measure in the MS field.

These four classes of measurement describe the types of measures, and provide a framework for assessment. The purposes of the measurements are, however, not restricted by the different classes. In other words, a particular research question could be addressed by a laboratory test, a measure of patient function, a clinical rating scale, or a self-report. In clinical medicine, more than one measure, and often many measures, are used to evaluate a patient’s status, check progress, alter the course of therapy, or make other recommendations. In a clinical trial, it is generally preferable to identify a single measure as the primary outcome and as the focus for decision-making. There is a natural conflict between a complete clinical assessment of a patient from a physician’s clinical perspective and the summary or index measure used in a clinical trial. Clinicians feel an obligation to understand in as detailed a manner as possible their patient, while a clinical trial outcome measure may ignore entirely important factors of a specific patient’s condition. This conflict may not show in the choice of instruments, but it can and does influence the interpretation of the results.

Some instruments are used to measure diseasespecific functions or conditions. Examples are ambulation, bladder infections, or angina. Other instruments aim to measure disease dysfunction in a non-specific manner, thus enabling comparison across diagnostic conditions. The Adult Functional Independence Measure[7] is a generic instrument used to measure impairment in a number of diseases or conditions. There are benefits and disadvantages both to disease-specific and to generic instruments, which must be related to the underlying research question. Clinicians generally prefer disease-specific instruments. In areas of psychosocial evaluation, disease-specific approaches are often too narrow, and broad-based assessments tend to be cumbersome or time-consuming, leading to a proliferation of choices and often a lack of consensus on measurement. In the context of a clinical trial, disease-specific approaches often have more merit with respect to the illness under investigation, while generic measures provide more generalizability and context for the results.

Another important measurement issue is whether to choose an instrument that explores a single dimension of impairment or one that addresses a broader spectrum of the patient’s condition. For example, measures of ambulation focus almost exclusively on leg
function in the MS patient, whereas the EDSS was developed as a composite score capturing nine functional systems, at least at the lower end of the scale. For certain clinical trials, a more specific outcome measure is preferred, while in other trials, multiple responses may be important. In testing an antispasticity drug, for example, a measure of leg spasticity might be preferred over a multidimensional measure because the outcome measure would be more responsive to the specific treatment question being asked—in this case whether the drug reduces leg spasticity. Such a specific outcome measure may not address the overall patient response to the drug. In a trial of disease-modifying therapy (e.g. an interferon trial), a more global measure such as EDSS may be preferable because the principal question relates to the overall condition of the patient.

Thus, while no single measure will ever be completely adequate to characterize an MS patient, a given clinical trial must choose an end-point that most appropriately addresses the question being asked. Because it is difficult to characterize impairments and disability associated with MS, and because the disease results in multiple clinical manifestations, optimal outcome measures in MS clinical trials are likely to be very specific to a narrow question of treatment, to be composite clinical measures for assessing the impact of treatment on a group of patients, or to be surrogate laboratory measures that have been shown to correlate, predict, and be tantamount to other clinical outcomes.

**THE MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE**

In February 1994, a meeting entitled ‘Outcomes Assessment in Multiple Sclerosis Clinical Trials’ was held in Charleston, South Carolina, USA. A meeting summary was published by Whitaker et al.[8] The Charleston meeting recommended development of an improved clinical outcome measure for MS clinical trials that met several criteria:

1. The measure should be multidimensional to reflect the varied clinical expression of MS across patients and over time.
2. The individual dimensions should change relatively independently over time.
3. Measures of cognitive function should be included, in addition to those clinical dimensions already incorporated into the Kurtzke EDSS.[5,9]

The results and recommendations from this meeting led the National Multiple Sclerosis Society’s (NMSS) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis to appoint the Task Force on Clinical Outcome Assessment. This group convened its initial meeting in Chicago in October 1994 and published a detailed set of criteria for defining new clinical outcomes and a set of guidelines for developing the new measure.[10] Two key components of the guidelines were, first, the exploration of quantitative functional measures as components of a composite outcome measure, and, second, specifications for a meta-analysis of primary and secondary outcome assessments in existing MS clinical data sets to provide an objective basis for a multidimensional component outcome assessment. Recommendations from the Task Force based on these guidelines have been presented elsewhere.[11]

The delineation of the Multiple Sclerosis Functional Composite (MSFC) resulted from a pooled data set of placebo control groups and natural history study databases. The use of multiple data sets ensured that decisions regarding the creation of the MSFC would not
be dependent on any single data set with its potential biases. The Task Force developed six guiding principles for the composite development:

• to use measures that reflect the major clinical dimensions of MS;
• to avoid redundancy;
• to use simple rather than complex measures;
• to improve on the valuable characteristics of the EDSS;
• to emphasize measures sensitive to change; and
• to develop an outcome measure that will be useful in clinical trials (and may or may not be directly useful for clinical care).

These principles helped to structure the analysis plan. The process drew, by necessity, on the experiences of previous investigations. The Task Force, based on clinical expertise, identified the major clinical dimensions of MS and specified criteria by which to proceed. The major clinical dimensions identified for evaluation were arm, leg, cognitive, and visual functions.

The criteria established by the Task Force to select candidate component measures were:

• good correlation with the biologically relevant clinical dimensions;
• good reliability of the measurement (the ability to obtain the same result on repeat testing when no change occurred);
• the ability to show change over time; and
• availability of a minimum of two data points in time 1 year apart.

Construct validity (the extent to which the measure of interest correlates with other measures in predicted ways, but for which no true criterion exists) was used to reduce the number of candidate measures. This was based on the logic that individual measures within the same clinical dimension should correlate with each other (convergent validity) and not with measures of different clinical dimensions (discriminant validity). Applying these criteria, a subset of candidate measures was selected. Reliability estimates observed from the literature, means and standard deviations of change, and the relationship between changes in these candidate variables and in the EDSS were assessed. To ensure that the Task Force recommendations for a refined clinical outcome measure were satisfied, both concurrent and predictive validity of the composite measure were evaluated. Concurrent validity was defined as change in the composite measure compared with concurrent change in the EDSS over a 1-year period. Predictive validity was defined as change in the composite occurring over the first year of follow-up compared with subsequent change in EDSS among those patients with no sustained change in EDSS during the first year. Predictive validity was felt to best illustrate and validate the composite construction. Detailed discussion of this process was reported by Cutter et al. The recommended MSFC is a unified score representing the combination of results from three performance tests: the nine-hole peg test, the timed 25-foot walk, and the Paced Auditory Serial Addition Test with a 3-second inter-stimulus interval (PASAT3). Results on these tests are combined to form a single score, as explained below. To calculate the MSFC score, the following scores are generated:

Measures of neurologic impairment and disability in multiple sclerosis 27
scores from four trials on the nine-hole peg test—two trials of the left hand are averaged and two trials of the right hand are averaged; scores from two trials of the timed 25-foot walk are averaged; and the number of correct answers from the PASAT3 test is used.

Thus, the MSFC score incorporates three clinical dimensions representing arm, leg, and cognitive function to create a single score that can be used to detect change over time in a group of MS patients.

Since the units of measurement differ between these tests (time in seconds for the nine-hole peg test and the timed 25-foot walk, the number of correct answers for the PASAT3), it was necessary to identify a sensible way to combine these variables. A Z-score was selected as a common metric for this purpose. The Z-score is a standardized number representing how close a test result is to the mean of a standard or reference population to which the result is compared. The Z-score is expressed in units of standard deviation and usually ranges from $-3$ to $+3$, although there are no restrictions on its values. The standard deviation of a measure is, on average, how far an observation is from the mean in the original units of measurement, whereas the Z-score is a relative measure. A Z-score of 2 always implies an observation is 2 standard deviation units from the mean or twice as far from the mean than an observation that is 1 standard deviation unit from the mean. In general, most of the other observations would be closer to the mean than 2. The clinical meaning of a standard deviation of 2 depends on what is being measured (e.g. seconds, minutes, number correct), and these underlying units would need to be known before the value could be considered as large or small, clinically. Commonly, in medicine, we define laboratory abnormalities in a similar way, marking them when they are two or three times the upper or lower limit of normal. The Z-score is obtained by subtracting the mean of the reference population from the test result, and then dividing by the standard deviation of the reference population.

Because the Z-score is a relative measure indicating how many standard deviation units the current observation is from the mean of a reference population, the units are the same irrespective of the underlying measurement scale. For example, the number of seconds required to perform a test can be represented on the same Z-score scale as the number of correct responses on the PASAT3. This allows the results from tests using different metrics (e.g. seconds and number correct) to be combined.

The three components of the MSFC are combined by creating a Z-score for each individual component, then averaging the three Z-scores to create the overall MSFC score. Implicit in this approach is the idea that patients who deteriorate or improve on all three component measures will have an overall larger change than patients who change on only one of the three measures. Also, patients who deteriorate in one area but improve in another may show no change on the MSFC, because the MSFC represents the average change in the three tests.

### Determining a Z-score for the nine-hole peg test

As an example, suppose we have five patients with nine-hole peg test times of 20, 25, 30, 35, and 40 seconds. The mean time for the test in this group of patients is 30 seconds, and the standard deviation is 7.906 seconds. To create a Z-score for the nine-hole peg test using these patients as the standard population to provide a standardized relative
representation, we subtract the mean from each score, and divide by the standard deviation of the population (Table 2.1). Thus, patient 1 is 1.265 standard deviation units better than the mean, patient 2 is 0.632 standard deviation units better than the mean, patient 3 is 0 standard deviation units from the mean, patient 4 is 0.632 standard deviation units worse than the mean, and patient 5 is 1.265 standard deviation units worse than the mean.

The general formula for creating the composite is given in Table 2.2. Detailed formulae that allow creation of the composite Z score are provided in Tables 2.3 and 2.4 and are further explained below.

**Adjustment of Z-scores to indicate improvement by a positive number**

To combine Z-scores from all three tests, it is necessary for the Z-score sign (direction) representing worse or better performance to be the same for all three tests. Increased raw scores represent worsening on the nine-hole peg test and the timed 25-foot walk, whereas decreased raw scores represent worsening in the PASAT3. Because the words ‘clinical decline’ suggest lower or negative values being worse, the Z-scores for the nine-hole peg test and the timed 25-foot walk are adjusted so that in both cases higher Z-scores correspond to an improved outcome, and lower Z-scores correspond to worsening, as is the case with the PASAT3. Changing the sign of the Z-scores for the timed 25-foot walk to ensure that a negative value implies worse function is called ‘transforming’ the data. The Task Force has recommended two transformations based on the best performance for

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**Table 2.1 Creating Z-scores using the test patients to standardize scores**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Formula For Z-Score, 9HPT</th>
<th>Z-Score9HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \frac{20 - 30}{7.906} )</td>
<td>-1.265</td>
</tr>
<tr>
<td>2</td>
<td>( \frac{25 - 30}{7.906} )</td>
<td>-0.632</td>
</tr>
<tr>
<td>3</td>
<td>( \frac{30 - 30}{7.906} )</td>
<td>0.000</td>
</tr>
<tr>
<td>4</td>
<td>( \frac{35 - 30}{7.906} )</td>
<td>0.632</td>
</tr>
<tr>
<td>5</td>
<td>( \frac{40 - 30}{7.906} )</td>
<td>1.265</td>
</tr>
</tbody>
</table>

Population mean=30, standard deviation=7.906 9HPT, nine-hole peg test

---

**Table 2.2 Formula for creating the MSFC score**

\[
Z_{\text{composite}} = \frac{Z_{\text{arm,average}} - Z_{\text{leg,average}} + Z_{\text{cognitive}}}{3}
\]
each. More information about these approaches is provided in the Scoring Manual.[13] These transformations use subtrac-

Table 2.3 Formula for creating the MSFC score to compare groups within a study (the preferred method)

\[
\text{Z}_{\text{composite}} = \frac{1}{3} \left[ \frac{\text{average} \left( \frac{1}{\text{NHPT}} \right) - \text{mean} \left( \frac{1}{\text{NHPT}} \right)}{\text{Baseline SD} \left( \frac{1}{\text{NHPT}} \right)} \right] - \frac{\text{average T25FW} - \text{baseline mean T25FW}}{\text{Baseline SD T25FW}} + \frac{\text{PASAT3} - \text{baseline mean PASAT3}}{\text{Baseline SD PASAT3}}
\]

NHPT, nine-hole peg test; T25FW, timed 25-foot walk; SD, standard deviation.

‘Average \left( \frac{1}{\text{NHPT}} \right)’ is the average of the inverse for the right- and left-hand trials from the test patient, baseline mean \left( \frac{1}{\text{NHPT}} \right) and SD \left( \frac{1}{\text{NHPT}} \right) are the baseline values from all treatment groups combined at the baseline assessment. ‘Average T25FW’ is the score from the test patient; similarly, baseline mean T25FW and SD T25FW are of all baseline groups combined. ‘PASAT3’ is the score from the test patient, and baseline mean PASAT3 and SD PASAT3 are from the baseline assessments of all patients.

Z-scores involve comparing each outcome to that found in a reference population, a process called standardizing the variable. This involves a decision about what population to use as the reference to derive the means and standard deviations to create the Z-scores. The preferred method for creating Z-scores provided in the Scoring
Table 2.4 Formula for creating the MSFC score using task force database to allow comparison between studies

\[
Z_{\text{composite}} = \frac{1}{3} \left[ \frac{\text{average} \left( \frac{1}{\text{NHPT}} \right) - 0.0439}{0.0101} \right] \nonumber \\
- \frac{\text{average } T25FW - 9.5353}{11.4058} \\
+ \frac{\text{PASAT3} - 45.0311}{12.0771} 
\]

NHPT, nine-hole peg test; T25FW, timed 25-foot walk SD, standard deviation

‘Average’ is the average of the inverse for the right- and left-hand trials from the test patient; 0.0439 and 0.0101 are the mean and SD of the inverse of the NHPT for the reference population, respectively.

‘Average T25FW’ is the score from the test patient; 9.5353 and 11.4058 are the mean and SD of the reference population, respectively. ‘PASAT3’ is the score from the test patient; 45.0311 and 12.0771 are the mean and SD of the reference population, respectively.

Manual\textsuperscript{[13]} instructs in the use of test results from the baseline assessments from all patients in a particular study cohort. The equation for this method is provided in Table 2.3. An alternative method is to use the results from a representative database with a broad spectrum of MS patients. The equation for this method, using data from the National Multiple Sclerosis Society Task Force database, is shown in Table 2.4. This method allows a comparison of disease severity in patients participating in different studies, because their scores are standardized against a common population. This method may not be the optimal method for demonstrating change in a particular population or for showing treatment effects.

The formula in Table 2.4 uses values derived from all patients in the Task Force dataset.\textsuperscript{[10–12]} Composite scores created using this formula should be comparable across different trials. The results from the formulae presented in Tables 2.3 and 2.4 will be similar but not necessarily identical. The recommended scoring rule for clinical trials is to use the study population baseline average for statistical comparisons of the two groups. When comparing among studies, using the Task Force database values for showing results relative to an external standard is appropriate. These recommendations are given because many studies use a restricted range of subjects, which can yield different standard deviations. Different standard deviations cause the three components to be weighted slightly differently from study to study. A second advantage of using the average of all study participants’ baseline measures in a clinical trial is that the means and standard deviations of the component Z-scores will be close to zero for the mean and
to 1 for the standard deviation, making comparison of the treatments easier for assessing baseline comparability. Thus, in a clinical trial, it seems relevant to weight the Z-scores in the context of the study baseline data.

Example of the MSFC in a hypothetical clinical trial

Suppose you are conducting a randomized clinical trial to compare drug B with a widely used therapy, RX, in MS patients. A total of 699 patients complete the study out of 800 randomized patients (400 per group). The MSFC should be computed based on the mean and standard deviation from all 800 patients randomized, but often the only data presented might be for those completing the trial (we will return to this point later in the example). So, consider that the MSFC is computed using the combined baseline values for the 699 completers with the results shown in Table 2.5.

Examination of the data on the patients completing the study shows that mean baseline EDSS averaged 2.7 and 2.8 (both groups showed a median EDSS of 2.5). Average EDSS did not change over 1 year for patients treated with drug B, but it worsened by an average of 0.5 points for patients on RX. A total of 16.2% of drug B-treated patients experienced a 3-month sustained worsening from baseline EDSS (defined as two consecutive EDSS ratings at least 3 months apart 1 step worse than baseline for patients with a baseline EDSS of <5.5 or 0.5 steps worse than baseline for patients with a baseline EDSS of ≥5.5). In comparison, 20.7% of the RX group experienced sustained EDSS worsening. The PASAT3 at baseline averaged about 45 for the RX group and 47 for the drug B group and it rose by nearly two and three correct responses, respectively. The timed 25-foot walk was completed in 7.8 and 7.1 seconds, respectively, at baseline. This slowed substantially at 12 months to 29.3 seconds and 13.7 seconds, respectively. The large standard deviations in the timed 25-foot walk are due to the increasing times to complete the measurement at follow-up, with few people improving and a few becoming severely disabled. The mean change in the nine-hole peg test was about a 1.5-second increase for both groups as well as a larger standard deviation, again indicating substantial deterioration in some patients. The MSFC for the RX group was slightly negative at baseline and declined almost 1 standard deviation unit after 12 months compared with a decline of 0.2 standard deviation units for the drug B group. The test of the hypothesis for a treatment effect is not statistically significant using the percentage with a sustained EDSS change (χ²=2.31, p=0.129), but it is significant for MSFC changes (t=2.17, p=0.030). In this example, EDSS and MSFC changes move in a consistent direction over the first year of observation, but only the MSFC changes are statistically significant.

There are several additional points to note. The number of patients who completed the study differed in the two treatment arms: 329 (82.2%) for group RX versus 370 (92.5%) for drug B. This differential drop-out (17.8% versus 7.5%) between the two groups should be examined. If the baseline data on all 800 patients were presented, it is likely that the groups were balanced at the start of the trial because of the large sample size and the power of randomization to equalize major covariates in such a large sample size. Comparing the data for each group, however, shows potential selection biases amongst those completing the study. There were no differences on the EDSS at baseline. Although the PASAT3 results at baseline showed a statistically significant higher score for drug B recipients (p<0.004), there were no differences on the timed 25-foot walk or the nine-hole
The MSFC in the drug B recipients was significantly better at baseline than in the RX recipients \((p<0.004)\). Assuming the groups were balanced at baseline when the entire randomized cohort was present, differences seen in subgroups completing the trial suggest that patients with higher MSFC scores in the RX group dropped out of the study. The meaning and implications of this are never clearly obvious, but the information contained within the MSFC allows for some suggestions, noting that the patients with better profiles dropped out. Such suggestions of potential differences should be investigated for a full assessment of trial results. In general, one would use the baseline of all 800 randomized patients to create the MSFC, and one could compare the characteristics of those completing and those dropping out of the study.

### Table 2.5 Results for patients completing clinical trial of drug RX versus drug B

<table>
<thead>
<tr>
<th>Variable</th>
<th>Drug RX (n=329)</th>
<th>Drug B (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS at baseline</td>
<td>2.7 ± 1.7</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td>EDSS at 12 months</td>
<td>3.2 ± 1.8</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td>EDSS change</td>
<td>0.5 ± 1.2</td>
<td>0.0 ± 0.9</td>
</tr>
<tr>
<td>Sustained change (%)</td>
<td>20.7 ± 16.2</td>
<td></td>
</tr>
<tr>
<td>PASAT3 at baseline</td>
<td>44.6 ± 12.7</td>
<td>47.2 ± 10.9</td>
</tr>
<tr>
<td>PASAT3 at 12 months</td>
<td>46.3 ± 13.1</td>
<td>50.2 ± 11.1</td>
</tr>
<tr>
<td>T25FW at baseline</td>
<td>7.8 ± 8.7</td>
<td>7.1 ± 5.5</td>
</tr>
<tr>
<td>T25FW at 12 months</td>
<td>29.3 ± 121.3</td>
<td>13.7 ± 66.8</td>
</tr>
<tr>
<td>NHPT at baseline</td>
<td>25.0 ± 8.7</td>
<td>24.1 ± 8.9</td>
</tr>
<tr>
<td>NHPT at 12 months</td>
<td>26.4 ± 13.0</td>
<td>25.8 ± 22.0</td>
</tr>
<tr>
<td>MSFC at baseline</td>
<td>−0.073 ± 0.767</td>
<td>0.084 ± 0.630</td>
</tr>
<tr>
<td>MSFC at 12 months</td>
<td>−0.970 ± 5.497</td>
<td>−0.115 ± 3.070</td>
</tr>
<tr>
<td>MSFC change</td>
<td>−0.897 ± 5.191</td>
<td>−0.199 ± 2.827</td>
</tr>
</tbody>
</table>

SD, standard deviation; T25FW, timed 25-foot walk; NHPT, nine-hole peg test

In the above example, the MSFC was more sensitive to change than the EDSS. This may not always be the case. The EDSS encompasses more clinical dimensions and could show changes in circumstances where the MSFC does not. The EDSS, however, is an ordinal scale with changes having very different meaning at differing points on the scale. The MSFC is a continuous measure, which should increase the power for demonstrating differences in impairment and disability within the clinical dimensions included in the MSFC. The EDSS, an ordinal measure with differing duration of times between steps of the scale, often requires the use of a rule for sustained change that alters the size of the required step (i.e. 0.5 steps for those 5.5 and over). This is equivalent to the recognition of the unequal intervals between later and earlier steps on the EDSS. The MSFC score is a continuous variable that can be used like any numerical variable in analyses. The value is subject to tests appropriate for continuous variables, such as t-tests, non-parametric tests (such as the Wilcoxon test), parametric and nonparametric analysis of variance, and
regression analyses. A composite based on such Z-scores can also measure change in performance over time. By computing the composite at one point in time and measuring the patient at a later point in time, the arithmetic difference between MSFC scores can be used to measure improvement or worsening.

**Special considerations regarding the MSFC**

*Handling data where some data points are missing for reasons other than inability to perform the test.*

In the event that a particular patient did not complete some of the tests (e.g. the patient was running late so only one trial per arm of the nine-hole peg test was completed), the available data can be used to calculate the MSFC. In this case, the MSFC is still the average of the three Z-scores as usual:

\[
Z_{\text{composite}} = \frac{Z_{\text{arm,average}} - Z_{\text{leg,average}} + Z_{\text{cognitive}}}{3.0}
\]

In the usual instance, the \(Z_{\text{arm,average}}\) is computed

\[
Z_{\text{arm,average}} = \left[ \frac{Z_{\text{arm,trial 1,left}} + Z_{\text{arm,trial 2,left}}}{2.0} + \frac{Z_{\text{arm,trial 1,right}} + Z_{\text{arm,trial 2,right}}}{2.0} \right]
\]

In the absence of two trials for each arm for the nine-hole peg test, the \(Z_{\text{arm,average}}\) would, however, be computed based on the trials available, as follows:

\[
Z_{\text{arm,average}} = \frac{Z_{\text{arm,trial 1,left}} + Z_{\text{arm,trial 1,right}}}{2.0}
\]

*Handling missing data because the patient was unable to perform the test as the result of disability*

It is recommended that data from patients who were unable to perform the test because of disability should be used. For example, suppose a patient completed the nine-hole peg test in an average of 55 seconds at the beginning of the trial, but was unable to complete the test at the end of the trial because of increasing disability. It is advantageous to capture the data in such a way that it indicates worsening, rather than leaving the data point missing, which would provide no information about change.

In most data sets used in the meta-analysis,[3,4] the inability to perform the nine-hole peg test was coded as 777. Keeping that convention, 1/777 was arbitrarily used to represent the inability to perform the test, providing a value that is close to 0 but nevertheless informative. Therefore, for the nine-hole peg test, the following formula is
recommended for a subject who could not complete either arm of the test because of disability:

\[
Z_{\text{arm,trial}} = \frac{1/777 - 0.0439}{0.0101} = -4.2191
\]

If the patient could complete one arm of the nine-hole peg test, say in 25 seconds for the right arm, but could not complete the test with the left arm, the Z-score would average the two arms, subtract the mean and divide by the standard deviation, thus:

\[
\begin{align*}
Z_{\text{arm,trial}} &= \frac{1/777 - 1/25 - 0.0439}{0.0101} \\
Z_{\text{arm,trial}} &= \frac{(0.00129 + 0.04)2 - 0.0439}{0.0101} \\
Z_{\text{arm,trial}} &= \frac{0.0206 - 0.0439}{0.0101} = -2.3026
\end{align*}
\]

For the timed 25-foot walk, using the inverse transformation (1/time) yielded a very restricted range on the transformed Z-score. The smallest Z-score was only −2 despite scores ranging from 20 to 30 seconds to over 400 seconds. Thus, it was decided to use the Z-score actually computed from the slowest time associated with any patients in the combined dataset used by the Task Force in its meta-analysis. The longest time to complete the timed walk yielded a Z-score in the Task Force dataset of −13.7. While this is a very extreme Z-score, it represents the actual time that a patient took to complete the test. The range of values is sufficiently wide such that an extremely high value had to be chosen to enable a person with declining ambulation to deteriorate in terms of their Z-scores (i.e. there were patients whose baseline Z-score was worse than −5 and others who at 6 months had Z-scores of −8 or −9 but who by 18 months were unable to complete the test). Therefore, while relative to usual thinking about Z-scores from normally distributed populations, where Z-scores of −3 or −4 are rare, the following formula is recommended for a subject who cannot complete the timed 25-foot walk:

\[
Z_{\text{leg,average}} = -13.7
\]

Data substitution is usually only done for the nine-hole peg test and the timed 25-foot walk; it is not generally recommended for the PASAT3, unless it is truly clear that the patient cannot do the test. This is because nearly all patients can achieve some score on the PASAT3, even if it is close to 0 or actually 0. In the event that an individual patient cannot complete the PASAT3 because of disability, a score of 0 is assigned.

The use of imputation allows all patients starting a trial to be used in the analyses. It is obviously important to ensure that no bias enters into the determination that a patient cannot do a test due to MS. In a randomized trial, assuming it is double-blinded, there would seem to be little real bias potential, but such consideration should be given to ensure that imputed values are used only for appropriate cases. In the event that the situation is not clear, the analysis can use any number of classical imputation tools (e.g. last observation carried forward, the worst value for that patient). As with the EDSS,
which provides for a score of 10 for death, the MSFC would use the imputing values for the nine-hole peg test, the timed 25-foot walk, and PASAT3 for patients who have died or who are so incapacitated that they cannot perform any tests.

**CONCLUSIONS**

The measurement of impairment and disability requires that the question being addressed should be sharply focused. Patient-specific clinical care questions may require measures of impairment and disability that are directed at guiding therapy. The approach is usually a measure of disease or specific physical ailment. When the question to be answered requires a controlled clinical trial, outcome measures of group performance are generally preferred. Continuous measures of impairments and disability are preferred over ordinal scales, because they allow more precise measures and smaller sample sizes. These measures may result in therapeutic benefits without obvious clinical benefits. Related studies to explore the clinical meaning of the continuous impairment measures, however, are important.

The MSFC is a new measure of impairment and disability. It is likely to undergo revision and improvement as information is collected about its use and better component tests are developed. The concept underlying the MSFC, however, goes beyond the current component measures. If newer or more reliable measures of arm, leg, and cognitive function become available, they could be substituted for current MSFC components measures. If newer informative measures of dimensions that are not currently included in the MSFC (e.g. vision) become available, they could be added to the composite.

A great deal has been learned about the MSFC. The measure has been shown to be reliable with an intraclass correlation coefficient of 0.93 when used in a multinational clinical trial and multiple languages using 436 patients.[14] The MSFC has a defined learning curve that requires at least three administrations to develop an accurate baseline from which to measure change. Use of the MSFC without taking into account the learning curve would still work in trials but would add noise to the measure of change. It would also underestimate the amount of decline, because of a lower or poorer performance at baseline than would be possible once the patient becomes experienced with the testing procedures. Several authors have shown that the MSFC correlates with magnetic resonance imaging parameters,[15–17] with health-related quality of life measures,[18] and with clinical outcomes measured prospectively,[18,19] confirming the predictive validity found in the development of the measure for long-term outcomes. While the MSFC needs more complete testing in the realm of clinical trials, it represents a potential improvement over ordinal clinical rating scales. Of particular importance is its ability to show small changes in active arm comparison studies. Without increasingly sensitive measures, progress in the MS field will be constrained by cost and the availability of patients for clinical trials.
REFERENCES

Assessment of neuropsychological function in multiple sclerosis
Jill S Fischer

RATIONALE FOR ASSESSING NEUROPSYCHOLOGICAL OUTCOMES IN MULTIPLE SCLEROSIS TRIALS

Cognitive function is often impaired in multiple sclerosis (MS) patients. Prevalence estimates derived from two large controlled cross-sectional studies are remarkably similar, once impairment rates in demographically matched healthy controls are taken into account: nearly half of all MS patients exhibit deficits on neuropsychological (NP) testing.[1,2] The functional consequences of MS-related cognitive impairment can be devastating. Cognitive impairment has a direct impact on the ability to maintain employment,[2–4] driving skills and safety,[5,6] involvement in social activities,[2] personal and community independence,[4,7–9] and the likelihood of benefiting from in-patient rehabilitation.[10] Not surprisingly, it is a major source of strain for caregivers.[11,12]

Cognitive impairment is directly related to cerebral abnormalities produced by MS: NP test performance correlates moderately to strongly with cerebral lesion burden on T2-weighted magnetic resonance imaging (MRI),[13–15] brain atrophy (e.g. whole brain volume or brain parenchymal fraction, ventricular diameter, callosal area),[15–18] microscopic pathology both in lesions and in normal-appearing brain tissue (e.g. magnetization transfer ratios),[15,18–20] and cerebral glucose metabolism rates.[21] Furthermore, deteriorating cognitive function has been associated in longitudinal studies with increasing cerebral lesion burden over 1-year[22] and 4-year[23] intervals, and with decreasing brain parenchymal volume over a 2-year period.[24]

Disease course and progression also have an impact on cognitive function, albeit a more modest one than cerebral pathology. In general, secondary progressive MS patients perform more poorly on NP testing than patients with relapsing-remitting or primary progressive MS.[25–27] Even so, groups of relapsing-remitting patients and primary progressive patients exhibit deficits relative to healthy controls.[8,28–30] Correlations between cognitive dysfunction and MS duration or neurologic disability as assessed by the expanded disability status score (EDSS) are surprisingly weak.[2,31,32] As a result, traditional clinical outcome measures are notoriously insensitive to MS-associated cognitive deficits.[33]

The purpose of this chapter is threefold: first, to summarize briefly what is known about the nature and evolution of cognitive dysfunction in MS; second, to provide an overview of controlled clinical trials of disease-modifying and symptomatic medications in which NP outcomes have been explicitly assessed, and third, to make recommendations regarding NP outcome assessment in future MS clinical trials. It emphasizes study design and analysis of NP outcomes, extending concepts advanced in previous chapters.[34,35] Readers interested in the clinical management of cognitive
impaired in MS patients are referred to chapter 42. Those interested in a more extensive review of MS-related cognitive dysfunction are referred to Fischer.\[36\]  

NATURE OF MS-RELATED COGNITIVE DYSFUNCTION  

Not all cognitive functions are equally susceptible to disruption by MS. Learning and recall of new information (often referred to as ‘recent memory’) are among the most vulnerable: 22–31% of the patients in the sample studied by Rao et al. had severe learning and memory deficits (i.e. scored below the fifth percentile for demographically matched healthy controls).\[2\] Impairment in the speed of information processing and in working memory (i.e. the ability to buffer and manipulate information simultaneously) is also extremely common, with 22–25% of the sample studied by Rao et al. exhibiting severe deficits.\[2\] Visuospatial abilities and executive functions (including reasoning, problem solving, and planning and sequencing) are also compromised surprisingly often: severe impairment was observed in 12–19% of the sample studied by Rao et al.\[2\] Deficits in auditory attention span or verbal abilities occur less often (in 7–8% of the patients studied by Rao et al.\[2\]), although recent studies of the natural history of MS suggest that deficits in these domains become evident when cohorts are followed for longer periods of time.\[4,37\]

Individual MS patients vary considerably in their specific cognitive deficits. Three distinct patterns of learning and memory performance have been consistently observed in cluster analytic studies of multitrial list learning task performance.\[25,38,39\] The most common pattern involves inefficient learning, which is characterized by deficient first-trial recall, mildly inconsistent recall across learning trials, and mildly deficient recall after a delay (observed in 43–56% of the patients sampled). Other patients (20–22% of each sample) exhibit more pervasive learning and memory deficits, including a flattened learning curve, extremely poor delayed recall, and numerous intrusion errors. The performance of many patients (24–36% of those studied) remains essentially intact, however.

This heterogeneity of performance extends to other cognitive domains as well. Six distinct subgroups emerged in cluster analyses of the comprehensive NP battery performance of two large samples of relapsing-remitting MS patients.\[28,40\] Many of the patients studied (34–46%) had no observable cognitive deficits. Among those who were impaired, the most common pattern was that of circumscribed deficits in one or two cognitive functions (e.g. attention and processing speed, learning and memory, or executive function); three subgroups with different combinations of deficits (a total of 37–49% of each sample) fit this pattern. The remainder (17% of each sample) exhibited more generalized cognitive deficits, either moderate or severe. Thus, MS is as variable in its NP presentation as it is in its physical manifestations.
NATURAL HISTORY STUDIES OF MS-RELATED COGNITIVE DYSFUNCTION

Far less is known about the natural history of MS-related cognitive impairment than is known about the course of neurologic impairment in MS. The longitudinal NP performance of MS patients has been compared with that of demographically comparable healthy controls in four published European studies,\[4,8,41,42\] two of which evaluated the same sample at different time points.\[4,8\] Initial sample sizes in these studies were small (50 patients or fewer) but each had a high retention rate. These studies differed considerably in terms of patients’ disease characteristics, the NP measures administered, and the methods used to analyse the data.

In the USA, Rao et al. followed their large cohort for 8 years,\[37\] although there was considerable attrition by the 8-year follow-up. The strengths of this study include a heterogeneous community-based sample, an unusually comprehensive NP battery, and the application of sophisticated regression-based techniques for identifying patients whose performance fell below that expected. Although our picture of the evolution of MS-related cognitive dysfunction is still incomplete, several points can be gleaned from these studies (Table 3.1).

Clearly, cognitive impairment is not inevitable in MS: a subset of patients appear to maintain reasonably intact cognitive function well into their disease. A large proportion of patients do develop cognitive impairment, however, even early in their disease. Once present, cognitive impairment is unlikely to remit to any significant extent: cognitive deficits may remain stable over time, but they often worsen. Progression rates vary considerably across patients and across cognitive functions: gradual cognitive deterioration is much more common than rapid progression, but cognitive function declines precipitously in up to 25% of patients. Specific risk factors for MS-related cognitive impairment and predictors of further deterioration have not been definitively identified. The heterogeneity of MS-related cognitive impairment and the variability in progression rates pose challenges in assessing NP outcomes in clinical trials.

CLINICAL TRIALS OF DISEASE-MODIFYING MEDICATIONS

Assessment of NP outcomes in clinical trials of disease-modifying medications is a relatively recent phenomenon. The first controlled clinical trial known to assess NP outcomes was the double-blind, placebo-controlled phase III trial of cyclosporine for progressive MS.\[43\] A measure of processing speed (the Symbol-Digit Modalities Test (SDMT)) was administered to patients as part of the Quantitative Evaluation of Neurologic Function (QENF) at baseline, and then every 3 months throughout the 24-month trial.\[44,45\] No significant treatment effects were observed on the SDMT, although substantial practice effects were evident in both the cyclosporine and placebo groups (Syndulko, personal communication).

As the prevalence and functional consequences of MS-related cognitive dysfunction became more widely recognized, several definitive trials of disease-modifying
medications for relapsing-remitting MS\cite{46-48} and progressive MS\cite{49-51} incorporated NP outcome measures.\cite{51-56} Tables 3.2 and 3.3 provide an overview of these trials. (One small (n=20) randomized 6-month trial of recombinant interferon alfa-2a\cite{57} with two

Table 3.1 Controlled natural history studies of MS-related cognitive dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial sample</th>
<th>Design and data analysis</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennekens-Schinkel et al.\cite{41}</td>
<td>39 patients (51% (51% RR) versus 24 HC</td>
<td>4-year follow-up (n=33)</td>
<td>Initial deficits (choice RT, verbal and visual learning, reading speed, and finger tapping) persisted over time; a few patients (6–12%) deteriorated markedly, and one improved</td>
</tr>
<tr>
<td></td>
<td>MS group: Mean DSS 3.5 (range 1–7) Mean age 42 years (range 17–73)</td>
<td>Cross-sectional between-group and longitudinal within-group comparisons on individual tests</td>
<td></td>
</tr>
<tr>
<td>Amato et al.\cite{4,8}</td>
<td>50 patients (88% RR) versus 70 HC</td>
<td>4.5-year (n=49) and 10-year (n=45) follow-up</td>
<td>Initial deficits in verbal memory and executive functions persisted and new deficits emerged at 4.5 years (verbal fluency and auditory comprehension) and 10 years (attention span); 12 out of 49 patients (24%) worsened by 4.5 years, and 19 out of 45 (42%) deteriorated by 10 years</td>
</tr>
<tr>
<td></td>
<td>MS group: Mean EDSS 2.0 (sd 1.5) Mean age 29.9 years (sd 8.5) Mean education 11.4 years (sd 3.6)</td>
<td>Cross-sectional between-group comparisons on individual tests</td>
<td></td>
</tr>
<tr>
<td>Kujala et al.\cite{42}</td>
<td>45 patients (86% CP) versus 35 HC</td>
<td>2- to 4-year follow-up (n=42)</td>
<td>Performance of ‘intact’ group remained relatively stable over time (though 35% worsened slightly);</td>
</tr>
<tr>
<td>'Intact' MS group (n=22):</td>
<td>Mean EDSS 5.0 (sd 1.8)</td>
<td>Mean age 43.3 years (sd 8.7)</td>
<td>Mean education 11.6 years (sd 3.5)</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>'Impaired' MS group (n=23):</td>
<td>Mean EDSS 5.5 (sd 1.3)</td>
<td>Mean age 43.3 years (sd 7.2)</td>
<td>Mean education 11.0 years (sd 2.9)</td>
</tr>
</tbody>
</table>

Bobholz et al. [37] 100 patients (39% RR) versus 100 HC 3-year (n=84) and 8-year (n=59) follow-up

Deficits in most domains were evident at all time points and some of these (verbal abilities, verbal fluency, processing speed and working memory, calculation ability, and visual perception) worsened significantly over time; 21 out of 84 patients (25%) met criteria for ‘significant deterioration’ at 3 years, whereas only 10 out of 59 (17%) did so at 8 years.

The test battery used by Jennekens-Schinkel et al. consisted of confrontation naming, word generation, reading (100 words), writing to dictation, figure copy, Knox cubes, Wechsler Memory Scale, 10-item list learning task (auditory and visual), 7/24 Spatial Recall Test, Stroop test, Wisconsin Card Sort (Nelson version), Raven’s Progressive Matrices, and finger tapping.

The test battery used by Amato et al. included Blessed Information-Memory-Concentration Test, Token Test, figure copy, Digit Span.
memory measures and a measure of visual construction is excluded from Table 3.2, owing to there being insufficient information about statistical analyses of the NP data. Other studies not meeting criteria for the list of randomized clinical trials include a small open label phase I combination trial of etretinate and interferon beta-1b in a mixed patient sample (14 patients with secondary progressive MS and three with relapsing-remitting MS), which revealed beneficial treatment effects on verbal memory but not on visual memory, processing speed/working memory, or verbal fluency; and two studies that compared patients treated with interferon beta-1b with healthy controls.

The trials listed in Tables 3.2 and 3.3 vary substantially in terms of their sample sizes, patients’ disease course and level of disability at study entry, the breadth and timing of the NP outcome assessment, and the statistical analyses performed. Nonetheless, beneficial effects were observed on the primary outcome measure in each of these trials. Consequently, it might be reasonable to expect positive NP effects as well. In fact, these trials provide unusually stringent tests of the NP effects of disease-modifying therapies. Cognitive impairment was not an explicit entry criterion, so trial participants varied widely in their cognitive function. Even effective disease-modifying medications cannot be expected to improve NP performance in cognitively intact patients, so NP effects of a treatment are undoubtedly attenuated in cognitively heterogeneous samples.

The trials listed in Tables 3.2 and 3.3 confirm that beneficial effects of disease-modifying therapies often do extend to cognitive function, although these effects may be subtle or gradual. The study design, choice of NP measures, and approaches to statistical analysis are all critical factors in determining whether a statistically significant treatment effect is observed. Importantly, no single NP measure consistently detected treatment effects when analysed in isolation using conventional methods (such as ANOVA of change scores). Statistically significant NP effects were most often observed on composite NP outcome measures (e.g. multivariate analyses or analyses of 'number of
failed tests’) and when demographic factors that can potentially affect NP test performance were carefully controlled (e.g. by converting raw scores to age- and education-corrected scores based on published norms\(^{[53]}\) or by using demographic variables as covariates in statistical analyses\(^{[52,55,56]}\)). Considerations in the selection and timing of NP outcome measures and the choice of statistical approaches are discussed later in this chapter.

**NP STUDIES OF SYMPTOMATIC TREATMENTS**

NP outcomes have also been assessed in a number of small (n<60) studies of symptomatic treatments for MS (i.e. medications and cognitive rehabilitation). Patients entering these trials all had definite or probable MS but their disease characteristics varied substantially. There were also differences in study design (cross-over versus parallel groups), choice of NP measures, and statistical analyses. In four studies, cognitive deficits were the specific target of the intervention, and only patients with documented cognitive deficits were included (Table 3.4).\(^{[61–64]}\) In most studies, the NP impact of these symptomatic treatments was of secondary interest, so cognitive impairment was not an explicit selection criterion (Table 3.5).\(^{[65–71]}\) (One study of cognitive rehabilitation in a cognitively heterogeneous

### Table 3.2 Randomized clinical trials of disease-modifying medications with NP outcome assessment: relapsing-remitting MS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial sample</th>
<th>NP measures and design</th>
<th>Primary NP analysis</th>
<th>NP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant interferon</td>
<td>372 patients</td>
<td>Focused battery (WMS Logical Memory and Visual</td>
<td>2-way ANOVAs (group× test time) of demographically</td>
<td>Significant treatment effect (group×test time interaction) on Delayed Visual Reproduction (p&lt;0.03), favoring high-dose group (p&lt;0.003), with a similar trend on Trails B (p&lt;0.14)</td>
</tr>
<tr>
<td>beta-1b(^{[46,53]})</td>
<td>0.0–5.5</td>
<td>Reproduction, Trails A and B, Stroop) at 2 years and 4 years only; n=30 at a single site</td>
<td>adjusted scores from individual tests</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate(^{[47,54]})</td>
<td>251 patients</td>
<td>Focused battery (Selective Reminding Test, 10/36 SRT, PASAT, SDMT, and Word List</td>
<td>2-way ANCOVAs (group× site×test time) of individual scores, with baseline score as covariate</td>
<td>No significant treatment effects</td>
</tr>
<tr>
<td></td>
<td>0.0–5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recombinant interferon beta=1a

EDSS 0.0–3.5

Generation) at baseline, 12 months, and 24 months; n=248

MANOVAs of demographically adjusted 2-year change scores on three sets of factor-analytically-derived variables, with baseline score as a covariate

Significant treatment effects on memory and information processing ($p=0.011$), with a trend on visuospatial abilities and executive functions ($p=0.085$); secondary analyses confirmed treatment effects on briefer battery (MANOVA) and PASAT deterioration (survival analysis)

*Caution is urged in interpreting NP outcomes from this study because NP measures were not administered before treatment was started and because the groups differed on several NP measures at the first (year 2) assessment

†Memory and information processing measures included CVLT Total 1–5, Ruff Figural Fluency Test (RFFT) Error Ratio, Stroop Interference Score, and CALCAP Sequential RT. Measures of visuospatial abilities and executive functions included WCST Perseverative Errors, Tower of London Total Number of Moves; 20 Questions % Good Hypotheses, WMS-R Visual Span Forward, and Rennick Visual Search Trials

EDSS, expanded disability status score; WMS, Wechsler Memory Scale; ANOVA, analysis of variance; 10/36 SRT, 10/36 Spatial Recall Test; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol-Digital Modalities Test; ANCOVA, analysis of covariance; MANOVA, multivariate analysis of variance; CVLT, California Verbal Learning Test; CALCAP, California Computerized Assessment Package; RT, reaction time; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale—Revised
### Table 3.3 Randomized clinical trials of disease-modifying medications with NP outcome assessment: progressive MS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial sample</th>
<th>NP measures and design</th>
<th>Primary NP analysis</th>
<th>NP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate&lt;sup&gt;[49,52]&lt;/sup&gt;</td>
<td>60 CPMS patients, EDSS 3.0–6.5</td>
<td>Broad-spectrum battery at baseline, 12 months, 24 months (n=40); focused NP battery every 6 weeks for 24 weeks to a subset of patients (n=35)</td>
<td>MANCOVA of 2-year change scores on five variables (15-item BNT, WAIS-R Block Design, PASAT-2&quot;, CVLT Long Delay Free Recall, and WCST Perseverative Responses), with age and education as covariates</td>
<td>Trend toward beneficial overall treatment effect (&lt;i&gt;p&lt;/i&gt;=0.07), owing primarily to effects on PASAT-2&quot; (&lt;i&gt;p&lt;/i&gt;=0.002); effect on PASAT was evident early in treatment</td>
</tr>
<tr>
<td>Interferon beta-1b&lt;sup&gt;[50,56]&lt;/sup&gt;</td>
<td>718 SPMS patients, EDSS 3.0–6.5</td>
<td>Focused battery (Selective Reminding Test, 10/36 SRT, PASAT, SDMT, word list generation) at baseline, 12 months, 24 months, and 36 months (n=476 patients and 197 healthy controls)</td>
<td>Non-parametric ANCOVAs of change from baseline to last visit on individual tests (stratified by country), with age, sex, education, and baseline score as covariates</td>
<td>No significant treatment effect on individual tests; secondary analyses indicated that fewer patients taking interferon beta-1b met criteria for ‘new or worsened cognitive impairment’ at 24 months (&lt;i&gt;p&lt;/i&gt;=0.039)</td>
</tr>
<tr>
<td>Recombinant interferon beta-1a&lt;sup&gt;[51]&lt;/sup&gt;</td>
<td>217 SPMS patients, EDSS 3.5–6.5</td>
<td>PASAT-3&quot; (as component of MS Functional Composite) at three baseline</td>
<td>Nonparametric ANCOVA of change from baseline to 24 months, stratified by baseline EDSS and gadolinium</td>
<td>Trend toward beneficial treatment effect on PASAT-3&quot; (&lt;i&gt;p&lt;/i&gt;=0.061)</td>
</tr>
</tbody>
</table>
visits, then enhancement every 3 months for 24 months (n=217)

CPMS, chronic progressive MS; EDSS, expanded disability status score; MANCOVA, multivariate analysis of covariance; BNT, Boston Naming Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; PASAT, Paced Auditory Serial Addition Test; CVLT, California verbal learning test; WCST, Wisconsin Card Sorting Test; 10/36SRT, 10/36 Spatial Recall Test; SDMT, Symbol-Digital Modalities Test; ANCOVA, analysis of covariance

The studies of symptomatic treatments for MS listed in Tables 3.4 and 3.5 are instructive in several respects. First, medications (specifically, cholinesterase inhibitors) and intensive cognitive rehabilitation both show promise in treating MS-related cognitive dysfunction (see Table 3.4). This is encouraging because, as more effective disease-stabilizing therapies become available, these symptomatic interventions may potentially ameliorate a symptom that significantly disrupts daily function. Second, as was seen in trials of disease-modifying medications, no single NP outcome measure was consistently sensitive to treatment effects. Third, beneficial effects were most likely when cognitive impairment was an explicit subject selection criterion: all four trials in patients with documented cognitive deficits were positive (see Table 3.4), whereas trials with cognitively heterogeneous patients yielded far less consistent results (see Table 3.5). This may be partly attributable to the treatments themselves (i.e. whether they were specifically designed to improve cognitive function or whether they were instead designed to treat other symptoms), but the nature of the samples undoubtedly played a role as well.

**FACTORS COMPLICATING NP OUTCOME ASSESSMENT IN MS TRIALS**

Several factors complicate the assessment of NP outcomes in MS trials, although none is insurmountable. The first methodological challenge is that cognitive impairment is inherently heterogeneous. Only about half of all MS patients develop measurable cognitive deficits, and those who do vary considerably in terms of which functions are involved and to what extent. This cognitive heterogeneity has implications both for patient selection and for the choice of NP outcome measures.
A second complicating factor is that the NP test performance of an MS patient can fluctuate over time. The variability in NP test performance is analogous in many respects to the variability observed on cerebral MRI.\(^{[75]}\) It can be controlled at the level of test selection, study design, and statistical analysis. Some fluctuations in test performance are attributable to transient situational factors; these can be minimized by standardizing testing conditions. Other fluctuations reflect the measurement error inherent in any test instrument.\(^{[76]}\) Memory tests are often less stable (i.e. more prone to measurement error) than tests of other cognitive functions.\(^{[77,78]}\) Test reliability should be a factor to consider in NP outcome measure selection. Another source of variability in NP test performance is fluctuation in the patient’s underlying disease (as occurs in exacerbations).\(^{[79]}\) Patients should be tested during periods of clinical stability unless the investigator is explicitly interested in the impact of disease fluctuations on NP performance.

A third challenge pertains not only to NP outcome measures but to all potential outcome measures in MS clinical trials: measures with

<table>
<thead>
<tr>
<th>Drug or intervention</th>
<th>Sample/study design</th>
<th>NP measures</th>
<th>Primary analysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous physostigmine(^{[61]})</td>
<td>Four patients (EDSS 3.0–6.0) with documented memory impairment 6-week placebo-controlled cross-over (no wash-out)</td>
<td>Buschke Selective Reminding Test and Digit Span (Forward) at baseline, then weekly for 6 weeks</td>
<td>Paired t-tests (1-tailed) on individual measures</td>
<td>Significant treatment effects ((p&lt;0.05)) on selected Buschke SRT Selective Reminding Test variables (LTS, LTR, STR) and consistent trends ((p&lt;0.10)) on others; no effect on Digit Span</td>
</tr>
<tr>
<td>Cognitive rehabilitation (three sessions a week for 6 weeks)(^{[62]})</td>
<td>40 in-patients with mean EDSS 5.6 (sd 1.7) and documented cognitive impairment 6-week parallel groups</td>
<td>Broad-spectrum battery at baseline, 6 weeks, and 6 months after treatment</td>
<td>T-tests of demographically adjusted t-scores effect on visual perception ((p&lt;0.04)) and visuospatial abilities</td>
<td>Significant treatment effects</td>
</tr>
<tr>
<td>Computerized process-specific attention training (four sessions a week for 3 weeks per module)</td>
<td>22 patients (EDSS 2.0–8.0) with documented attentional impairments</td>
<td>Computerized Wilcoxon matched pairs tests comparing baseline with post-training; Mann-Whitney test comparing effects of specific and non-specific training on individual tests</td>
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<tr>
<td>18-week parallel groups, with cross-over to second module</td>
<td>attentional battery (TAP-1.02c) at three baseline visits, then every 3 weeks for 18 weeks</td>
<td>Significant process-specific training effects for alertness, selective, and divided attention ($p&lt;0.05$); non-specific effects for alertness, divided attention; gains maintained at 9-week follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donepezil hydrochloride$^*$ (5 mg for 4 weeks, then 10 mg for 8 weeks)</th>
<th>17 MS patients (nursing home residents) with MMSE$\leq$25</th>
<th>Repeated measures ANOVA comparing baseline versus 4 weeks, 4 versus 12 weeks, and baseline versus 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-week open-label study</td>
<td>Broad-spectrum battery at baseline, 4 weeks and 12 weeks</td>
<td>Significant treatment effects on MMSE, HVLT Recognition Memory, and BNT at 4 weeks ($p&lt;0.05$); significant effects on these and secondary outcome measures at 9 weeks</td>
</tr>
</tbody>
</table>

Assessment of neuropsychological function in multiple sclerosis 49
Caution is urged in interpreting NP outcomes from this study, since it was an open-label study

EDSS, Expanded Disability Status Score; MMSE, mini mental state examination; HVLT, Hopkins Verbal Learning Test; BNT, Boston Naming Test; ANOVA, analysis of variance

<table>
<thead>
<tr>
<th>Drug or intervention</th>
<th>Sample and study design</th>
<th>NP measures</th>
<th>Primary analysis</th>
<th>NP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine hydrochloride (100 mg, twice daily)⁶⁵</td>
<td>29 patients (55% with RRMS) with mean EDSS 4.0 (sd 1.4) and symptomatic daily fatigue for 3 months; 10-week placebo-controlled cross-over (including 2-week wash-out)</td>
<td>Broad-spectrum battery at baseline; focused battery (Grooved Pegboard, Trails, SDMT, Consonant Trigram, Stroop, CPT, COWAT) at baseline, 4 weeks, and 10 weeks</td>
<td>Repeated measures ANOVA (condition×test time) of individual tests</td>
<td>Significant treatment effect on Stroop Interference (p&lt;0.05) and trend on Stroop Color Naming (p=0.08)</td>
</tr>
<tr>
<td>4-aminopyridine (up to 10 mg four times daily)⁶⁶</td>
<td>20 patients (90% with CPMS) with EDSS 2.5–8.0; 4-week placebo-controlled cross-over (no wash-out)</td>
<td>Focused battery (16-item verbal learning, 10/36 SRT, PASAT, SDMT, Word List Generation) at baseline, 2 weeks and 4 weeks</td>
<td>T-tests comparing conditions on change scores for individual measures</td>
<td>No significant treatment effects, but trends on PASAT-2&quot; (p=0.09) and 10/36 SRT Delayed Recall (p=0.06)</td>
</tr>
<tr>
<td>3,4-diaminopyridine (up to 100 mg/day in divided doses)⁶⁷</td>
<td>36 patients (81% with CPMS) with EDSS 2.5–9.0 and leg weakness; 90-day placebo-</td>
<td>Focused battery (Buschke Selective Reminding, 10/36 SRT, PASAT, SDMT, Word Paired Wilcoxon signed rank tests comparing scores on individual measures</td>
<td>No significant treatment effects</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Participants</td>
<td>Study Design</td>
<td>Evaluation</td>
<td>Findings</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Multimodal group therapy</strong> (weekly 3-hour sessions for 24 weeks)(^{[68]})</td>
<td>25 patients</td>
<td>24-week parallel groups (group therapy versus wait list)</td>
<td>Focused battery (10-item verbal list-learning, SDMT, Shipley) at baseline, 12 weeks, and 24 weeks</td>
<td>T-tests comparing groups on change scores for individual measures</td>
</tr>
<tr>
<td>Amantadine (100 mg twice daily) versus pemoline (56.25 mg)(^{[69]})</td>
<td>45 patients with EDSS &lt;6.5 and documented fatigue</td>
<td>6-week placebo-controlled parallel groups</td>
<td>Focused battery (Digit Span, SDMT, Trails, Buschke Selective Reminding, BVRT) at baseline and 6 weeks</td>
<td>ANOVAs (group x test time) of individual measures</td>
</tr>
<tr>
<td>Amantadine (100 mg twice daily)(^{[70]})</td>
<td>24 patients (58% with SPMS) with EDSS≤6.5 and documented fatigue (FSS&gt;4)</td>
<td>Placebo-controlled cross-over, including 10-day wash-out</td>
<td>Computerized visual selective attention task twice, 2 weeks apart (once in each condition)</td>
<td>MANOVA (condition×test time) on RTs</td>
</tr>
<tr>
<td>4-aminopyridine (32 mg once daily)(^{[71]})</td>
<td>54 progressive MS patients</td>
<td>12-month placebo-controlled cross-over</td>
<td>Focused battery</td>
<td>Between-group change on individual tests</td>
</tr>
</tbody>
</table>

EDSS, Expanded Disability Status Score; RRMS, relapsing-remitting
multiple sclerosis; CPMS, chronic progressive MS; SPMS, secondary progressive multiple sclerosis; FSS, Fatigue Severity Scale; SDMT, Symbol-Digit Modalities Test; CPT, Continuous Performance Test; COWAT, Controlled Oral Word Association Test; 10/36 SRT, 10/36 Spatial Recall Test; PASAT, Paced Auditory Serial Addition; BVRT, Benton Visual Retention Test; ANOVA, analysis of variance; MANOVA, multivariate analysis of variance; RT, reaction time

good discriminative properties (i.e. measures that can detect impairment in MS patients relative to healthy controls) do not necessarily have optimal evaluative properties (i.e. they may not be sensitive to change over time). For example, even though MS patients exhibit deficits on most measures of learning and memory, these tests are not uniformly sensitive to treatment effects in clinical trials. The differential sensitivity of specific tests is undoubtedly related to several factors, including test difficulty, the potential range and distribution of scores, and test reliability. Guyatt et al.\cite{80} presented a method for evaluating sensitivity to change (‘responsiveness’) that has been applied to the evaluation of MS neurologic rating scales, functional abilities scales, and MS quality of life instruments.\cite{86} In addition, Syndulko and colleagues evaluated the relative sensitivities of varied quantitative measures of function in the QENF using a different, but related, statistical approach (the ‘signal-to-noise ratio’).\cite{44,45} Responsiveness is an important factor to consider in selecting both NP outcome measures and specific variables from these measures to be used in statistical analyses.

A fourth factor complicating NP outcome assessment is inherent in many (if not most) NP tests and other performance-based measures: they are often subject to practice effects, regardless of the length of the intertest interval.\cite{78,87,88} Practice effects may differ across populations (e.g. patient groups versus healthy controls) and even among patients within the same population.\cite{78,87,89} Furthermore, practice effects are not entirely eliminated by using alternate forms.\cite{76,90,91} NP measures that are prone to practice effects can detect differential change between groups over time provided that practice effects are taken into account in designing the trial (i.e. selecting a control group and establishing the timing of assessments) and in planning statistical analyses.\cite{92}

A final challenge in assessing NP outcomes in MS trials is the definition of abnormal performance. On most NP measures, normal performance is not intuitively obvious; instead, it must be defined with respect to some normative group (i.e. demographically comparable healthy controls). A placebo or ‘standard treatment’ control group in a randomized clinical trial can serve as a reference for evaluating treatment effects, but not for defining the presence and magnitude of cognitive impairment. Assessment of NP outcomes is similar to assessment of other quantifiable functional abilities (e.g. timed gait, fine motor speed, co-ordination) in this respect. Development of normative databases for quantitative functional outcome measures (including NP tests) would greatly facilitate analysis and interpretation of clinical trial data.

Despite encouraging NP findings in several recent MS trials of disease-modifying and symptomatic treatments, therapeutic trials in MS still do not routinely incorporate NP outcome measures. Furthermore, studies of symptomatic treatments targeted at MS-related cognitive dysfunction are still rare. Many MS investigators remain unfamiliar with both NP measures and the nuances of assessing NP outcomes in clinical trials. The remainder of this chapter is intended to guide NP test
selection, study design, and statistical analysis for those wishing to incorporate NP outcome assessment into their clinical trials.

**RECOMMENDATIONS FOR DESIGN AND ANALYSIS OF NP OUTCOME ASSESSMENT IN MS TRIALS**

**Is a single NP measure adequate?**

This question applies principally to trials of disease-modifying medications, since trials of symptomatic interventions for MS-related cognitive dysfunction will most likely include measures assessing several domains of interest. Investigators may wonder, for example, whether the cognitive component of the MS Functional Composite [93–96] (i.e. the Paced Auditory Serial Addition Test [2,97]) is sufficient for assessing NP outcomes in a clinical trial. Although the MS Functional Composite (MSFC), which comprises quantitative tests of arm and hand, leg, and cognitive function, clearly represents an important advance in MS clinical outcome assessment, it was not designed to comprehensively assess either cognitive or physical function. Just as neurologic function in MS cannot be adequately captured by assessing only one functional system, no single NP test can provide a comprehensive assessment of the treatment effects in a cognitively heterogeneous disease such as MS.

The Paced Auditory Serial Addition Test (PASAT) might serve as a ‘micro-NP’ assessment, however. A ‘micro-NP’ assessment would be a test (or perhaps two or three brief tests) that could identify large beneficial or adverse effects of a treatment, but not necessarily effects that are subtle or effects in domains not covered by the ‘micro-NP’ instrument. The PASAT has several features to recommend it for this purpose. It is brief: the Rao version (with 3-second and 2-second interstimulus intervals) [2] can be administered within 10 minutes. It is multidimensional and therefore capable of detecting change in more than one domain of cognitive function. Specifically, the PASAT taps calculation ability, processing speed and working memory, [98] which have been shown to deteriorate over time in MS [37]. Finally, the sensitivity of the PASAT to treatment effects or trends has already been demonstrated in several MS clinical trials [51,52,55,66].

The PASAT does have some disadvantages as a ‘micro-NP’ assessment, however. It does not cover learning and memory, which are commonly impaired in MS. It is a challenging task, one that may meet with resistance from both patients and examiners. Furthermore, patients may adopt strategies while performing the PASAT that effectively alter task demands and potentially compromise the task’s sensitivity, particularly at faster stimulus presentation rates [99]. Consequently, supplemental scores (e.g. ‘dyad scoring’) [99] should be incorporated into statistical analyses of PASAT performance.

**Which NP measures should be included in future MS trials?**

Comprehensive assessment of the NP effects of a disease-modifying or symptomatic treatment will necessarily involve several measures that capture different cognitive domains (‘macro-NP’ assessment). Unfortunately, faced with a plethora of available NP measures, each MS investigator group has chosen a slightly different combination of
tests. Some have adopted a broad-spectrum approach (i.e. selecting measures that together assess a broad range of cognitive domains), whereas others have opted for more focused batteries that cover only one or two domains of interest.

The broad-spectrum approach has been fruitfully applied in longitudinal studies of cognitive dysfunction, trials of disease-modifying treatments (methotrexate and interferon beta-1a) and studies of symptomatic treatments (donepezil hydrochloride and cognitive rehabilitation). It is a reasonable approach when little is known about the potential effects of an experimental treatment or about the psychometric properties of the NP measures. However, broad-spectrum batteries can be time-consuming. Use of a broad-spectrum NP battery may also increase the risk of type 2 statistical errors (i.e. failure to detect a true treatment effect) if the battery includes unresponsive measures or if alpha level adjustments to accommodate multiple statistical tests are too stringent.

The focused approach has been adopted in most trials of disease-modifying and symptomatic treatments in MS. It is an efficient approach when specific hypotheses about treatment effects can be formulated, as in studies of symptomatic treatments for MS-related memory or attentional deficits. However, it may have disadvantages in trials of disease-modifying medications in cognitively heterogeneous samples when little is known either about the range of potential treatment effects or about the psychometric properties of the tests themselves. For example, although the Brief Repeatable NP Battery (BRB) is effective in detecting MS patients’ deficits relative to healthy controls, it proved to be insensitive to treatment effects in a recent trial of glatiramer acetate for relapsing-remitting MS. Several psychometric factors, identified in studies published after the glatiramer acetate trial was under way, may compromise the responsiveness of the BRB: performance fluctuates considerably from visit to visit, many of its component measures (e.g. the PASAT) are subject to practice effects, and alternate forms of some of its component tests (e.g. the 10/36 Spatial Recall Test, Word List Generation, the Symbol Digit Modalities Test) may not be truly equivalent.

Acknowledging the need for a practical broadspectrum battery for monitoring MS patients in clinical practice and in clinical trials, the Consortium of MS Centers (CMSC) convened an expert panel in New Orleans in April 2001 to develop a consensus regarding a ‘minimal’ NP examination. Neuropsychologists with extensive clinical or research experience in MS were invited to review pertinent literature on MS-related cognitive dysfunction and on psychometric issues relevant to repeated NP assessment, to identify the optimal characteristics of a minimal NP examination in MS, to propose candidate NP measures, and to rate both the conceptual and psychometric merits of each candidate measure (including reliability and responsiveness). Table 3.6 presents the expert panel’s recommendation—the Minimal Assessment of Cognitive Function in MS (MACFIMS).

The MACFIMS assesses cognitive domains that are often disrupted in MS (learning and memory, processing speed and working memory, visuospatial ability, and executive functions) within approximately 90 minutes. It can be supplemented by additional NP measures when needed to evaluate specific hypotheses of interest or to develop a more detailed understanding of an individual patient’s deficits. Studies to confirm the psychometric properties of the MACFIMS in an MS population and to derive regression-based norms for change that take into account demographic factors, initial level of
performance, and practice effects are planned. The component measures of the MACFIMS are currently available and would constitute a reasonable ‘macro-NP’ assessment in controlled clinical trials of disease-modifying medications.

Table 3.6 Tests in the Minimal Assessment of Cognitive Function in MS (MACFIMS)

<table>
<thead>
<tr>
<th>Test</th>
<th>Estimated administration time</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Processing speed and working memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paced Auditory Serial Addition Test (PASAT)</td>
<td>10 minutes</td>
<td>Rao version, using 3.0- and 2.0-second interstimulus intervals; two equivalent forms available</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test (SDMT)</td>
<td>5 minutes</td>
<td>Oral administration only; multiple forms available, although their equivalence has not been established</td>
</tr>
<tr>
<td><strong>Learning and memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California Verbal Learning Test-II (CVLT-2)</td>
<td>25 minutes</td>
<td>Two equivalent alternative forms</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test-Revised (BVMT-R)</td>
<td>10 minutes</td>
<td>Six equivalent alternative forms</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California Sorting Test (CST)</td>
<td>25 minutes</td>
<td>Two equivalent forms available; to conserve time, only free sort condition may be administered</td>
</tr>
<tr>
<td><strong>Visuospatial perception</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Judgment of Line Orientation Test (JLO)</td>
<td>10 minutes</td>
<td>Two forms are described in the manual but are actually the same test items administered in a different order</td>
</tr>
<tr>
<td><strong>Language and other abilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Oral Word Association Test (COWAT)</td>
<td>5 minutes</td>
<td>Two alternative forms available</td>
</tr>
</tbody>
</table>

It is recommended that the MACFIMS be supplemented by a measure of estimated premorbid abilities (e.g. National Adult Reading Test ‘NART’, North American Adult Reading Test ‘NAART’, WRAT-3 Reading, or selected WAIS-R Verbal subtests) at the baseline study visit, a measure of self-reported depression (Chicago Multiscale Depression Inventory ‘CMDI’ at all study visits, and other measures of potential confounding factors as appropriate for the study population.
Who should undergo NP assessment?

Just as participants in MS clinical trials are evaluated neurologically at study entry, all trial participants should be assessed neuropsychologically to characterize their baseline cognitive function. In the absence of a normative database, demographically matched healthy controls should be assessed to establish criteria for defining impairment in the MS sample, as was done in the interferon beta-1b trial for secondary MS. The EDSS has been used as a stratification variable in MS trials, and initial cognitive status can also be used as a blocking factor to assign patients to treatment conditions to ensure the NP equivalence of participants in different treatment conditions. Participants in different groups should also be equated on demographic factors that can influence NP test performance (age, sex, and education).

Ideally, all trial participants would receive a ‘macro-NP’ assessment not only at baseline but also at scheduled intervals throughout the treatment phase. If there are practical constraints on the number of participants who can be comprehensively monitored, the investigator can divide the sample into a subset of patients who are monitored more intensively (i.e. patients who receive the ‘macro-NP’ assessment at scheduled intervals during the treatment phase) and a subset who are not (i.e. those who receive only the ‘micro-NP’ assessment). Although patients can be selected for comprehensive monitoring but randomly or by site (i.e. without regard to their baseline performance), accumulating clinical trial data suggest that the strongest test of the beneficial NP effects of a disease-modifying medication may come from evaluating these effects in patients whose cognitive function is already compromised. Consequently, investigators should ensure that a sufficient number of impaired patients are included in the comprehensively monitored subset to allow examination of treatment response in these patients.

When should NP measures be administered in MS trials?

The frequency with which NP outcome measures are administered will depend in part on theoretical factors (e.g. hypothesized action of the treatment under study, anticipated time course of treatment effects) and in part on practical considerations (e.g. number of other secondary outcome measures). Traditionally, outcome measures have been administered once before treatment is initiated in order to obtain a baseline assessment of function, and again at the end of the treatment phase to gauge treatment effects. However, the conventional ‘pre-post’ study design has limitations when it comes to assessing NP outcomes in MS trials.

First, treatment effects may be difficult to disentangle from practice effects when NP measures are administered only twice. Second, NP change in MS is likely to be a continuous and probably non-linear process. There is no guarantee that peak treatment effects will coincide precisely with the end of the treatment phase. Furthermore, conventional ‘pre-post’ designs do not allow the application of sophisticated data analytic techniques, many of which require multiple observations on each study participant.

An alternative to a single baseline NP assessment is to administer NP outcome measures several times before treatment is initiated. This would be analogous to performing an MRI ‘run-in’ at the outset of a trial. It would not only permit estimation of the natural variability in test performance in clinically stable patients but also allow test
performance to be stabilized, thereby minimizing practice effects during the treatment phase. Repeated baseline assessment has been advocated in previous chapters on this topic,\cite{34,35} and this approach was adopted in the clinical trial of interferon beta-1a for secondary progressive MS.\cite{51} Given uncertainties about the timing of natural changes in cognitive function and of treatment effects, NP outcome measures should be administered several times during the treatment phase. In previous trials, the frequency of on-study NP assessments has ranged from every 6 weeks\cite{52} to once a year.\cite{54,56} A pragmatic approach might be to administer the ‘micro-NP’ assessment at frequent intervals during treatment (e.g. every 3 months) and to administer the ‘macro-NP’ measures less often, perhaps at 6-month or annual intervals.

**What should be done to ensure the quality of NP data collected during clinical trials?**

Several steps can be taken to increase the likelihood that NP data collection will be complete and accurate, thereby reducing error variance. First, the neuropsychologist responsible for this component of the clinical trial should ensure that examiners who will be administering and scoring the NP outcome measures are appropriately trained. Optimal reliability is achieved when training is centralized and when a standardized manual and training procedures are used.\cite{103} Second, examiners should practice administering and scoring the NP outcome measures several times before administering them to study participants. Finally, all test protocols (including ‘practice protocols’) should be reviewed at a central NP co-ordinating center, which should provide timely feedback to examiners about the accuracy of test administration and scoring. The NP co-ordinating center should also be responsible for transcribing data onto case report forms.

**How should NP outcome measures be analysed statistically?**

Analysis of NP outcomes in MS clinical trials has typically consisted of comparing the mean change in test performance from baseline to the end of the treatment phase in patients in different treatment conditions, applying ANOVA methods or analogous non-parametric procedures. In most trials, NP measures have been analysed individually for evidence of treatment effects, and demographic factors that can influence NP test performance have not been controlled. The conventional approach to NP outcome assessment has not consistently yielded statistically significant results, however, even for treatments with documented effects on other outcome measures.

Several steps can be taken to improve the sensitivity of NP outcome analyses. First, it is essential to minimize irrelevant sources of variance (‘noise’) in order to be able to detect treatment effects (‘signal’), which are often subtle. One method for minimizing error variance is to standardize test procedures and testing conditions, as recommended earlier. Irrelevant variance can be further reduced by statistically ‘extracting’ the effects of demographic factors that can affect test performance. Adjustment of raw test scores or covariance analysis is only appropriate when treatment groups are demographically comparable at baseline, however.

Second, subtle treatment effects may be more evident when multiple outcome measures are analysed simultaneously.\cite{104} If data from demographically matched healthy
controls are available, analysis of aggregate NP outcomes might include counting the ‘number of failed tests,’ as was done in a secondary outcome analysis for the interferon beta-1b trial in secondary progressive MS.[56] An alternative approach would be to construct an NP composite variable or to perform a multivariate analysis of variance (MANOVA). (Both yield identical results statistically if equal weightings are used in constructing the composite.) In order to maximize the sensitivity of an NP composite, its component variables must not be highly correlated and the individual measures should be sensitive to change within the time frame of the trial (as in the interferon beta-1a trial for relapsing-remitting MS,[55] in which treatment effects or trends were observed on composites of domains commonly compromised in MS but not on a composite measure of attention span and overall verbal abilities).

Third, when NP outcome measures are administered several times during the treatment phase, statistical techniques that make use of all available data should be employed. One such approach is random-effects regression modeling (also known as hierarchical linear modeling (HLM)), in which slopes and intercepts are calculated for each individual patient in order to characterize different patterns of change over time.[105–108] HLM can not only accommodate variable follow-up intervals, but it also permits interpolation of missing data. In addition, it can incorporate adjustments for demographic variables, practice effects, and regression to the mean. Applications in neurologic disease have included analysis of NP progression in Alzheimer’s disease[108] and HIV infection,[109–111] treatment outcome analysis in an ALS clinical trial,[112] and secondary analyses of NP outcome data from the interferon beta-1a trial.[55]

Another statistical approach that makes use of all available data is survival analysis, which calculates the length of time it takes for patients to reach a predetermined criterion for significant deterioration.[113,114] An extension of survival analysis that incorporates both deterioration and improvement, termed multi-state analysis, is also available.[115] Survival analysis has been widely adopted as the primary method for analysing clinical outcomes in trials of disease-modifying medications for MS.[43,48–51,116] It was also used in a secondary NP outcome analysis in the trial of interferon beta-1a in relapsing-remitting MS.[55] In that trial, a conventional statistical cut-off was used as the criterion for significant deterioration (i.e. change of at least 0.5 standard deviations relative to baseline); alternatively, the reliable change index[92,117–119] or regression-based norms for change[88,120,121] could be used to establish the criterion for meaningful change.

Finally, variations in treatment response among patients assigned to the same treatment condition can be obscured if analyses are confined to treatment groups as a whole. Consequently, subgroup analyses should be performed. One simple method for subdividing patients neuropsychologically is to perform a median split based on patients’ initial NP performance. A more sophisticated method for grouping patients would be to use cluster analysis to identify patients who differ in their baseline pattern of performance on several different NP measures.[28,40] If healthy control data are available, patients can be categorized on the basis of whether they are neuropsychologically intact or impaired at baseline. NP subgroup membership can then serve as a between-subjects factor (or potentially a covariate) in analyses of treatment response.
CONCLUDING COMMENTS

The widespread prevalence of MS-related cognitive dysfunction, its direct relationship to cerebral MS pathology but weak relationship to physical disability, and its devastating functional impact are now widely recognized. There is convincing evidence from clinical trials, both of disease-modifying therapies and of symptomatic treatments, that NP outcome measures can detect even subtle treatment effects, provided that sensitive measures are chosen and appropriate statistical techniques are applied. Despite this, NP outcomes are still not consistently assessed in trials of disease-modifying medications. Furthermore, studies of symptomatic treatments for MS-related cognitive dysfunction need to be replicated and extended using broad-spectrum NP batteries, rigorous study designs, and sophisticated statistical techniques. Now that there is consensus regarding a comprehensive, yet practical, approach for assessing cognitive function in MS, attention can turn to development of a normative database, methods for aggregating test scores, and empirically supported criteria for significant change so that NP outcome assessment can move forward in the next generation of MS clinical trials.

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Multiple sclerosis therapeutics


Health-related quality of life assessment in multiple sclerosis
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ROLE OF HEALTH-RELATED QUALITY OF LIFE ASSESSMENT IN THE CONDUCT OF EVIDENCE-BASED MEDICINE

Health-care providers are placing increasing emphasis on the practice of evidence-based medicine (EBM)—‘a conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients’. As for other chronic progressive conditions of unknown cause or cure, the practice of EBM for people with multiple sclerosis (MS) is generally directed to one of three goals:

• preventing disease progression;
• reducing the duration and severity of exacerbations; and
• effectively managing symptoms of the disease.

Three types evidence are generally accepted for guiding treatment decisions:

• anatomical or biological evidence (e.g. magnetic resonance imaging, cerebrospinal fluid measurements);
• clinical evidence (e.g. the Multiple Sclerosis Functional Composite, the Expanded Disability Status Scale); and
• patient-derived evidence.

The patient-derived category of evidence may be evaluated at several levels of complexity, including general quality of life (QoL), more specific health-related quality of life (HRQoL), or in terms of discrete indicators of functional ability or functional status. This chapter considers HRQoL assessment.

Patient-derived data are increasingly accepted as an important assessment domain in clinical research for most chronic conditions including MS. The goal of treating conditions that produce morbidity but that have minimal impact on mortality is arguably to reduce disease impact on patients’ lives and to ensure that interventions result in more good than harm. The achievement of these goals can be demonstrated only with patient input; however, measures of patient perception and clinical data derived from examiners are not redundant. Moreover, patient functioning in the somewhat artificial setting of the treatment center is not always duplicated at home indicating that clinical assessments do not always reflect a person’s abilities in the home setting.
Currently, most of the empirical evidence available to inform the practice of MS EBM is anatomical, biological, or clinical. The Multiple Sclerosis Council for Clinical Practice Guidelines noted that the lack of data on patients’ perceptions and preferences about treatment options has effectively left the recipients of care removed from systematic clinical decision-making. This chapter addresses these important patient perceptions in terms of HRQoL, as well as defining HRQoL, reviewing the assessment techniques, discussing the measures used and the research findings that relate to MS-HRQoL, and giving recommendations for future directions for MS-HRQoL assessment.

DEFINITION OF HRQoL

A generally accepted definition of HRQoL remains to be established as researchers refine the construct and develop valid and reliable ways to measure it. Progress in HRQoL research is changing in a manner similar to the evolution of the use of magnetic resonance imaging (MRI) markers in quantifying MS severity. As with MRI markers of MS, researchers and clinicians are in the process of understanding the meaning of HRQoL abnormalities in the MS population. Traugott drew an analogy between HRQoL and immunological studies, noting a number of quantitative and qualitative abnormalities of the immune system that are associated with MS. These immunological changes are considered important but their cause and significance and the relationships among the immunological markers and the disease are not fully understood. So it is with HRQoL measurement.

QoL is considered to be but one domain of health as defined by the World Health Organization (WHO), and HRQoL is a discrete component of general quality of life. Guyatt et al. noted that, although general QoL can be affected by many factors that are beyond the scope of health care, including economic instability, civil unrest, or poor environment, these general factors have only an indirect relationship with HRQoL and are not included in its definition. Schipper et al. agree that although such factors as equal opportunity and social security are important to community health, these factors extend beyond the more immediate goal of treating the sick. These authors offer the following definition of HRQoL: “Quality of life” in clinical medicine represents the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient’. This construct includes four broad domains:

- physical and occupational function;
- psychological function;
- social interaction; and
- somatic sensation.

Schipper et al. established several operational characteristics of HRQoL assessment that help to define the construct further. First and foremost, HRQoL is subjective. As Schipper et al. explain, ‘…in clinical medicine the ultimate observer of the experiment is not a dispassionate third party but a most intimately involved patient’. They note that, since the goal of treatment is to minimize the manifest consequences of disease, HRQoL represents ‘the final common pathway of all the physiological, psychological and social inputs into the therapeutic process’.
The second characteristic of HRQoL is multifactoriality. Having operationally defined HRQoL as the integration of four domains it is important to assure that patients’ daily experiences in all these respects are explored in the questionnaire, albeit in a manner that is parsimonious and minimizes respondent burden.

The third characteristic is self-administration. Because HRQoL is subjective, there is concern that external administration would in some way influence the patient report.

The final characteristic is that HRQoL is time-variable, meaning that it fluctuates with time.

CHARACTERISTICS OF HRQoL MEASURES

For scientifically rigorous investigations, HRQoL measures must meet the same criteria of meaningfulness and dependability that are used to evaluate other assessment measures (see chapters 2, 3, and 5, for example). These measurement criteria are typically referred to as reliability and validity.

Reliability

Hobart described reliability as the demonstration that results produced by a measure are accurate, consistent, stable, and reproducible. He described four types of reliability—internal consistency, test-retest reliability, rater reliability (inter- and intra-rater), and parallel forms. Each of these types assesses a different source of random error and each is important in establishing the value of a measure. Guyatt et al. suggested an additional form of reliability—'signal-to-noise ratio', which he defined as the ability to detect actual changes in a measure over time (the signal) in relation to error that occurs in any measurement process (the noise). For measures that evaluate change over time, he referred to the signal-to-noise ratio as ‘responsiveness’. While it cannot be directly measured, responsiveness is defined theoretically as the size of the difference in scores between subjects who have actually experienced change and those who have not. A significant threat to reliability occurs when measures demonstrate floor and ceiling effects. This could occur, for example, when a measure designed for a seriously ill population is implemented in people who are less ill. In that situation, respondents will cluster at the top of the scale and share the maximum score, but may in fact differ in their states of well-being. The difference is not demonstrated because the measure is not sensitive at that range of difference.

Validity

Validity is the second necessary attribute of a HRQoL measure and concerns the relationship between the concept that is being measured and the instrument that assesses it. Typical categories of validity include content-related validity, construct-related validity, predictive ability validity, and criterion-related validity. Methods used to establish the validity of an instrument are drawn from clinical and experimental psychology.
Content validity addresses the extent to which the items in the instrument relate to the domain being measured; it is typically established by comprehensive literature reviews and by surveying patients and health-care professionals. According to Guyatt et al., Feinstein integrates face validity and content validity into the construct ‘sensibility,’ which relates to the applicability of a measure, its clarity and simplicity, the likelihood of bias, its comprehensiveness, and the inclusion of redundant items.

Construct validity refers to the extent that the instrument under consideration performs as expected in relation to other measures.

Closely related to construct validity is the capacity of a measure to be predictive of future health states—the predictive validity.

Because there is no gold standard for demonstrating the real level of HRQoL it is not possible to establish criterion validation for HRQoL measures. HRQoL measures may be compared with biological or clinical measures of MS, but these measures cannot be considered gold standards for criterion validation of HRQoL measures.

USES OF HRQoL DATA

HRQoL data are used for three general purposes:

• to classify or group patients by levels of disease severity;
• to predict the health of subjects at a future point in time; and
• as outcome variables.

Guyatt et al. describe these applications. A discriminative index is used to differentiate among groups or individuals along a given dimension, as may be done in an epidemiological study when there is no gold standard to set as a validation criterion. Assessing the HRQoL of patients with MS in comparison to patients with rheumatoid arthritis or inflammatory bowel disease requires a discriminative instrument, as does a study that compares MS patients who were divided into three levels of disability according to the expanded disability status score (EDSS). A predictive index is used to classify subjects into pre-established present or future categories. Some MS studies that include an HRQoL measure for discriminative purposes are those by Rudick et al. and Hermann et al. An appropriate use of an HRQoL measure for predictive purposes would be to determine if changes in patients’ self-reports indicate a current need for rehabilitative services or future job loss as a result of disability. Such a study was conducted by Nortvedt et al. In another sense, a measure may also be considered predictive when it is highly correlated with a longer or more cumbersome measure that is believed to assess the same construct as the new measure. Evaluative indexes are those that measure the amount of change in an individual or group or period of time as the result of disease progression or treatment intervention. A number of MS intervention studies that have included HRQoL endpoints are discussed below. Sugano and McElwee note that these three types of instruments (discriminative, predictive, and evaluative) represent a continuum from epidemiological measures that are a static means of classification (descriptive) through risk factors (predictive) to outcome or response measurements (evaluative).
APPROACHES TO HRQoL MEASUREMENT

Generic versus specific assessments

HRQoL measures look at patients’ reports of their perceived health in either very general or very particular terms. Measures that assess the former are referred to as generic assessments, and those that measure the latter as disease- or symptom-specific assessments. Generic measures assess general well-being and are intended to be broad assessments. They tap a wide range of health concepts and are useful in making broad comparisons across general populations or between people with different conditions and in comparing the relative benefit of different treatments on the well-being of a community.

In contrast, disease-specific measures focus on aspects of health that are significant to the disease or intervention under consideration. The major reasons for adopting this approach is to ensure that the measure is sensitive to different health states within a condition. It is especially useful in clinical trials because it increases the ability to detect change produced by the intervention and, equally importantly, allows intense assessment of both positive and negative impacts of the intervention. For this reason in particular, the use of disease-specific measures is especially important in conditions such as MS, which can manifest a broad range of symptoms that fluctuate over time. In order to allow both the detailed assessment inherent in disease-specific measures as well as a more general comparison of a study sample with the general population or with other disease groups, it is commonly recommended that short generic measures are combined with disease-specific ones.

Health profile versus econometric assessments

Health profile assessments are based on psychometric techniques and typically include several subscales that assess theoretically and empirically distinct domains of HRQoL. These subscales can be calculated into summary or global scores (or both). The majority of HRQoL research reported in this chapter includes health profile assessments.

Utility measures are derived from economic and decision theory, reflect patient preferences for different health states, and are summarized in a single summary score. These measures incorporate preference measurements and allow patients to assess their willingness to accept various health states in relation to death. Kaplan and Anderson explain that they use this approach at the health policy level to explain the benefits of medical care, behavioral intervention, or prevention programs in terms of well-years, in order to compare outcomes across very different interventions. At the individual level, this method is useful in helping patients with life-threatening conditions to make judgments about their willingness to accept potentially life-saving treatments that have profound negative cost or health status side effects. Discussion of econometric assessment of MS can be found in chapter 12.
Epidemiological studies

Much has been learned about the natural history of MS through observational and epidemiological studies. Using the same principles, important natural history can be gained about the evolution of HRQoL in the MS population. Generic health profile measures are particularly useful in epidemiological studies that monitor the health of a diverse population or of individual patients with a medical condition, such as MS, that has a diverse set of signs and symptoms associated with it. Epidemiological data using a disease-specific measure can determine how changes in HRQoL relate to change in employability. They can be used for hypothesis generation, such as proposing interventions that improve QoL. Cross-sectional data can be used to construct statistical norms for generic measures that allow comparison of one disease group with other illness groups or with the general population. Longitudinal assessments could help delineate the temporal associations among biological, clinical, and HRQoL measures in MS. For instance, a longitudinal epidemiological study might reveal a delay between biological indications of disease activity and their manifestation in clinical and HRQoL outcomes. This information would be important in designing clinical trials and in providing indications for the timing of assessments in relation to interventions, the frequency at which assessments should be made, and the duration of studies necessary to demonstrate a hypothesized change.

Health services outcomes research

Health services research is ‘a field of inquiry that examines the organization, financing and management of health care and their impact on access, delivery, cost, outcomes and quality of such care’. While much health services research is conducted using the same methods used in randomized clinical trials, a subset of this research—outcomes studies—is intended to investigate or improve the usual processes of care. These outcome studies take place in ‘usual practice’ settings and they place as much emphasis on patient perceptions as on clinical assessments. Outcomes studies can indicate the potential uses of generic and disease-specific HRQoL measures to serve as screening instruments for patients who report changes in symptom severity or functional ability that signal the need for rehabilitative interventions. Econometric HRQoL measures can be used in outcomes studies to examine how QoL data can be used to involve patients and families in clinical decision making. On a larger scale, econometric HRQoL measures are often used by policy makers to allocate scarce health care resources.

Clinical trials

Clinical trials provide essential information about potential therapeutic interventions when optimal treatment for a condition is unknown. In chronic conditions of unknown cause with no cure, the goals of treatment are to prevent worsening of disease, to reduce the severity and duration of exacerbations, and to provide symptom management. When multiple interventions are equally effective in achieving these goals, it is important to compare their side-effect profiles on disease-specific HRQoL to determine optimal treatment. There are many reasons why HRQoL measures should be used in MS clinical trials. The first of these reasons is to determine if the intervention has an impact on...
subjective well-being, an important endpoint in conditions that do not affect mortality. Given the progressive nature of MS, it is important that the direction and magnitude of the expected impact on HRQoL are clearly specified. In the case of interventions intended to provide symptom relief, the impact may be an immediate improvement in HRQoL. Alternatively, interventions intended to slow or halt the progression of disease may not improve the HRQoL for study subjects; rather, they are intended to slow the decline or sustain the well-being of subjects over a number of years.

Another reason for including HRQoL assessment in clinical trials is to determine the potential negative effects of the treatment for subjects and to compare them with the benefits of treatment. As in the case of the available MS disease-modifying treatments, until the relative and ultimate benefits of the interventions are determined, the side effects of the medicines (e.g. the severity of flu like symptoms) and of the method of administration (e.g. injection site reactions) are crucial aspects in comparing the treatments.

Because both the costs of life-long disability from MS and the disease-modifying treatments for MS can be very high, a third reason to include HRQoL assessments in clinical trials is to assess the cost benefit and cost utility of the treatments. Because the well-being of patients is as important as morbidity and mortality in chronic illnesses, a number of regulatory bodies responsible for the approval of new interventions rely on HRQoL data in their deliberations. These data are considered so significant that the Onco-logic Drugs Advisory Committee (ODAC) of the Food and Drug Administration (FDA) in the USA has recommended that QoL data along with survival data should be the major efficacy endpoint in approving new anticancer agents.

Finally, LaRocca et al. note that these HRQoL data can be important in helping patients to make decisions about accepting those interventions as part of their ongoing care. Thus, a fourth reason for using HRQoL data is that the organizations that are responsible for approving new interventions consider these data to be important in their deliberations.

FDA officials urge that, if HRQoL measures are to be used in clinical trials, both generic and disease-specific instruments with well-documented psychometric properties should be used. They note that phase 3 randomized control trials are the ‘obvious venue for QOL assessment, given that the findings of such trials will likely have an impact on future clinical practice…Most importantly, these trials allow valid use of a highly subjective instrument’. It is important that the HRQoL measures used in clinical trials represent the multidimensional nature of the construct rather than a discrete aspect of well-being.
**MEASURES USED IN MS RESEARCH**

**Generic health profiles**

Two well-known generic measures that have been used in MS research are the Medical Outcomes Study Short Form-36 (SF-36)\(^{[30–31]}\) and the Sickness Impact Profile (SIP).\(^{[32–34]}\)

The SIP is a behaviorally based, 138-item measure that includes 12 subscales. The response set to each question is ‘True’ or ‘False’. It can be summarized using two dimension scores or a total score. The Physical Dimension is composed of the ambulation, mobility and body care and movement scales. The Psychosocial Dimension incorporates the communication, alertness behavior, emotional behavior, and social interaction scales. The remaining five categories are considered to be independent and although they are not included in either summary score, they are included in the total score. It is also appropriate to report individual subscale scores. Higher scores indicate poorer performance on all of the scales. The SIP has had extensive psychometric evaluation.\(^{[32–36]}\) It was used in the development of an MS-specific measure\(^{[2]}\) and to criterion-validate the Multiple Sclerosis Functional Composite (MSFC).\(^{[37]}\) The SIP was used in a cross-sectional study of the relationship between depression and MS,\(^{[38]}\) and in an 8-year study of factors that effect change in HRQoL over time.\(^{[39]}\) It has also been used as a dependent variable in rehabilitation trials of aerobic training\(^{[40]}\) and intrathecal baclofen.\(^{[41]}\) Most recently, it was used as an outcome variable in a trial of interferon (IFN)-β-1b.\(^{[42]}\)

SF-36 is a well-known and widely accepted generic measure that was developed using data from the Medical Outcomes Study.\(^{[30,43,44]}\) It includes eight subscales. Physical functioning (10 items), role—physical (four items), bodily pain (two items) and general health (five items) constitute the Physical Component Summary. Vitality (four items), social functioning (two items) role—emotional (three items) and mental health (five items) are included in the Mental Component Summary. Subjects can select from three to five responses for each of the questions. Extensive use of the SF-36 has produced longitudinal normative data in many different illness groups. Consequently, its developers are able to recommend score changes in its subscales that are considered clinically relevant in different sample sizes, including sample sizes of one.\(^{[44]}\) Consequently, the SF-36 has been used both in studies intended to identify group differences and to monitor the health of individual patients. The SF-36 has been used in cross-sectional studies that assess the impact of MS on people in Canada\(^{[45,46]}\) and Norway\(^{[47]}\) and on rehabilitation patients in England,\(^{[48]}\) and in a cross-cultural comparison of patients in the USA, the Netherlands, Belgium, France, and the UK. It has been used to assess the impact of MS compared with other chronic diseases\(^{[49]}\) and the association between cognitive function and HRQoL,\(^{[50]}\) and as a dependent variable in a study of factors that predict future disability.\(^{[15]}\) In addition, the SF-36 has been included in studies of rehabilitation interventions.\(^{[5,48,51]}\) It has been used as an endpoint in investigations of disease-altering therapy using a retrospective cohort\(^{[52]}\) a prospective cohort with no comparison group,\(^{[53]}\) and a randomized trial.\(^{[54]}\) A recent report raises some concern about the reliability of the SF-36 with some segments of the MS population.
because of demonstrated floor and ceiling effects, but it has generally been found to demonstrate effective psychometric properties in the MS population.

Other less commonly used generic health profiles have been used in descriptive studies of the MS population. Aronson used the Canadian General Social Survey (GSS) in a large-scale survey in Ontario, Canada. Gianino et al. used the Ferrans and Powers Quality of Life Index (QLI) in assessing the impact of intrathecal baclofen. Rudick et al. used the Farmer QoL Index in a cross-sectional comparison of people with MS, inflammatory bowel disease, and rheumatoid arthritis. Murphy et al. implemented the Functional Status Questionnaire (FSQ) and the SIP to compare the HRQoL of patients in France, Germany, and the UK. Gulick used the Life Satisfaction Survey to identify concurrent factors that contribute to HRQoL. Another generic measure, the Disability and Impact Profile (DIP) has had more extensive use in the MS population that these other, less well-known, generic measures. It includes three symptoms and 36 disability questions in five domains—mobility, self-care, social activities, communication and psychological status. These disability questions are followed by the respondent’s indication of the impact of that symptom. The DIP has been used in a study of 43 MS rehabilitation patients in Denmark. Although the appropriateness of this measure has been tested in the MS population, the psychometric properties of the ‘Impact’ component and concern about the number of patient errors in responding to the DIP have been raised by two of these investigators.

**Generic econometric measures**

One of the best known approaches to utility measurement, the Quality-Adjusted Time Without Symptoms and Toxicity (Q-Twist) was used by Schwartz et al. to evaluate the impact of IFN-β-1b on HRQoL. One other group assessed the impact of IFN-β-1b on quality-adjusted life years.

**MS-specific HRQoL measures**

Beginning in the 1990s, three research groups began developing measures that integrated generic and disease-specific measures for use in the MS population. The resulting measures include the Multiple Sclerosis Quality of Life Inventory (MSQLI), the MSQOL-54, and the Functional Assessment in MS (FAMS).

Cella et al. used the Functional Assessment of Cancer Therapy (FACT) as the basis for the FAMS. The FAMS includes 59 items, of which 44 are scored. These 44 items are contained in six subscales: mobility (seven items), symptoms (seven items), emotional well-being (seven items), general contentment (seven items), thinking and fatigue (nine items), and family and social well-being (seven items). These six items demonstrated good internal consistency and test-retest reliability. The construct validity of the FAMS was supported by the predictable patterns of correlation among its subscales and other measures and self-assessed physical impairment. This measure has been translated into Spanish.

The MSQOL-54 was developed by Vickrey et al. using the SF-36 as the core generic measure and supplementing it with 18 items identified by MS experts as important in MS HRQoL assessment. These additional items included overall quality of life (two
items), health distress (four items), sexual function and satisfaction (five items), cognitive function (four items), energy (one item), pain (one item), and social function (one item). Validation of this measure was conducted on 179 of 231 consecutive clinic attenders and 88 of 94 patients who completed and returned a second administration of the measure a short time after the first mailing. Testing demonstrated adequate internal consistency reliability and test-retest reliability on all but the role—physical dimension. Construct validity was established on the basis of moderate associations with self-reported symptom severity, ambulation status, employment-role status, and the presence of depressive symptoms. The MSQOL-54 has been used to assess the impact of depression on HRQoL of people with MS. While a strong association was found between depression and poor quality of life, the cross-sectional design could not demonstrate the direction of this relationship. This measure was also used in a health services study of patient perception of quality of care provided by specialists and generalists.

The MSQOLI was developed by a research group under the auspices of the Consortium of Multiple Sclerosis Centers. Like the MSQOL-54, the MSQOLI includes the SF-36 as its core measure; unlike the MSQOL-54 or the FAMS, the MSQOLI consists of the generic measure plus established scales when available, rather than individual items, to gain disease-specific sensitivity. This approach allows comparison with the general population and other illness groups using the generic instrument and comparison with other illnesses that share the same symptoms. The MSQOLI scales assess generic HRQoL, fatigue (the 21-item Modified Fatigue Impact Scale (MFIS) and the four-item SF-36 vitality subscale), pain and disturbing sensations (the six-item MOS (Medical Outcomes Study) Pain Effects Scale and the two-item SF-36 bodily pain subscale), sexual functioning (the four-item scale developed for the MSQOLI), bladder function (the four-item scale developed for the MSQOLI), bowel function (the five-item scale developed for the MSQOLI), perceived visual function (the five-item scale adapted from the Functional Capacity Assessment of the Michigan Commission for the Blind), perceived cognitive functioning (the 20-item Perceived Deficits Questionnaire (PDQ)), emotional status (the 18-item Mental Health Inventory (MHI-18)), and social functioning (the 18-item MOS Social Support Survey (SSS)). The development process included two phases: first, instrument selection and content validation, and secondly, reliability assessment, construct validation, and item reduction. Details are available in the MSQOLI user manual and have been published. Scale reliability was demonstrated for the SF-36 and all disease-specific scales. Generally, construct validation was supported for the MSQOLI. The MSQOLI was used to assess the benefit of IFN-β-1b in patients with secondary progressive MS and is an endpoint in an ongoing trial of the benefit of rehabilitation after relapse.

These three MS-specific HRQoL measures, their development approach, and their intensity of assessment have been previously reviewed. In their review, Fischer et al. recommended the following assessment criteria:

- established acceptable psychometric properties;
- applicability of the measure to patients with a broad array of symptoms and disability;
- measure responsiveness to change;
- availability of normative data to compare study subjects to other MS patients, other disease groups, or the general population;
- availability of verified translations for use in international studies; and
In reviewing the MSQOL-54, FAMS and MSQLI, Fischer et al. determined that each of the measures had acceptable psychometric properties but found that the MSQLI assessed the broadest range of symptoms and disability with the other measures ignoring visual dysfunction and including limited items (MSQOL-54) or no items (FAMS) regarding bowel function.\textsuperscript{[78]} No longitudinal data are currently available on the responsiveness of these measures. Because both the MSQLI and the MSQOL-54 include the SF-36, results of the generic component of those measures can be compared with normative data. The FAMS does not have this advantage. The FAMS has been translated into Spanish\textsuperscript{[71]} and the MSQOL-54 has been translated into Italian.\textsuperscript{[81]} While the MSQOL-54 and FAMS are brief measures, the MSQLI includes 80 items, and the more comprehensive assessment requires a longer administration time, although patients are accepting of its length. Freeman et al. assessed the psychometric value of the MSQOL-54 compared with the generic SF-36 and found that the 18 additional items that constitute the MSQOL-54 add limited information to that obtained by the generic measure alone.\textsuperscript{[82]}

More recently, Pfennings et al. developed the Health-Related Quality of Life Questionnaire for Multiple Sclerosis, which includes scales from the SF-36 (physical functioning, mental health, and vitality) and the DIP (mobility, self-care, and psychological status).\textsuperscript{[83]}

In addition to these disease-specific measures that incorporate generic measures, several other disease-specific measures have been developed recently. The Multiple Sclerosis Impact Scale (MSIS-29), was developed from a pool of 129 items recommended by patients, expert opinion, and literature review, and the item reduction phase was based on the responses from 766 randomly selected subjects who responded by postal questionnaire.\textsuperscript{[84]} The time frame given to subjects for endorsing items is 2 weeks, rather than the 4 weeks that is usually set for questionnaires intended for use with chronically ill populations. A preliminary responsiveness study was conducted with patients admitted for in-patient rehabilitation or intravenous corticosteroid treatment. Two domains were identified empirically within the items included in the final measure; the MSIS-29 assesses physical (20 items) and psychological components (nine items). Its authors have demonstrated its data quality, scaling assumptions, acceptability, reliability, and validity and they have conducted a preliminary responsiveness assessment.

The Hamburg Quality of Life Questionnaire in MS (HAQUAMS)\textsuperscript{[85]} is a German-language measure that assesses both quality of life and the impact of common MS symptoms. Items include modifications of SF-36 and FAMS questions as well as items developed for the measure. Twenty-eight of the 38 items are computed into five subscales—fatigue, mobility (lower limb), mobility (upper limb), social function, and mood, which can be averaged for a total score. The final instrument consists of 38 items, 28 of which are aggregated into five sub-scales (fatigue/thinking, mobility lower limb, mobility upper limb, social functioning, and mood). The remaining ten items do not contribute to the scale scores or total score but are included because of their clinical relevance. Those items were retained because of their clinical significance in assisting with treatment planning.

The RAYS Scale, developed by Rotstein et al., was based on a 600-item pool generated by MS experts and literature review that were subsequently reduced to 50 questions by a team of MS experts.\textsuperscript{[86]} Three domains—physical functioning,
psychological functioning, and social functioning—are each represented by 15 items with a standard five-point response scale. There are five ‘additional concerns’ questions. Instrument validation was conducted with 50 patients by comparing RAYS results with the SF-36 and the EDSS.

In the light of the criteria proposed by Fischer et al. for evaluating these instruments, all of these more recently developed measures have reported some level of psychometric assessment. Based on published reports, Hobart’s group has taken the most rigorous approach with regard to item generation and reduction and assuring applicability to patients with a broad range of symptoms and disabilities during the development of the Multiple Sclerosis Impact Scale (MSIS-29). This group has also provided preliminary data about the measure’s responsiveness to change. However, the MSIS-29 does not directly cover the full range of common MS symptoms (e.g. visual impairment is not included), and it does not allow comparison with other populations, owing to a lack of normative data. None of the recently developed measures has been translated into other languages. While there is no clear-cut method to test the feasibility of administration, all of these measures have been tested in the process of their development and have been accepted by study subjects. As is the case in any emerging field, the value of each of these MS-specific measures will become apparent through a process of longitudinal study, recalibration, and comparison with other measures. It will be particularly helpful to identify which of these measures will be useful as screening instruments to be used in clinical practice and which are appropriate for use in clinical studies. The latter group of measures includes those that assess a broad range of symptoms that may be the target of disease-modifying treatment as well as symptom management and will be sensitive to the positive and negative effects of treatment.

REPORTS OF HRQoL ASSESSMENT IN MS-RELATED CLINICAL ASSESSMENT

Symptom management

Petajan et al. assessed the impact of outpatient aerobic training on fitness and HRQoL using the SIP. Fifty-four subjects with an EDSS of 6.0 or less were randomly assigned to treatment or control groups. The intervention consisted of three 40-minute sessions of aerobic exercise for 15 weeks. Control subjects agreed not to increase their activity level during the study period. Study assessments were taken at baseline and at 5, 10, and 15 weeks. A significant group-by-time interaction was found on the physical dimension of the SIP for the study group at the end of the study. Study subjects improved on all three components of the physical dimension (ambulation, mobility, and body care and movement) at some point during the intervention. The control group demonstrated no change on the SIP physical dimension during the study period. There were no changes in the psychosocial dimension of the SIP for either the study group or the control group, although there was a general trend towards improvement in the study group. The total SIP score was significantly improved at week 10 for the study group but did not change significantly for the control group.
Gianino et al. evaluated the effect of intrathecal baclofen on QoL in a prospective, single group design of 15 MS patients and 10 patients with other neurological conditions using the Ferrans and Powers QLI and the SIP. These questionnaires were administered before the administration of intrathecal baclofen and then at 3-month intervals for 1 year. While there was a significant improvement in clinical measures of spasticity, the QLI demonstrated a trend towards improvement but no significant change at any assessment. There were significant improvements in all components of the SIP at 3 months that persisted to the end of the study.

Freeman et al. assessed 50 subjects at 3-month intervals for 1 year in a single group prospective longitudinal study of progressive MS patients who had received a 6-week course of in-patient rehabilitation. Routine demographic, diagnostic, and disease severity data were collected for all patients. Two major endpoints were disability as assessed using the Functional Independence Measure (FIM) and handicap using the London Handicap Scale. HRQoL measured using the SF-36 was included as a secondary endpoint. The researchers found that emotional well-being, measured by the SF-36 Mental Component Summary, improved a maximum of 16.5 points at 6 months and returned to baseline in 171 days. The SF-36 Physical Component Summary achieved a maximum improvement of 22 points at 6 months and returned to baseline in an average of 293 days. The study found that HRQoL improvements were sustained for an even longer period than the disability and handicap measures.

Solari et al. also conducted an assessment of in-patient rehabilitation on impairment, disability, and QoL. In this case, subjects had been free of exacerbations for 3 months and the study used a randomized, single-blind, controlled design. Twenty-seven subjects were admitted to the hospital for a 3-week course of intensive therapy, while the remaining 23 subjects were given home exercise programs. Outcome assessments were made at baseline and at 3, 9, and 15 weeks. As in the previously reported study, the primary endpoint was the FIM, and the SF-36 was the secondary endpoint. There were significant differences on the FIM between the study and control groups at all assessment points. Overall, the SF-36 profile improved for patients who underwent the study treatment in all but the bodily pain scale. The difference between the study group and the control group was statistically significant for general health and mental health at all three assessment points, for vitality at 3 and 15 weeks, and for role—emotional and social functioning at 9 weeks. The study group demonstrated improvements that did not achieve statistical significance in the physical component score, while improvement in the mental component score was significant compared with the control group. The authors speculated that lack of statistical significance in PCS may have resulted from floor effects at baseline. Use of a disease-specific measure might have avoided this problem.

**Disease-modifying therapies**

The benefits and adverse effects of interferons and glatiramer acetate on patient well-being have been studied increasingly over the past few years. Schwartz et al. collected clinical and QoL data for subjects who participated in a random allocation lottery for treated with IFN-β-1b. Thirty-four subjects who received treatment and 45 who did not were followed for 12 months. HRQoL data were analysed using the Extended Q-TWIST, a utility measure that evaluates treatment trade-offs by incorporating several QoL
domains and patient preferences regarding those domains. Over the 12-month follow-up, the treated patients reported 10.6 months of quality-adjusted time and the untreated control subjects experienced 10.4 months of quality-adjusted time ($p=\text{ns}$). They concluded that during the first year, IFN-β-1b treatment neither improved nor diminished HRQoL.

Rice et al. conducted a cross-sectional comparison of the HRQoL using the SF-36, with 117 patients, who initiated IFN-β-1b treatment during the pivotal phase 3 study, and 152 historical controls, who were patients who had declined participation in the trial. The treated group demonstrated significantly better scores compared with the untreated controls on three of the eight SF-36 scales (physical function, role—physical, and general health). Between-group differences were most pronounced in patients with EDSS of 3.0 or less, and were most evident with physical function scores. The results demonstrated that SF-36 was informative about physical well-being at different levels of disability, and suggested that treatment improved HRQoL. The SF-36 demonstrated floor effects at the highest level of disability, which may have had a negative impact on the results in the high disability strata.

Nortvedt et al. evaluated the impact of IFN-α-2a treatment on HRQoL using the SF-36 in a randomized, double-blind, placebo-controlled trial of 97 relapsing-remitting MS patients. Subjects with a mean EDSS of 2.9 were divided into three groups—32 subjects who received low-dose treatment, 32 subject who received high-dose treatment, and 33 control subjects. They were followed during a 6-month treatment phase, and a subsequent 6-month drug-free period. Data were collected at baseline and at 3, 6, and 12 months. The main effect of the treatment on HRQoL was defined as the differences in SF-36 change scores between the two treatment groups and the placebo group from baseline to 6 months. Adverse events were also computed. At the end of treatment (at 6 months), the high-dose group had a greater worsening in seven out of the eight scales compared with the control group, although none of the differences reached statistical significance. Throughout the study there was a trend to decreased HRQoL scores for both treatment groups compared with baseline, although none of the changes was statistically significant. There was an association between side effects and diminished HRQoL for both the high-dose group and the low-dose group at 3 months and 6 months, but this relationship was no longer evident at the end of the drug-free observation period. While the absence of new MRI lesions was associated with better HRQoL in the placebo group, lower MRI activity was associated with worse HRQoL in the treated groups. The authors concluded that IFN-α-2a treatment did not have short-term benefits on HRQoL.

Arnoldus et al. assessed the effects of IFN-β-1b and IFN-β-1a on HRQoL using the SF-36 in a convenience sample of 51 subjects with EDSS of 6.0 or less during their first 6 months of treatment. Data collected at baseline, and at 1, 3, and 6 months included EDSS, SF-36, and the Montgomery and Asberg Depression Rating Scale (MADRS). Overall, SF-36 role—physical showed a significant improvement over the study period, bodily pain demonstrated a transient worsening at 1 month but returned to baseline by 3 months, and the other scales remained generally stable. When subjects were categorized into EDSS quartiles, there was symmetry between subgroups for the physical scales of the SF-36. Subjects with the highest depression scores (the highest MADRS quartile) demonstrated the largest improvement in the role—physical over the study. After a significant increase in adverse events at 1 month, mean total of adverse events decreased
over the remainder of the study but remained above baseline at the end of the study. Those in the most side effects quartile at each follow-up had significantly worse vitality, general health, role—physical, and role—social than the subjects in the quartile with fewest side effects. The investigators note that, surprisingly, these outer-quartile differences were already present at baseline, indicating that factors other than the treatment may have influenced these results. There were no differences in outcomes noted between those patients receiving IFN-β-1b and IFN-β-1a.

Most recently, Freeman et al. reported on the impact of IFN-β-1b on HRQoL in a multicenter, randomized, double-blind, placebo-controlled study of 531 patients with secondary progressive MS and EDSS 3.0–6.5.[42] The SIP, in which lower scores indicate better function, was a tertiary endpoint. Data were collected at baseline and at 6-month intervals during the 3-year study. The treatment group experienced small but consistent improvement in total SIP scores for the first 18 months and then a gradual increase for the remainder of the study period. The placebo group experienced a consistent worsening in the total score over the study. There were no significant between-group differences in total SIP scores at any assessment. Both groups experienced persistent worsening in SIP physical dimension over the study, although the IFN group had significantly less worsening at 6, 12, and 36 months. The SIP psychosocial dimension indicated a small improvement in both groups at 6 months. Subsequently, the IFN group continued to improve until 30 months but the placebo group had a consistent worsening for the remainder of the study. The only significant difference between the two groups in the psychosocial dimension was at 18 months. Patients with confirmed progression on EDSS, regardless of treatment assignment, reported deterioration in the SIP physical dimension, whereas patients without progression showed no change in that score. Patients in both study groups who experienced progression showed limited worsening in the psychosocial dimension.

CONCLUSIONS

HRQoL assessment is a unique and important component in assessing best care for persons with MS. A number of measures have been developed to assess HRQoL in MS. Three of these batteries incorporate generic and disease-specific elements.[93–95] One measure has been developed that includes modified scales from two generic measures.[96] Three disease-specific measures have been developed for use in MS.[16,84,85] These measures are presented in journal articles that describe their initial development. Studies related to validity and reliability are ongoing; these studies require both cross-sectional and longitudinal data. The relative value of these measures and the situations in which they are most appropriately used will be determined with experience.

To date, MS researchers have had limited experience with the disease-specific measures, having selected generic instruments for virtually all published clinical investigations. Of the generic measures, SF-36 has been used most often.[81,89–92] There is concern, however, that this generic measure may not be appropriate in all MS studies.[55,81,97] Selection of the most appropriate disease-specific measures by investigations should be based on available validity and reliability data for those measures and the specific questions that the researcher hopes to answer. Investigators
need to be mindful of the measurement characteristics of the selected instrument. Is it to be used for discriminative, predictive, or evaluative purposes? Does it provide more or less information than is needed? Will subjects accept the measure? While investigators are urged to use disease-specific measures, they are also encouraged to include an established generic measure in their investigations, both to help establish the properties of the disease-specific measures and to assure the interpretability of their data.

There are a number of other issues that must be explored for HRQoL data to yield useful results and contribute the patient perspective to the practice of EBM. Among these issues are methods of test administration that accommodate physical disability of the patients. Also, we must consider cognitive impairments and their effect on assessment of HRQoL. While we are able to determine the statistical significance of HRQoL scores, we need to gain familiarity with the clinical significance of the scores and of changes in scores. It is also essential that we become more precise in our hypotheses about HRQoL change. In some instances we anticipate that HRQoL will improve in study patients compared with controls. In other studies, we may expect to see HRQoL initially stabilize and perhaps eventually improve compared with controls, depending on the amount of time it takes for the benefit of the intervention to manifest itself. As we learn more about HRQoL in MS patients, we shall continue to learn the best ways to monitor it. Although this developmental approach will lead to some temporary imprecision, it is crucial that we systematically obtain patient reports of their well-being as it is affected by their MS and by our treatments.

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5
Magnetic resonance imaging in multiple sclerosis: an overview
David H Miller

INTRODUCTION

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are now applied widely in patients with multiple sclerosis (MS). Three main areas of clinical application have emerged since the first description of findings in MS more than 20 years ago:

• diagnosis and prognosis;
• understanding of disease mechanisms; and
• therapeutic monitoring.

This chapter provides an overview of MRI/MRS in diagnosis and prognosis, studies of pathogenesis, and therapeutic monitoring. Chapters 6–11 provide detailed information on specific methods.

DIAGNOSIS AND PROGNOSIS

Imaging characteristics of MS

MRI has become an extremely valuable tool in the diagnostic work-up of MS. T2-weighted imaging, using the spin echo, fast spin echo, or fast fluid-attenuated inversion recovery (FLAIR) technique, is highly sensitive in detecting MS plaques, the majority of which are clinically silent. Brain MRI is abnormal in 95% of patients with clinically definite MS, and spinal cord MRI reveals lesions in about 75%—together, one region or the other will reveal abnormalities in all but a very small number of patients. MRI assists the diagnosis by demonstrating disseminated white matter lesions in space and also by showing a pattern of abnormalities that are characteristic of demyelination. Typical features include:

• predominantly periventricular lesions with asymmetrical and irregular involvement;
• oval or round-shaped lesions;
• corpus callosum involvement;
• lesions abutting the corticomedullary junction;
• brain stem lesions, especially in the floor of the fourth ventricle or abutting the subarachnoid surface;
• gadolinium enhancement for the first few weeks after a lesion appears but not thereafter;
• nodular or ring-shaped enhancement, sometimes with an open (incomplete) ring; and
• spinal cord lesions of less than one vertebral segment in length, with partial cross-sectional involvement and often wedge-shaped and extending to the subarachnoid surface on axial images.

Despite these ‘typical’ features, the specificity of MRI findings is limited, and many other conditions produce white matter lesions (Table 5.1). Often, the clinical picture and pattern of MRI abnormalities are such that MS is not part of the differential diagnosis. Furthermore, no MRI finding is pathognomonic of MS, and the diagnosis remains primarily clinical. A common problem is that aging per se produces cerebral white matter lesions as a result of small vessel disease; brain MRI is therefore less specific in older adults. Age-related lesions do not occur in the cord—MRI of this region is especially useful in older patients or when results from brain imaging are normal.[6]

Table 5.1 Causes of white matter lesions on MRI

<table>
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<th>Common causes</th>
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<tr>
<td>Aging (small vessel disease)</td>
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<td>Symptomatic cerebrovascular disease</td>
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<td>Multiple sclerosis</td>
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<td>Less common causes</td>
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<td>Acute disseminated encephalomyelitis</td>
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<td>Decompression sickness</td>
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<td>Fat embolism</td>
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<td>HIV encephalitis</td>
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<td>Hydrocephalus</td>
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<td>Irradiation</td>
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<td>Isolated CNS vasculitis</td>
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<td>Leukodystrophies (many types)</td>
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<td>Migraine</td>
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<tr>
<td>Mitochondrial encephalopathy</td>
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<tr>
<td>Neurosarcoidosis</td>
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<td>Phenylketonuria</td>
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<td>Progressive multifocal leukoencephalopathy</td>
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<td>Subacute sclerosing panencephalitis</td>
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<td>Systemic lupus erythematosus</td>
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<td>Toxic leukoencephalopathy</td>
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MRI, magnetic resonance imaging; HTLV, human T cell leukemia virus; CNS, central nervous system.
New diagnostic criteria and implications for patients with clinically isolated syndromes

The traditional diagnosis of MS requires clinical evidence for dissemination in time and space. Thus, a diagnosis of clinically definite MS using the Poser et al. criteria[3] requires two separate symptomatic episodes affecting central nervous system white matter, each accompanied by appropriate abnormal physical signs, and occurring more than 1 month apart. These criteria were published in 1983, before MRI was generally available. The following decade saw numerous publications that described multifocal cerebral white matter lesions that were indistinguishable from those of MS in about two-thirds of patients presenting with their first clinical episode of suspected demyelination (clinically isolated syndrome, e.g. optic neuritis, brain stem and spinal cord syndromes).[7–10]

Follow-up studies have subsequently reported that MRI abnormalities at the time a patient presented with a clinically isolated syndrome increased the likelihood of developing clinically definite MS.[11,12] The longest follow-up to date reported that 88% of those with an abnormal MRI scan at presentation had gone on to develop clinically definite MS after 14 years, compared with 19% of those with normal baseline imaging.[12] A closer inspection of MRI lesion characteristics has identified several factors that increase the likelihood of developing clinically definite MS within the next 1–3 years. These include:

• the presence of gadolinium-enhancing lesions at baseline;[13,14]
• nine or more T2 lesions at baseline;[13]
• spinal cord lesions as well as brain lesions at baseline;[15] and
• new T2 lesions after 3 months’ follow-up.[16]

An international panel recently updated the diagnostic criteria for MS, particularly by incorporating MRI evidence for dissemination in time and space.[17] The committee concluded that MS could be diagnosed in patients with clinically isolated syndromes when there is MRI dissemination in space and time (Tables 5.2 and 5.3). The criteria of dissemination in space were drawn from two published studies that showed that the presence of at least three of the four brain imaging features listed in Table 5.2 provided a relatively high specificity and sensitivity for the development of clinically definite MS.

At the time that the criteria were published, there was no evidence base for the recommended inclusion of one spinal cord lesion in the criteria for dissemination in space or for the requirement that a new lesion must have appeared at least 3 months after clinical onset in the criterion of dissemination in time. We have since evaluated the criteria in a cohort of patients with clinically isolated syndrome who were re-evaluated after 3 months, 1 year, and 3 years. Development of MS by the new criteria at 3 months and 1 year had a high specificity (93% and 83%, respectively) and
positive predictive value (85% and 77%, respectively) for developing clinically definite MS after 3 years (C Dalton, unpublished data). Compared with Poser-defined, clinically definite MS, the numbers diagnosed as MS by the new criteria were much higher after 3 months (21% versus 7%) and 1 year (48% versus 20%). The new criteria thus appear to provide an early and accurate diagnosis in many patients with clinically isolated syndrome.

The new criteria will have practical implications for scanning protocols and follow-up in clinically isolated syndromes, and they will involve neuroradiologists more closely in diagnosis at this early stage. It is clearly important that experienced clinicians who are familiar with the MRI findings in MS and with the new criteria should evaluate the scans.

**Prognosis for disability**

In general, there is only a weak correlation between the number or load of T2- or gadolinium-enhancing lesions and disability in established MS. However, many

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**Table 5.2 MRI criteria for dissemination in space**

<table>
<thead>
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<th>Three of the following:</th>
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<td>One gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium-enhancing lesion</td>
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<td>At least one infratentorial lesion</td>
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<tr>
<td>At least one juxtacortical lesion</td>
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<td>At least three periventricular lesions</td>
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**NOTE:** One spinal cord lesion can substitute for one brain lesion

MRI, magnetic resonance imaging.
From McDonald et al.[17]

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**Table 5.3 MRI criteria for dissemination of lesions in time**

If a first scan is 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T2 or gadolinium-enhancing lesion at this time then fulfills the criterion for dissemination in time.

If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice.

MRI, magnetic resonance imaging.
From McDonald et al.[17]
correlative studies have been performed cross-sectionally in large and heterogeneous patient cohorts; longitudinal studies have had only short follow-up periods (e.g. 2–3 years), so that median disability changes are small. A recent study described a group of patients followed up over 14 years from onset with a clinically isolated syndrome.\textsuperscript{[12]} T2-weighted MRI was performed at baseline and at 5, 10, and 14 years, and the expanded disability status score (EDSS) was measured at each follow-up visit. There was a median 10-fold increase in T2 volume during the follow-up. Only three of 71 patients examined after 14 years had received disease-modifying treatments; thus the data represent natural history. There was a significant correlation between T2 volumes at all earlier time points and disability at year 14, but the strongest correlations were with the T2 volume at year 5 and the change in volume over the first 5 years ($r=0.6$ and 0.61, respectively).\textsuperscript{[12]} The correlation coefficient for baseline T2 volume was $r=0.48$. These findings indicate that MRI lesions load and accumulation in the early years of relapse-onset MS is predictive of long-term disability but the influence is only moderate, accounting for about one-third ($r^2=0.37$) of the subsequent disability. The predictive value at a later stage appears weaker, in line with the observations made in many other shorter-term studies.

UNDERSTANDING DISEASE MECHANISMS

New lesions, inflammation, and the clinical course

Serial MRI studies in patients with early relapsing-remitting MS have demonstrated the frequent occurrence of new T2 lesions as well as showing that almost all such lesions initially exhibit a breakdown of the blood-brain barrier manifested as gadolinium enhancement on T1-weighted scans.\textsuperscript{[18–20]} Gadolinium enhancement is correlated with pathological evidence of inflammation, including perivascular lymphocytes and extensive macrophage infiltrates, and active myelin breakdown.\textsuperscript{[21,22]} Not surprisingly, there is a correlation between new gadolinium-enhancing lesions and clinical relapse,\textsuperscript{[23]} especially when the lesions occur in clinically eloquent locations such as the optic nerves or the spinal cord.\textsuperscript{[24]} Gadolinium enhancement usually lasts 2–6 weeks, a similar duration to that of a relapse, and such lesions are more often seen during relapse than remission.\textsuperscript{[25]} In optic neuritis, enhancement of the symptomatic lesion correlates with acute visual loss and conduction block (reduced amplitude of the visual evoked potential).\textsuperscript{[26]} Taken together, these data suggest that the new T2 lesions that enhance with gadolinium are markers of inflammatory demyelination and that these lesions are reasonable surrogates for the acute relapsing component of MS. New lesions occur much more frequently than relapses because they are often in a clinically silent location, and probably also because some of the inflammatory lesions are not associated with damage to myelin or axons, thus leaving function intact.\textsuperscript{[27]}

The long-term follow-up study referred to above provides insight into the contribution of inflammation to long-term disability.\textsuperscript{[12]} It is reasonable to assume that total early T2 lesion load provides an indication of the extent of inflammation since such lesions almost invariably emerge in association with blood-brain barrier breakdown and inflammation. The correlations suggest that early inflammation (in the first 5 years) may account for one-third of the long-term disability. Mechanisms for this association include:
• epitope spreading, with more complex mechanisms of immune-mediated tissue damage that is less easily regulated;
• widespread early axonal loss, which is known to coexist with inflammation\textsuperscript{[28]} and may reduce axonal reserve at a later stage; and
• widespread demyelination, which may provide a hostile environment for long-term axonal survival.

The observations from prolonged follow-up also imply that about two-thirds of the disability is related to factors other than the extent of inflammatory brain lesions. The use of more pathologically specific magnetic resonance techniques, together with quantitative measures of tissue loss (atrophy) and abnormality in normal-appearing brain tissues, accompanied by functional MRI (fMRI) to study the mechanism of cortical adaptation, have shown that there are multiple additional aspects in the complex pathology that contribute to disability and dysfunction.

**Demyelination and axonal loss**

Demyelination and axonal loss are the major causes of functional impairment in MS. Conduction block results from demyelination, although it is not necessarily permanent, and it may be restored by the reorganization of sodium channels along the internodal membrane. Progressive axonal loss is most likely to underlie the irreversible and progressive disabilities so often seen in the later years of the disease. Several magnetic resonance methods have been proposed to monitor these pathologies and have been correlated with disability or clinical course (or both).\textsuperscript{[29–35]} These techniques include magnetization transfer ratio (MTR) imaging, measurements of T1-hypointense lesions, MRS, measurements of atrophy in the brain and spinal cord using two-dimensional and three-dimensional sequences, and diffusion tensor imaging using echoplanar hardware. These newer methods are being applied to clinical trials and treatment monitoring.

A problem with conventional imaging is its limited pathological specificity. The distinction between demyelination and axonal loss remains problematic; probably both pathological processes produce similar and overlapping alterations in T1 imaging, diffusion imaging, and MTR. Even remyelinated lesions may appear T1 hypointense or exhibit a reduced MTR, probably because the new myelin is morphologically different from normal myelin, although the magnetic resonance abnormalities are less than those found with complete demyelination.\textsuperscript{[36]} Reduced N-acetyl aspartate (NAA) is more specific than other measures for axonal damage or loss, and progressive atrophy most likely indicates a progressive neurodegenerative process since axons are the largest bulk constituent of normal white matter.\textsuperscript{[37]}

**Normal-appearing white matter**

Microscopic pathology is found in macroscopically normal-appearing white matter (NAWM) in MS, and quantitative abnormalities of T1, T2, MTR and diffusion imaging and NAA have all been found.\textsuperscript{[35,38–41]} These abnormalities may indicate a local pathological process such as perivascular inflammation, astrocyte hyperplasia, or microglial activation,\textsuperscript{[42]} or they may reflect wallerian degeneration secondary to axonal transection at sites distant from the NAWM.\textsuperscript{[43,44]} The functional significance of
abnormalities in NAWM are still being investigated, but the potential for widespread pathological change to be a significant mechanism for disability and progression is recognized.[45–47] Prelesional quantitative magnetic resonance abnormalities are found in NAWM for several months before a lesion appears,[44] which suggests that pathogenically important events are occurring in NAWM.

Cortical pathology and synaptic adaptation

Cortical synaptic adaptation may contribute to functional recovery in MS and can be explored using functional MRI (fMRI). A preliminary study of patients who had recovered from an episode of isolated unilateral optic neuritis and who had normal brain imaging revealed abnormal areas of activation beyond the primary visual cortex following stimulation of the previously symptomatic eye.[48] Motor paradigms have identified new areas of activation in patients with mild early MS compared with healthy controls,[49] and significant correlations have been observed between the cortical adaptation responses and underlying lesion load and markers of axonal damage,[50] suggesting that the response helps maintain function in the face of structural damage.

Cortical plaques are rarely seen on conventional MRI but they are frequently found post mortem.[51,52] There have been recent reports of gray matter atrophy even in early relapsing MS[53] and of intrinsic abnormalities of MTR, diffusion,[54], T1[55] and NAA.[56] A correlation between gray matter MTR and EDSS has been reported in both relapsing-remitting and primary progressive MS.[57,58] Caution is needed in interpreting such studies because of the potential for partial volume effects caused by atrophy.

Future developments in magnetic resonance studies

A number of promising developments are emerging. In particular, the increasing availability of reliable high-field scanners (3T and above) will allow studies with improved resolution and signal-to-noise ratios. Combined with phased array coils, such approaches may assist in detecting small lesions or diffuse pathological changes in the cortex and spinal cord that have hitherto been inaccessible but are likely to be functionally important. Higher fields will allow the investigation of subtle abnormalities of blood-brain barrier permeability and perfusion, and more detailed exploration of putative markers of myelin-associated water (and, by implication, demyelination per se) using T2 decay analysis[59] and quantitation of the bound water fraction using magnetization transfer methods.[60] Improved resolution of fMRI and diffusion tractography will allow exploration of the relationships between lesions, wallerian and retrograde degeneration, and cortical response. Improved resolution with MRS may provide an assessment of axonal damage in small but vital regions such as cerebellar peduncles and spinal cord. Another new development is the use of contrast agents for cell imaging; the first of these, ultrasmall particles of iron oxide (USPIO), is a marker of activated macrophages, and detects a subpopulation of gadolinium-enhancing lesions.[61]

It is anticipated that receptor ligand-specific magnetic resonance contrast agents will be developed to characterize the specificity of cellular inflammation further.
THERAPEUTIC MONITORING

Although definitive evaluation of new therapies is based on clinical outcomes, it is difficult to conduct treatment trials in MS with clinical end-points such as relapse rate or disability progression. The slow clinical evolution requires large studies (several hundred patients) of long duration (2–3 years), with an active treatment group being compared with a control group. There has been much effort to identify alternative measures of disease activity. To be an effective surrogate, the measure should be objective, sensitive, accurate, and reproducible. It should reflect and predict a clinically meaningful outcome. This section considers the role of magnetic resonance techniques in monitoring MS clinical trials and in monitoring individual patients.

Objectivity

Objectively measuring clinical outcomes is difficult. Blinding may be broken when patients experience treatment-related side effects or when investigators observe overt side effects or inadvertently discuss the patient’s experiences during the trial. MRI outcomes avoid unblinding because:

- the investigator can analyse the scans away from the patient; and
- it is improbable that the placebo effect has much effect on MRI.

Sensitivity

In relapsing-remitting MS, monthly T2-weighted and standard-dose (0.1 mmol/kg) gadolinium-enhanced T1-weighted brain MRI reveals about 10 active new or enhancing lesions for every clinical relapse. Slightly lower levels of activity are found in secondary progressive MS, and much lower levels in primary progressive disease.

New enhancing lesions are twice as common as new T2 lesions on monthly brain MRI in relapsing-remitting MS. The number of enhancing lesions is increased by weekly scanning, spinal imaging, triple-dose gadolinium (0.3 mmol/kg), magnetization transfer T1-weighted sequences, delayed scanning, and thinner slices. Triple-dose gadolinium provides a 50% increase in the number of new enhancing lesions compared with single-dose gadolinium; however, there is little reduction in sample size requirements for trials because interpatient variability increases.

Accuracy and reproducibility

An accurate technique should detect all macroscopic lesions and quantify the microscopic disease in NAWM and gray matter. On 5-mm slice thickness, small lesions are missed: there is a 9% increase in lesion load when slice thickness is reduced to 3 mm. Fast FLAIR also detects some lesions not seen on spin echo, especially subcortical or cortical lesions, but it is less sensitive in the posterior fossa and spinal cord. There is no increase in lesion load when going from 3-mm to 1-mm slice thickness. T2 load has proved a sensitive measure of treatment effects.

The MRI measure should have good reproducibility, otherwise changes over time might result from measurement error rather than biological events. Rules are available to
improve the reproducibility of counting enhancing lesions.\textsuperscript{[73]} For T2 load, semiautomated methods are more reproducible than manual lesion outlining.\textsuperscript{[74,75]}

**Clinical predictive value**

The most important validation of an MRI outcome measure is to demonstrate that it is predictive of future clinical outcome, especially sustained progression of disability. Imaging factors that potentially influence the imaging-clinical relationship are discussed in the section ‘Understanding disease mechanisms’. The limitations of T2 and gadolinium-enhancing measures are most evident in progressive forms of MS, and their most robust correlations with relapse and disability occur in the early years of relapsing disease. Putative markers of tissue damage, demyelination, and axonal loss are more relevant later in progressive MS, when neurodegeneration is more closely related to disability. The methodological issues in applying techniques such as MTR imaging, diffusion imaging, and spectroscopy are more complex in multicenter trials.

Inadequacies in the commonly used clinical scales also contribute to the limited relationship between magnetic resonance measures and clinical status. Improvements in correlations between magnetic resonance measures and clinical manifestations are likely with improved clinical and neuropsychological scales. The MS Functional Composite Scale is one such development,\textsuperscript{[76]} and it has recently been used in a trial of interferon beta-1a in secondary progressive MS.

**SPECIFIC DESIGNS FOR CLINICAL TRIALS OF MAGNETIC RESONANCE TECHNIQUES**

**Pilot therapeutic trials—safety and efficacy (phases I and II)**

Phase I and phase II trials are practical only in relapsing-remitting MS and secondary progressive MS. Monthly T2-weighted and gadolinium-enhanced brain imaging is usual. In relapsing-remitting MS, a parallel group design with a placebo arm requires about $2 \times 40$ patients to show a 60% reduction in new enhancing lesions over 6 months.\textsuperscript{[77]} A 1-month run-in scan reduces the sample sizes by about 30%.\textsuperscript{[62]} Slightly larger sample sizes are required in secondary progressive MS.

Cross-over designs are more powerful because variability in MRI activity is less within individual patients than between patients. A single cross-over design with 6 months’ run-in followed by 6 months’ treatment requires about 10 patients to show a 60% reduction in activity.\textsuperscript{[77]} Therapy-induced reductions in the number of active lesions have been demonstrated in as few as seven patients.\textsuperscript{[78]} Double cross-over designs are equally powerful, but there needs to be a wash-out period between the two phases.

Parallel-group studies provide a more robust assessment of therapeutic effect, since cross-over studies are susceptible to selection bias and regression to the mean (for instance, glatiramer acetate was found to reduce MRI activity by 60% in a small cross-over study\textsuperscript{[79]} but by only 35% in a large parallel-group study).\textsuperscript{[80]} If a safe, inexpensive drug shows a moderate reduction in activity (say 50%) in a cross-over study, this might
justify going straight to a phase III trial. If the drug has significant side effects or is expensive, a parallel-group phase II trial with a larger sample size is desirable. Early phase I and phase II MRI studies identify agents most likely to be successful in phase III if their proposed action is to prevent new lesions. Many trials with positive MRI outcomes have been reported (Table 5.4). Phase I and phase II studies are not large enough to detect infrequent side effects.

Definitive trials (phase III)

MRI provides information additional to the primary clinical outcomes (usually disability or relapse rate). T2 scans are used to measure lesion load or to count new lesions. In a large trial in secondary progressive MS, the number of new lesions was as efficient as lesion load in demonstrating treatment efficacy and in correlating (modestly) with disability.\[81\] Counting new lesions is easier than measuring lesion volume on electronic data.

Enhanced scanning evaluates the effect of treatment on inflammation over the study period. Putative markers of demyelination and axonal loss should be measured. Their implementation in multicenter trials is technically more challenging.\[82\]

Table 5.4 Studies showing a reduction in MRI activity

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Design (type of clinical picture)</th>
<th>Effect</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
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<td>Parallel groups (RR)</td>
<td>60–75%</td>
<td>IFNB Study Group[91]</td>
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<td>Glatiramer acetate</td>
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<td>Anti-VLA4 antibody</td>
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<tr>
<td>Stem cell transplantation</td>
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<td>Mancardi et al.[101]</td>
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<tr>
<td>Beta interferon-1a</td>
<td>Parallel groups (CIS)</td>
<td>50%</td>
<td>Jacobs et al.[85]</td>
</tr>
</tbody>
</table>
Glatiramer acetate Parallel groups (RR) 35% Comi et al.[80]
Beta interferon-1a Parallel groups (CIS) 30–50% Comi et al.[86]

MRI, magnetic resonance imaging; RR, relapsing-remitting; SP, secondary progressive; CIS, clinically isolated syndrome; VLA, very late acting.

T1-hypointense lesion load and measures of brain atrophy are the most feasible for multicenter studies. These techniques may be better than conventional measures at predicting long-term disability. Where interferons markedly reduce the frequency of new enhancing lesions, an effect on progressive cerebral atrophy is less apparent[83,84] Direct measures of pathological progression in the NAWM and gray matter may be important—this is now achievable with quantitative MTR, diffusion, or T1 measures, although issues of quality control and standardized acquisition in multicenter trials are not trivial. Selective atrophy of gray and white matter can now also be monitored.[53]

**Clinically isolated syndrome trials**

In trials aimed at delaying the conversion from a clinically isolated syndrome to definite MS, MRI abnormalities are required as an entry criterion. Concordant clinical and MRI outcomes have been recently reported in studies of interferon beta-1a in patients with a clinically isolated syndrome.[85,86] The long-term relevance of trials, which in essence study only the interval between the first and second relapse, appears limited. Prolonged follow-up of such patients to investigate whether early disease-modifying therapy has a long-term impact in delaying disability and secondary progression would be well worthwhile. Measurement with MR markers of neurodegeneration from the earliest stages onwards would also be welcome in such studies.

The new diagnostic criteria[17] are already being used as an entry criterion for clinical trials. Now that interferons are licensed and widely prescribed to patients with clinically definite relapsing-remitting MS, placebo-controlled trials of new agents in that patient population have become difficult to perform. The new diagnostic criteria for MS includes patients who have had a single relapse and who are not currently eligible for existing therapies in many countries; such subjects may be recruited more readily to new trials.

**Primary progressive MS trials**

Recent follow-up of a cohort of 160 patients from six European centers revealed a 5–10% mean increase in T2 lesion load per annum, which should be a sufficient change against which to demonstrate a treatment effect.[87] It is important to measure putative tissue damage markers such as atrophy.[87] A European collaborative follow-up study (magnetic resonance in MS, MAGNIMS) and the placebo-controlled trial of glatiramer acetate (PROMISE study) will provide important MRI data.
**Acute relapse treatment trials**

MRI techniques can monitor the effect of treatment on the course of acutely symptomatic lesions. Potential outcomes include the extent of the residual T2 lesion, the duration and intensity of enhancement, and the pathological severity of the residual lesion. Poor visual recovery in optic neuritis is associated with more extensive optic nerve lesions, and intravenous methyl prednisolone does not modify the length of the MRI lesion.\(^{[88]}\) Methods for quantifying optic nerve diffusion, MTR, and atrophy are available.\(^{[89]}\)

**Repair and remyelination treatment trials**

Remyelination might be inferred by reversal of abnormalities such as low MTR, although resolution of edema or the development of gliosis may result in a similar magnetic resonance evolution. Remyelinated lesions are T2-hyperintense.\(^{[27]}\)

**MONITORING INDIVIDUAL PATIENTS**

For practical reasons, the possibility of monitoring individual patients applies only to T2-weighted and gadolinium-enhanced scans to assess the number of active lesions and overall load. Volumetric or quantitative studies, especially of other magnetic resonance measures, are not yet feasible in day-to-day care. Given the limited overall correlations between standard MRI and clinical findings, it is premature to use imaging features as a primary tool to make treatment decisions. The clinical aspects should be the primary determinant for treatment decisions. As a supplement to the clinical context, MRI findings can sometimes be helpful (e.g. a normal scan in a patient with mainly subjective relapses might discourage treatment, whereas a highly active scan with multiple enhancing lesions in a patient with frequent but mild sensory relapses might encourage treatment). Protocols have been suggested for MRI monitoring of patients in different clinical settings,\(^{[90]}\) but these protocols have not achieved a broad consensus. There is still little justification for using MRI in routine monitoring of the treatment of individual patients. The situation will change when practical and robustly prognostic magnetic resonance measures become available.

**FUTURE ISSUES IN CLINICAL TRIALS**

Adequate quality assurance procedures are needed in longitudinal studies. The methods of statistical analysis are crucial. A composite magnetic resonance score based on several individual measures may better reflect the underlying pathology and correlate with disability. Further correlation of magnetic resonance findings with pathology in experimental and human diseases is needed. Technological progress continues apace, and it is hoped the newer approaches will improve the relevance of magnetic resonance as a surrogate tool.
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INTRODUCTION

Gadolinium-enhancing lesion counts have become standard measures in clinical trials in multiple sclerosis (MS), providing an index of inflammatory activity around the time of the magnetic resonance imaging (MRI) study, as well as a cumulative index of disease activity over intervals when used in a serial monthly MRI scan format. As MS therapies, both approved and experimental, target the inflammatory aspects of the disease, counts of enhancing lesions provide a sensitive, convenient, and rational measure of efficacy. As a result, enhancing lesion measures have become primary outcome measures in many phase II trials. In phase III trials, counts of enhancing lesions are recorded either at half-yearly or yearly intervals to determine residual inflammation as a secondary outcome measure or at monthly intervals in a subset of patients to evaluate potential short-term effects of therapy. More recently, counts of enhancing lesions have been introduced into phase I trials as a safety measure.

This chapter includes a review of the natural history of enhancing lesions in MS and their underlying pathology, as a basis for interpreting their importance as measures of subclinical disease in clinical trials. The immediate and long-term relationships between enhancing lesions and the clinical expression of disease—relapse or disability—are then considered, since these relationships are the basis for viewing enhancing lesions as surrogate measures in MS clinical trials. Finally, practical aspects of the imaging of enhancing lesions are considered, including phase I, II, and III trial designs and technical aspects of MRI that are relevant to the use of enhancing lesion measures in MS clinical trials.

NATURAL HISTORY AND PATHOLOGY OF INDIVIDUAL ENHANCING LESIONS IN MS

Monitoring the blood-brain barrier

By convention, enhancing lesions in MS are focal areas that appear hyperintense (bright) on T1-weighted MRI scans after, but not before, administration of standard magnetic resonance contrast agents. For practical purposes, enhancing lesions are typically 2–3
mm or more in diameter, although it should be recognized that smaller foci of pathologic enhancement could exist but cannot be reliably separated from enhancement of vascular structures, artifacts such as motion-induced ghosts, or random ‘noise’ in an image. Detection of very small regions of enhancement is in theory feasible but is not practical as yet, and is not the standard for evaluation of enhancement either for following individual patients or in clinical trials.

In normal conditions, the mid-molecular weight, clinically approved magnetic resonance contrast agents (i.e. ionic or non-ionic gadolinium chelates of 500–1000 Da) are confined within the intravascular space in the brain and spinal cord by tight junctions between endothelial cells that comprise the blood-brain barrier.[1,2] After administration of an intravenous bolus of magnetic resonance contrast, there is a rapid vascular enhancement phase followed by decay that can be approximated as a biexponential function.[3] The half-life of gadolinium chelate in the blood pool is approximately 90 minutes. There is a corresponding slow increase in the concentration of gadolinium chelate in normal leaky regions of the central nervous system (CNS), such as the choroid plexus and dorsal root ganglia, as well as in the circumventricular organs that have fenestrated capillaries, including the median eminence, area postrema, pineal gland, and neurohypophysis.[2]

CNS pathology may result in disruption of the normally intact blood-brain barrier. The factors that lead to disturbance of the blood-brain barrier are recognized as early events accompanying inflammatory demyelination. Antigen-specific T cells are thought to enter the CNS, where they recognize antigen and subsequently trigger a cytokine cascade that mediates disruption of the blood-brain barrier seen on contrast-enhanced MRI.[4] The kind of enhancement detected by MRI in MS patients probably represents relatively severe focal and transient phenomena associated with the acute inflammatory event, and includes leakage of small molecules and moderate-sized protein past tight junctions and into the interstitial spaces. Inflammatory and dysimmune events that are central to MS pathology and that primarily or secondarily disrupt the endothelial tight junctions make gadolinium enhancement a convenient marker for many of the early events in the inflammatory demyelination cascade. The association between enhancing lesions and the acute inflammatory stage of individual MS lesions is consistently supported by correlative MRI autopsy and MRI biopsy studies in humans, and this association has become a well-accepted principle.[5–8] Further support for the association between inflammation and lesion enhancement is provided by experimental demyelination observed in experimental allergic encephalomyelitis models, in which a good temporal and spatial correlation between enhancement and inflammation has been established.[9–11] In addition to the severe focal leakage of contrast into acute MS lesions, which is readily determined by visual inspection, there is known to be chronic, low-grade leakage that is below the visual threshold but that may be detectable in tissue samples if sensitive immunohistochemical techniques are used for serum protein leakage; this finding has been documented in mature MS plaques.[12]

Although pathologic enhancement is typically recorded as an all-or-none phenomenon in imaging (i.e. enhancing lesions are either present or absent), there is evidence of heterogeneity in the visualized lesions based on a range in blood-brain barrier permeability, with some lesions showing maximal enhancement in less than 10 minutes, and other lesions enhancing over two hours.[13] In addition to lesion heterogeneity based
on time of maximal enhancement after injection, enhancement heterogeneity can be observed using relatively high (triple-dose) gadolinium chelate, since a fraction of lesions are detected only with high-dose contrast agent administration. There is also heterogeneity in the appearance of enhancing lesions; most start as small, homogeneously enhancing areas, whereas others may appear initially as ring-enhancing lesions, although the latter tends to be a finding that develops over a period of weeks. Recent studies suggest that ring-enhancing lesions may be a subset of lesions in more severe focal injury.

Once gadolinium enhancement is observed in the acute focal MS lesion, it remains visible by MRI for a period of 3–8 weeks in most cases, although this interval varies from 1 week to as long as 16 weeks (Fig. 6.1). In one series based on weekly MRI scans, enhancement was seen on only one scan in 5% of lesions, and enhancement was present for less than 4 weeks in 29% of lesions.

Although enhancement may precede hyperintensity on T2-weighted imaging in acute MS, the vast majority of enhancing lesions are also T2-hyperintense. After reaching a maximal T2-hyperintense lesion size over a period of about 4–8 weeks, both the T2 hyperintensity and the underlying gadolinium-enhancing area decreases over a period of weeks. Although enhancement decreases and may disappear by visual inspection during these late subacute stages of lesion evolution, the blood-brain barrier probably continues to be partially damaged, as indicated by leakage of serum protein observed in biopsy specimens from lesions, irrespective of activity, and as seen in long-standing MS plaques. After stabilization, the vast majority of the T2-hyperintense lesions do not change over a period of many years, although re-enhancement and lesion activity along the periphery or, at times, centrally, does occur in a minority of lesions within a few years. A T2-hyperintense residuum is left permanently in more than 95% of instances, and it is believed that this T2 hyperintensity represents a ‘foot-print’ of the prior acute inflammatory-demyelinating event.

Although enhancing lesions are considered the
Fig. 6.1 Duration of enhancement in 25 lesions followed by once-weekly MRI. Note that the majority of lesions enhance for 3 weeks or more. Shaded columns simulate analysis points on monthly MRI. The study suggests that the small increase in sensitivity of weekly scanning does not justify its use in preference to monthly scanning in monitoring treatment. From Lai et al., [23] with permission.

earliest signs of acute regional abnormalities detectable by MRI, several studies show that there are MRI-detectable changes in brain tissue that precede the acute enhancing lesion. [29–33] The relationship between abnormalities detected by T2 relaxation measurements, magnetization transfer ratios, or diffusion methodologies and the subsequent development of an enhancing lesion months later is not known. The favored interpretation is that these focal abnormalities are directly related to the subsequent pathology observed weeks or months later as enhancing lesions. An alternative theory is that these specialized methodologies are detecting focal areas of previous injury, which are more likely to be subsequent sites of essentially unrelated new acute events.
Pathologic and MRI outcomes of acute focal enhancing lesions

Conventional (T2- and T1-weighted) MRI studies suggest that the pathologic outcome of individual enhancing lesions is variable. There are three recognized patterns. Most often, long-term follow-up of individual enhancing lesions over a period of 6–12 months reveals chronic, focal areas of T2 hyperintensity but normal appearance on corresponding T1-weighted images. In about one-third of the lesions, the outcome is a T2-hyperintense region with corresponding T1-hypointensity, termed a T1 black hole. These T1 black holes have been associated with relatively severe axonal loss and matrix disruption. On rare occasions, enhancing lesions leave no T2-hyperintense or T1-hypointense residuum. Such lesions are probably a subset of lesions with relatively mild chronic focal injury, or they may represent lesions that have undergone remyelination and repair. Using ‘more specific’ MRI techniques, the pathologic sequelae of enhancing lesions can be further characterized on the basis of their magnetization transfer index or their diffusion characteristics.

Since lesion enhancement results in variable pathologic outcomes, there has been interest in determining lesion characteristics that predict these differential focal outcomes. One approach is based on the pattern of enhancement. In one study, lesions that enhanced over relatively longer intervals (‘persistently enhancing lesions’) were more likely to result in chronic T1 black holes and decreased magnetization transfer ratios, but the size of the enhancement, its location, and its configuration were unrelated to the MRI outcome. Lesions visualized only after high (triple-dose) magnetic resonance contrast infusion tend to be smaller and less destructive than those detected by a single dose. This is important because treatment may differentially affect small and large enhancing lesions. Ring-enhancing lesions are associated with intense macrophage infiltration and tend to be larger and of longer duration than homogeneously enhancing lesions; they may be associated with a poor clinical outcome and show a relationship, albeit a weak one, with persistent T1 black holes.

There is now good evidence from biopsy and autopsy studies that acute inflammatory MS lesions may be associated with axonal injury, including axonal transection within the lesion and along its borders. The magnetic resonance spectroscopy (MRS) literature also suggests that axonal injury occurs in early MS lesions. MRS studies demonstrate reduced N-acetylaspartate, a neuronal marker, in acute lesions in patients at the time of a clinically isolated syndrome as well as in acute lesions identified during the relapsing stages of MS. Longitudinal studies of patients at risk of MS show that focal enhancing lesions are also the precursor to neuronal tract injury, as determined by Wallerian degeneration or transcallosal band patterns. One informative case report provides strong evidence that focal inflammatory MS lesions may lead to distant axonal degeneration.

The relationship between inflammation and subsequent injury is less clear in other instances. In primary progressive MS, which tends to have a poor functional outcome, there is relatively little inflammatory activity. Moreover, most MS lesions in the cerebral gray matter have relatively low inflammatory activity, but there is axonal transection, dendritic transection, and neuronal death by apoptosis. Nevertheless, neuritic transection correlates with inflammatory activity within these lesions, as described previously for white matter lesions. As discussed below, the long-term
relationships between inflammation and disability and between inflammation and atrophy are not straightforward.

**Contrast enhancement as a measure of inflammatory activity?**

The gold standard for contrast enhancement has been visualization on standard imaging by an experienced observer. More sensitive methods are likely to be revealing, since there is evidence that serum proteins leak across the blood-brain barrier barrier in old plaques. Detection of focal enhancement can be improved, in theory, by using computerized image processing to detect enhancement below the human visual threshold. An interesting application of computerized image processing is the detection of low levels of more diffuse enhancement, for instance in the normal-appearing white matter. In one pilot study, this approach showed trends toward greater enhancement in primary progressive MS compared with normal controls, although the differences were not statistically significant. Dynamic contrast infusion MRI methods have been developed but have not been used systematically in MS or in a clinical trial setting. Optimized acquisition technique to reduce motion artifacts combined with computerized and automated image post-processing have been developed to analyse contrast enhancement to improve reproducibility in determining focal contrast enhancement. In practice these methods are not entirely automated, since they require review and confirmation by an experienced observer, but in some settings they may be advantageous because they are likely to reduce interobserver and intersession variability. More exquisite probes of the blood-brain barrier or cellular trafficking based on iron- or gadolinium-tagged monocytes, lymphocytes, and macrophages have been proposed. Early pilot studies in humans are under way and these may prove to be important measures of disease in the future.

**Enhancing lesion profile in individual patients and in populations**

There is great variability in the number and volume of enhancing lesions within MS patients over time. This has been demonstrated in serial monthly and weekly MRI studies. As a result, the number of enhancing lesions in an individual patient cannot be accurately predicted on the basis of a prior examination. The factors underlying this highly variable expression of enhancing lesions over time are not understood. Variability in clinical disease expression has been related to intercurrent infection, seasonal factors, hormonal status, and pregnancy, all of which may have an impact on counts of enhancing lesions and the variability in enhancing lesions over time, although the short-term variability based on MRI lesion counts is striking and not well explained by these factors. Despite the short- and long-term variability, counts of enhancing lesions are the basis of much of what we have learned about the natural history of MS as revealed by MRI, and they are a cornerstone of MS treatment trial methodology. The key to the success of monthly enhancing lesion analyses in MS, recognized in the early evaluation of this approach, is that the magnitude of the peak number and the frequency of the peaks varied among patients, and that these relationships showed some stability over time (Fig. 6.2).
There are three important points relevant to the monitoring of MRI activity in populations in treatment trials. First, this relationship improves if multiple points (e.g., monthly evaluations) are sampled and then averaged. McFarland et al. showed that three MRI studies provide a good estimate of an individual patient’s enhancing lesion activity over an interval of years, and that there is limited gain in averaging studies over longer intervals. Analysis of a population of patients rather than of individual patients renders the results meaningful. Second, there is a general trend such that disease in patients with little or no MRI enhancing activity tends to remain inactive at least over short intervals, although exceptions have been noted. Third, activity based on greater than average MRI enhancing lesions tends to remain active over short intervals. As a result, in population studies with a sufficient sample size (typically in the range of hundreds of patients), even sampling at infrequent intervals has been a successful strategy. For high frequency sampling at monthly intervals, an informative sample size can be relatively small, as discussed below.

**Contrast enhancement patterns based on disease stage and phenotype**

The number or volume of enhancing lesions varies with disease stage and phenotype. The earliest identifiable stage of relapsing-remitting MS is the clinically isolated syndrome. The vast majority of patients with a clinically isolated syndrome and an abnormal cranial MRI scan go on to develop clinically definite MS. Approximately 30–60% of patients with a clinical isolated syndrome have contrast-enhancing lesions at the time of their presentation. In the prospective CHAMPS trial, admission to the trial required a clinically isolated syndrome and a positive MRI with two or more characteristic MRI lesions. In this trial, enhancement was seen in 30% of the 387 patients on their baseline MRI scan. This probably underestimates the true frequency of enhancement in untreated patients, since all the CHAMPS patients had received a standardized treatment with high doses of intravenous methylprednisolone for 4–14 days before their MRI scan. About 59% of the patients with relatively early disease and initial unifocal or multifocal presentations in another large study had enhancing lesions at baseline.

In relapsing MS, the frequency of contrast enhancement has been reported to be in the range of 28% to 65% (53–65% in the larger studies) Some variability is probably dependent on the criteria used in recruitment. For example, some trials allow recruitment of patients with recent clinical activity, while others prohibit enrollment around the time of a clinical attack. Lesion number in studies that do not select for MRI activity tends to be small. A mean of 2.7 lesions (median 1) was seen in one study, while in another study that required a positive screening MRI scan, 82% of patients had a mean of 4.3 lesions. Enhancing lesion frequency decreases in the later stages of disease, as does the reported relapse rate. Decreasing frequency of enhancing lesions has been documented in late versus earlier relapsing MS and by comparing relapsing-remitting MS with secondary progressive MS. The best estimates for enhancing lesion frequency in secondary progressive MS come from the large, multicenter trials, in which enhancement has been observed in 36–48% of patients. This is consistent with clinical and immunologic studies that suggest that the inflammatory component of the disease may decrease over time. In the IMPACT trial of secondary progressive MS patients, the frequency of enhancing lesions at baseline was 36%, with a mean of about 1.5 lesions. In
the European trial of interferon beta-1b in secondary progressive MS,\[82\] 48% of the patients had enhancing lesions at baseline with a mean of 2.5 lesions. In contrast to early

<table>
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<th>Activity*</th>
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**Fig. 6.2** An example of numbers of enhancing lesions on monthly MRI over 6 months in relapsing-remitting MS and secondary progressive MS. Note that although the number of lesions varies widely from month to month, trends are easily identified, with some patients showing little or no activity (one lesion or none) over the full interval and others tending to have active lesions on most monthly evaluations. From Nauta et al.,\[61\] with permission.
relapsing MS and secondary progressive MS, acute lesions in primary progressive MS appear to be less intensely inflammatory,\cite{83} based on histopathology and a reduced number of enhancing lesions by MRI.\cite{50,83,84} Despite this quantitative difference, primary progressive MS may show otherwise typical imaging features seen in relapsing-remitting MS.\cite{85}

**CLINICAL AND PATHOLOGIC SIGNIFICANCE OF ENHANCING LESIONS**

**Enhancing lesions and relapse**

Gadolinium-enhancing lesions are generally accepted as markers of subclinical disease activity, are considered surrogate markers of inflammation, and (at least in some cases) may reflect an early stage in the processes that lead to irreversible injury, including axonal transection. However, the relationship between enhancing lesions and clinical signs, symptoms, and disability is not straightforward. While population studies may show a modest correlation between enhancing lesion activity and clinical relapses over time,\cite{86} there may be no relationship in individual cases even over periods of years. This presumably occurs when focal disease activity occurs in clinically silent regions of the CNS (Fig. 6.3). On the other hand, a single enhancing lesion may have severe clinical consequences if it is located in a functionally critical region, such as the optic nerve, brainstem, or spinal cord. The correlation between enhancing lesions and fixed disability over short intervals is poor or nonexistent. Yet there is some evidence for a significant, albeit weak, relationship between enhancing lesions and long-term disability. The apparent relationship may be weakened by a temporal offset between inflammatory activity and disability and by the short duration of follow-up in most studies.

Acute relapse in MS is thought to be caused by an inflammatory event event.\cite{87} When inflammatory, enhancing lesions occur in functionally exquisite regions, they result in imaging findings, symptoms and electrophysiologic disturbances with a similar time course,\cite{88} and a strong correlation has been noted between periods of clinical worsening and periods of increased enhancing lesion frequency.\cite{86} Consistent with this expectation, enhancing lesions are more frequent during relapse.\cite{86,89,90} However, it is also clear that the correlation between new enhancing lesions and new clinical activity is poor, with between five and 10 MRI events for every clinical event;\cite{91} in some studies this figure is as high as 100 (see Fig. 6.3). Frequent MRI series reinforce the message that ongoing enhancing activity occurs during periods when patients are clinically stable.\cite{68} The discrepancy between enhancing or new T2-hyperintense lesions and clinical activity is a strong rationale for using MRI to monitor subclinical disease.

When results are averaged for large numbers of subjects, a significant relationship between enhancing lesion frequency and relapse rate is observed, but the relationship is not strong.\cite{69,75,86,92,93} For example, in one large prospective multicenter study in patients with relapsing-remitting MS and only mild to moderate disability, the correlation coefficient (r) between the number of relapses and the cumulative number of enhancing lesions over 2 years was only 0.3 in the untreated population.\cite{75} A metaanalysis based on monthly MRI scans in patients with relapsing or secondary progressive MS found a weak
but significant relationship between relapse over 1 year and enhancing lesions over 6 months.\cite{92} In another study there was a significant correlation between enhancing lesions at study entry and subsequent relapse rate in both relapsing and secondary progressive MS.\cite{94}

Although the relationship between enhancing lesions and relapse is weak, most studies reveal a

\textbf{Fig. 6.3} Poor relationship between enhancing lesions and clinical activity. Results of one untreated patient from the CHAMPS trial. During the 18-month evaluation, there were no new clinical events, yet the patient developed 63 new or enlarging T2 lesions, and had 33 enhancing lesions at 18 months. Open boxes represent enhancing lesions, solid boxes represent enlarging T2 lesions

curiously strong relationship between enhancing lesions on a single MRI at the time when a patient presents with a clinical isolated syndrome and a subsequent diagnosis of MS based on a second attack. Enhancing lesions on the initial MRI are consistently very good and are often the strongest predictors of conversion from a clinically isolated syndrome to clinically definite MS.\cite{95-99} Rather than MRI activity being predictive of MS, an alternative interpretation is that it predicts future activity, at least in the short
term, and an increased likelihood that a random lesion on MRI will occur in a functionally exquisite area of the CNS and so elicit a clinically evident event and a diagnosis of clinically definite MS.

**Relationship between enhancing lesions and disability**

The correlation between enhancing lesions and disability based on either the expanded disability status score or functional composite measures is poor or nonexistent. The relationship between relapse and progression of disability is also poor. Nevertheless, there do appear to be populations that show some relationship, most likely those with relatively active or severe disease. Several studies with short-term follow-up have shown some relationship between MRI activity and change in disability. A dissociation between enhancing lesions and disability was seen in the CAMPATH-1H study, in which disability, brain atrophy, and spinal cord atrophy progressed despite a marked reduction in the number of enhancing lesions. The risk of progression to disability and cerebral atrophy, however, seemed to be related to the amount of inflammation in the brain before treatment, as judged by enhancing lesions. One interpretation of this result is that the progression of disability and atrophy seen in this trial resulted from temporally remote inflammatory events. In primary progressive MS, clinical deterioration occurs with little or no enhancement or new T2 lesions, underscoring the point that inflammation alone as measured by the number of enhancing lesions is not a sufficient explanation for disability in MS. A complex model of injury, incorporating lesion characteristics, anatomic location, host, and other factors, may be more relevant.

**Global enhancing lesions and subsequent pathology**

Although the demonstrated relationship between enhancing lesions and clinical expression of disease is weak, enhancing lesions nevertheless show important relationships with future pathology. Gadolinium-enhancing lesion activity appears to be the best predictor of subsequent new and enlarging T2 lesions or T2 lesion volume increments in relapsing and progressive MS over periods of months or years. Enhancing lesions predict subsequent enhancing lesions, suggesting that the activity pattern by MRI is relatively stable over a period of at least 1–2 years, despite the known month-to-month fluctuations that are seen on MRI studies.

Although inflammatory lesions are associated with axonal injury and demyelination, large studies have failed to date to show strong relationships between inflammatory activity and concurrent or future brain or spinal cord atrophy. Several studies, but not all, show a significant but weak correlation, but in most studies the strength of this correlation is less than with other MRI measures such as T2 lesion volume. In a study of secondary progressive MS, progression of brain atrophy and clinical disability occurred despite early and effective suppression of inflammation by CAMPATH-1H as measured with enhancing lesions. However, atrophy during the study correlated with the extent of enhancement in the pretreatment phase, suggesting the possibility of linkage between enhancing lesions and atrophy, somewhat temporally dissociated. In the trial of interferon beta-1a in relapsing MS, treatment resulted in a
decreased number and volume of enhancing lesions and in a delayed reduction in the rate of atrophy until the second year, again possibly reflecting temporal dissociation between inflammation and atrophy.\[^{112}\] One can hypothesize that effective therapy may slow atrophy progression but that this therapeutic effect is delayed because pathologic events already set in motion before treatment play out over several months to a year.\[^{117}\] This hypothesis is supported by the protracted time course of atrophy and Wallerian degeneration in the CNS after stroke.\[^{118}\]

**MONITORING MS THERAPY USING ENHANCING LESIONS**

There are no standardized rules for use of MRI in monitoring MS clinical trials, but guidelines have been published.\[^{119}\] Counts of enhancing lesions are well accepted as primary outcome measures in phase II trials and as secondary outcome measures in phase III trials. More recently, counts of enhancing lesions have been used in phase I and phase II trials as a measure of safety and for stopping rules. In addition, counts of enhancing lesions are being used increasingly to select patients with active disease for trials. In theory, counts of enhancing lesions can also be used in the randomization process to achieve balance in the study arms of a trial.

**Phase II trials**

The results for various phase II MS trials are reported in detail in this book. Here the general principles for the use of enhancing lesions in phase II trials are reviewed. The purpose of phase II trials is to determine efficacy and provide additional data about safety. Additional goals may be to select outcome measures for subsequent use in phase III trials and to address hypotheses related to the pharmacokinetic behavior of the drug being studied.\[^{120}\] Phase II trials may be used for ‘early’ screening of promising therapies, within an acceptable time frame with a modest sample size. Alternatively, phase II trials may be configured as more definitive or ‘late’ multicenter studies with a large number (100–400) of patients. Therapies showing acceptable safety and efficacy profiles can be subsequently evaluated more formally by a larger, longer, and more detailed phase III clinical outcome-based trial.

High-frequency, monthly enhanced MRI studies provide a convenient and informative basis for using MRI as the primary outcome measure in MS phase II trials.\[^{60,121}\] Enhancing lesions are a surrogate marker for inflammation, and are thought to be a relevant measure related to some clinical aspects of disease (e.g. relapses). Enhancing lesions are also thought to have pathologic significance in their relationship to demyelination and irreversible injury to the axon. Various MRI-based phase II strategies based on enhancing lesions have been proposed, and these have been evaluated through simulations using existing MS data to determine overall design, optimal sample size, and duration and frequency of the MRI evaluation required to achieve statistically relevant outcomes.

There are two major types of phase II designs—cross-over designs and parallel-group designs.\[^{20,60,61,68,119,120,122–125}\] As shown in Fig. 6.4, the classic open-label cross-over design, evaluating baseline versus treatment, is based on an initial set of serial magnetic
resonance examinations, typically at monthly intervals for 3–6 months, to provide a profile of the enhancing lesions and the clinical profiles of the patients. After treatment is initiated, monthly MRI followup and clinical evaluations continue over a predetermined interval, typically for up to six additional studies. The cumulative number of enhancing lesions for the baseline and treatment intervals would be the primary outcome. Analysis

**Fig. 6.4** Three primary monthly MRI trial designs based on enhanced MRI. Vertical lines signify monthly scans. (a) Cross-over trial design. A typical design would include 6 months’ baseline followed by 6 months’ treatment. (b) Parallel-group design with cross-over. (c) Parallel-group trial with baseline run-in period. From Frank and McFarland,[120] with permission.
of enhancing lesion activity over time also provides potentially valuable information about the kinetics of the therapeutic effect. In the cross-over design, each patient may serve as his or her own control, in which case the confounding effect of patient variability is minimized. Estimates for sample size for this design are 10–12 patients, with a 6-month baseline phase and a 6-month treatment phase, which would provide power to detect a 50% reduction in lesion frequency (Fig. 6.5). The major advantage of this design is the small sample size, allowing studies to be undertaken with minimal expense and at one recruitment center.[120] A limitation of the design is that if a decrease in magnetic resonance activity occurs independently of treatment, the decrease may be misinterpreted as being treatment-related. In theory, this phenomenon can occur when a population with active disease or recent disease activity is recruited and the natural decrease in activity occurs over time owing to regression to the mean, a phenomenon that has been reported using clinical outcome measures such as relapse rate. An additional limitation of the open cross-over design can be lack of blinding if the presence of new enhancing lesions is used as the measure, since this will require the reader to have knowledge of the previous study and the month of the study. Despite some limitations, the open-label, single cross-over design can provide valuable information.[126–129]
Another approach is the two-arm randomized cross-over trial. Each patient serves as his or her own control, and the concurrent parallel arm allows comparison of placebo versus treatment in the population. For this design to be effective, the wash-out interval must be sufficient relative to the duration of the pharmacologic effect. Unfortunately, this interval is rarely known at the time of the study, and it can be surprisingly long.\cite{130} Nevertheless, this design has considerable strength related to its inherent property of allowing statistical comparison between individual patients and between groups.

The third classical trial design is the parallel-group trial, which is also used in the setting of the phase III trials. One important modification of the parallel-group design is the use of additional baseline studies, a run-in series before randomization, which has the beneficial effect of reducing sample size.\cite{60}

**Phase III trials**

In phase III (definitive) clinical trials, which are typically based on 300–800 or greater patients and which incorporate trial durations of 2–4 years, primary outcome measures are clinical parameters while magnetic resonance measures are used as secondary outcome measures.\cite{119} A typical trial would include yearly or half-yearly assessments of T2 lesion load and accumulation of new and enlarging T2-hyperintense lesions; additional measures of active scans may also be included.\cite{131,132} There are two strategies for using enhancing lesions in phase III trials. The most common approach is to evaluate only a subset of the full study population with monthly or 6-weekly MRI scans for counts of enhancing lesions or new T2 lesions,\cite{133} or a combination of the two. High frequency sampling of a sub-population provides a powerful approach for determining the effect of therapy on inflammatory activity and gives insight into the effects of treatment over time, yet it avoids the expense associated with full population sampling. In this design, the full population is evaluated by standard clinical outcome measures and by measures of T2 lesion number or volume. While extrapolation of the results to the full population may be imperfect, in most studies the sample size of the high-frequency sub-population has been substantial, minimizing this potential error. For phase III trials that last for several years, one approach is to sample at monthly intervals only at the beginning and at a later interval during the trial, preferably the end, for example over 6-month periods.\cite{82}

In a second approach, the full phase III population is evaluated by enhanced MRI scans, but typically with sampling separated by longer intervals, either every 6 months\cite{74} or every year.\cite{75,81} Despite the known fluctuation in enhancing lesion counts over short intervals in individual patients, this has been an effective approach, owing to the large sample sizes. Counts of enhancing lesions in this setting provide unique information as to inflammatory activity in the full population at various times during the study. By sampling the full population at baseline, enhancing lesions can also be used as a covariate in analyses.

**Gadolinium enhancement as a safety measure**

A relatively new and under-explored role of gadolinium-enhanced MRI is its use as a safety measure in phase I and phase II trials.\cite{120} Here, enhancing lesions are used as an indicator of greater than expected inflammatory activity that might be induced by an
Fig. 6.6 Enhancing lesion profile in an individual patient over 104 months. Contrast-enhancing lesions in a relapsing—remitting MS patient who was entered into three separate baseline-versus-treatment trials at the National Institutes of Health in the USA. The patient was initially entered into a study evaluating cyclosporine A (CSA), which had some effect on decreasing the frequency of enhancing lesions. Following a wash-out period, the patient returned to his natural history baseline enhancing lesion frequency of 11 lesions per month. At month 35, the patient was started on interferon (IFN) beta-1b and responded to therapy for 18 months, at which time he developed severe depression and suicidal ideation, and IFN beta-1b was terminated. Approximately 6–8 months elapsed before the patient returned to his
natural history baseline lesion frequency. The patient entered into an early phase II trial of altered peptide ligand and after 2 months on therapy experienced a severe exacerbation accompanied by an increase in number of enhancing lesions, from 20 lesions to more than 90 lesions, which exceeded the predetermined stopping rule for this phase II trial. The patient was treated with intravenous corticosteroids and started on standard therapy. From Frank and McFarland,[120] with permission.

active treatment (Fig. 6.6). One strategy is to compare the enhancing lesion profile of individual patients based on their monthly MRI scans to look for greater than expected increases in activity as an indication of an adverse effect. An increase in an individual patient’s count of enhancing lesions could also be compared with enhancing lesion activity in an untreated cohort or with historical data. This is a practical approach within a trial setting because of the relative ease and speed in which counts of enhancing lesions can be performed by experienced imagers.

Using enhancing lesions to select for greater disease activity

A common strategy in phase II clinical trials is to use enhanced MRI to select patients with greater disease activity or ‘active disease’, based on one, two or three MRI scans. The advantage of such preselection is that it minimizes potentially uninformative scans generated in studies from patients who are likely to show no new disease activity. Ideally, enhancing lesions on consecutive studies (e.g. three of three) or on a majority of consecutive studies (e.g. two of three) would provide the most informative appraisal; however, one common strategy is to permit trial entry after a single positive MRI scan in consecutive MRI evaluations over monthly intervals. In addition to minimizing uninformative scans, recruitment of only active patients may have a secondary advantage of reducing intra-patient variability. Unfortunately, preselection has the undesirable effect of making the results less generalizable to potential treatment recipients with less disease activity. This may not be a critical problem, since positive phase II trials would be followed by definitive phase III studies using a clinical outcome. Another disadvantage of preselection is the increased chance of regression to the mean, which can confound interpretation of the results, depending on the study design.

Multiple studies have established that enhancing lesions are the strongest predictors of clinically definite MS in patients with a clinically isolated syndrome.[95–98] The conversion to clinically definite MS is probably the consequence of greater activity in the population with enhancing lesions; consequently, a strategy can be developed for
selecting a more active patient group based on the presence of enhancing lesions after a clinically isolated syndrome.

Statistical considerations

Several reports have addressed optimal sample size for MS trials using enhancing lesions as a marker, and guidelines for sample size have been published for each of the major trial designs.\[60,67,68,121,123–125,134\] Conservative sample size estimates have been recommended, since the predictive analyses have been based on relatively small data sets, which may include a mixture of patients at various stages of disease. The optimal statistical methodology for analysing enhancing lesions has been considered.\[135\] Because new enhancing lesion counts in MS are not normally distributed, nonparametric methods have been used in phase II studies, whereas standard approaches based on normal approximations have been used in larger phase III studies. Specific parametric models for new enhancing lesion counts in MS have recently been shown to be applicable to MS trials.\[134,136\]

MRI as a post-selection, pre-randomization strategy

The number of enhancing lesions can be used in post-selection, pre-randomization procedures to insure balanced stratification of study arms.\[137\] Ensuring balance in treatment groups can be important because the small sample sizes in phase II trials may not result in equivalent treatment arms. This can significantly complicate study analysis. Imbalance in enhancing lesion activity between treatment arms can even have an impact in large populations in phase III trials, since studies demonstrate that an important factor in the development of new T2-lesions, new enhancing lesions, and T2-lesion volume is the number of enhancing lesions at trial study entry.\[75\] While a post hoc factor analysis may be applied, this is less satisfactory than achieving a balance before randomization. The effect of enhancing lesions on subsequent activity can be dramatic. In one large prospective trial, untreated patients presenting with enhancing lesions showed a median 2-year change in T2-hyperintense lesion volume of 2.98 ml compared with only 0.67 ml for patients with no lesions on their initial MRI study, and the enhancing lesion rate was about five-fold greater for untreated patients with enhancing lesions on their baseline MRI study.\[75\] Consequently, imbalance at entry may mask detection of a significant treatment effect.

Equivalence of counts of enhancing lesions and counts of T2 lesions

Given the relationship between acute enhancing lesions and acute T2-hyperintense lesions, there is overlap in using these two outcomes for determining disease activity in trials. The correlation between new T2 lesions and new enhancing lesions is strong in series in which MRI is conducted weekly,\[24\] monthly,\[127,138\] and every second month.\[72\] In theory, counts of T2 lesions could replace counts of enhancing lesions in studies with monthly MRI, after baseline inflammatory activity has been established with enhancing lesion analyses, however with some cost due to decreased new lesion detection. In one series, 15% of new (T2) lesions were missed because of their small size and another 5%
were missed because of their periventricular location.\textsuperscript{127} The converse situation, in which a new lesion is detected on a T2-weighted image but not detected as an enhancing lesion on monthly studies, is less likely, but may occur in primary progressive MS, which is characterized by a lower degree of focal inflammatory activity.\textsuperscript{139} The benefits of replacing counts of enhancing lesions with counts of T2 lesions are the cost savings and the avoidance of intravenous injections. However, more experienced, and optimally expert readers are required for counting new T2 lesions compared with those needed for counting enhancing lesions, although the latter requires careful training and standardization as well. A strategy of determining new lesions by T2 lesion counts rather than enhancing lesions will be more successful in early MS, in which lesions rarely overlap anatomically, and less successful in more advanced relapsing MS, in which confluent and closely spaced T2 lesions make counts of T2 lesions less reliable. For trials in which the scan interval is 6 months or longer, counts of new T2 lesions provide a good index of interval activity, whereas counts of enhancing lesions would provide an index of inflammatory activity only around the time of the MRI scan.

**IMAGING METHODOLOGY FOR ENHANCING LESIONS**

Many MRI acquisition methodologies suited to displaying enhancing lesions are available, and most of these techniques can be readily accomplished (Table 6.1). As described above, the magnetic resonance contrast agents used to assess the blood-brain barrier are gadolinium chelates, which are visualized by MRI in the CNS on the basis of their paramagnetic effect. The gadolinium chelates affect the T1 relaxation time of the innumerable water molecules in their vicinity, shortening it from seconds to several hundred milliseconds, and this provides a mechanism for separating and observing their anatomic

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<td>Minimal cost</td>
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<td>Maximal compliance</td>
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<td>Standard T1-weighted plus magnetization transfer</td>
<td>Increase in number of lesions detected</td>
<td>False-positive lesions (blood flow-induced motion artifacts)</td>
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<td>Need pre-magnetization transfer image</td>
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<td>Variation in technique among magnetic resonance instruments</td>
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<tr>
<td>Standard T1-weighted plus delayed imaging</td>
<td>Increase in number of lesions detected</td>
<td>Increased imaging time (and therefore cost)</td>
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<td>Fewer false-positive vascular enhancements</td>
<td>Edges of lesions may be ill-defined since contrast diffuses outwards</td>
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**Table 6.1 Summary of imaging methodologies for enhancing lesions**
Standard T1-weighted plus triple-dose contrast
Combination of above (optimized protocol)

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<th>Increase in number of lesions detected</th>
<th>Direct purchase cost</th>
<th>Potential for increase in false-positive lesions</th>
<th>Cost</th>
<th>Imaging time</th>
<th>Potential increase in false-positive scans</th>
<th>May not have a meaningful impact on sample size</th>
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distribution. To observe this distribution, images are created with a set of MRI pulse parameters biased towards display of these short T1 relaxation time water molecules (T1-weighted images). Short T1 fractions appear bright or hyperintense relative to other water fractions.\[140\]

For clinical trials, T1-weighted imaging is most commonly accomplished using a classic two-dimensional spin-echo technique with short repetition time and short echo delay time. Imaging is based on slices that are 3 mm or 5 mm thick, without gaps and with a pixel size (plane resolution) of 1 mm×1 mm or less. Good signal-to-noise ratios are achieved using this approach, particularly with increased averaging, since the signal-to-noise ratio in two-dimensional imaging is proportional to the square root of the number of excitations. An alternative method is the use of a three-dimensional T1-weighted acquisition, based on a spoiled gradient echo methodology or magnetization-prepared gradient echoes, both of which allow thinner slices (or, in three-dimensional terminology, partitions).\[141,142\] With a three-dimensional acquisition, partitions are typically 1–2 mm with no gaps, with a good signal-to-noise ratio since signal-to-noise in a three-dimensional acquisition is proportional to the square root number of slices, which is relatively high. An advantage of three-dimensional acquisition is that it allows nearly seamless post hoc image reconstruction in any scan plane, which may help in image evaluation. A disadvantage is the greater transmission of motion-related noise through the image.

Other MRI factors can be introduced into the imaging paradigm to increase the conspicuity of enhancing lesions. One common approach is the use of a magnetization transfer pulse.\[143,144\] Here, an additional radiofrequency pulse, which is offset from the resonance frequency of free water and does not directly affect the free water, is added to the standard magnetic resonance pulse sequence to influence the bound water fraction (i.e. water interacting with protein, lipid, and membranes in general). The effect of this pulse when seen by bound water fractions is a transfer of magnetization to the free water fractions and a subsequent decrease in the measurable water signal, which is most extreme in intact CNS tissue. As a result, areas of disruption to the blood-brain barrier that ‘leak’ and are enriched for gadolinium chelates, will show relatively greater signal intensity than normal tissues and their surrounding tissue-containing lesions. This strategy can be used to increase sensitivity to abnormal contrast enhancement. There are disadvantages to using magnetization transfer pulses as a strategy to increase the detection of enhancing lesions. Because the magnetization transfer pulse causes relatively increased signal in some regions of normal brain (e.g. basal ganglia) and abnormal brain (e.g. chronic lesions), it is critical that the postcontrast images are always compared to precontrast images. In addition, the magnetization transfer images are sensitive to normal
blood pools (intravascular blood) and as a result flow-related ghost artifacts may be strong and may confound interpretation. Magnetization transfer pulse sequences vary between magnetic resonance instruments, more so than conventional sequences, and there is evidence of increased interobserver error using magnetization transfer pulse sequences with, for example, single-dose contrast as compared with conventional imaging combined with triple-dose MR contrast.\[^{145}\] Nevertheless, contrast-enhanced imaging based on magnetization transfer pulses are occasionally used today in MS clinical trials and, with attention to the potential problems, they can be a reasonable trials methodology.

An increased dose of contrast also increases the relative signal intensity of enhancing lesions, since dose and signal are nearly linearly related for normal and abnormal tissues in the brain. Unfortunately, dose and cost are linearly related as well. Triple-dose contrast increases the number of enhancing lesions in relapsing and secondary progressive MS, of the order of 25–75% in most studies. Triple-dose contrast increases lesion contrast, and to a lesser extent the fraction of patients with enhancing lesions.\[^{146,147}\] In primary progressive MS, where lesion detection is generally poor with conventional approaches, triple-dose contrast can be especially beneficial,\[^{148}\] although this has not been so in all studies.\[^{106}\] There is a good safety profile for high-dose (triple-dose) contrast,\[^{149}\] as there is for multiple repeated single doses of MR contrast.\[^{150}\]

A third approach to improving detection of contrast-enhanced MS lesions is the use of delayed imaging after injection. Here, rather than obtaining an image immediately after injection, which is the relatively poor standard adopted from clinical practice, the T1-weighted image acquisition is delayed for 5–6 minutes or longer beyond the completion of the intravenous injection. There is a positive relationship between signal intensity and time for enhancing MS lesions, with signal intensity increasing for as long as 20–60 minutes in many lesions. Apart from the expense associated with increased imaging time, the benefits of long delays may be offset by blurring of the edges of lesions caused by diffusion of contrast agents away from lesions.

Combined approaches to optimizing enhancing lesion counts

It is clear that higher doses of magnetic resonance contrast, magnetization transfer pulses, or delayed imaging may all individually increase the yield of contrast-enhancing lesions in clinical trials. While not necessarily fully additive, in combination these techniques consistently improve lesion conspicuity and increase the number of enhancing lesions and the percentage of patients with enhancing lesions.\[^{143,151}\] Recently, Silver et al. evaluated conventional imaging with a standard magnetic resonance contrast dose compared with a modified protocol based on delayed imaging (40 minutes), the addition of a magnetization transfer pulse, and triple-dose contrast.\[^{143}\] In a study of eight patients with relapsing MS and eight patients with secondary progressive MS, the modified protocol increased the total number of brain lesions by a factor of 2.17 and the number of new enhancing lesions by a factor of 1.6. However, there was only a 7% increase in the proportion of active scans. Enhancing spinal cord lesions were observed in 22% of cases with the modified protocol, compared with 16% with the standard protocol. Despite the increased yield by these methodologies, the effect on sample size in clinical trials may be inconsequential. Silver et al. found with their modified, optimized protocol that, although the sample size could be decreased in a cross-over study, the benefit was not apparent for
a parallel-group design.\textsuperscript{143} Finally, any method that increases lesion yield may increase the false-positive rate, particularly for a less experienced imager. This problem is mitigated when using delayed imaging, because enhancement of vascular structures is less problematic.

**Accuracy of counts of enhancing lesions**

One of the major benefits of counts of enhancing lesions in MS clinical trials is the ease with which these counts can be made by an experienced imager. However, few studies have addressed the issues of accuracy, inter- and intraobserver error, and reproducibility over time. In one detailed study by Barkhof et al., there was 100\% agreement between observers for scans with no activity.\textsuperscript{152} For scans with one or more lesions, there was agreement as to presence of lesions in 96\% of the observations. Agreement on the number of lesions decreased with increasing numbers of lesions, however, the agreement rate was 80\% for scans with five lesions or fewer.

Enhancing lesion volume is also used as a trial measure. In practice, enhancing lesion number and volume are highly correlated but, in theory, treatment may have a differential effect on these two outcomes. Enhancing lesion volume can be determined by relatively simple image processing methodologies, which can be semiautomated.\textsuperscript{56,57,153} As for T2 lesion volume measures, training and predetermined rules are important.\textsuperscript{154}

**Counts of enhancing lesions based on imaging of the spinal cord and optic nerve**

The enhancement patterns in the spinal cord are similar to those in the brain, the key difference being a reduced number of lesions compared with the brain, proportional to the volume of these structures.\textsuperscript{143,155,156} Imaging the spinal cord for enhancing lesions is complicated by its small size and by artifacts induced by adjacent cerebrospinal fluid and cardiac or respiratory motion transmitted over the cord. The approaches that have been applied to brain imaging to increase the yield of enhancing lesions also increase the yield in cord imaging.\textsuperscript{143,157} However, the small gain derived from adding spinal cord imaging to MS trials may not justify its inclusion, even with optimized methodology, because there is no significant impact on sample size when lesion number is the outcome.

Optic nerve imaging is useful for understanding the pathophysiology of MS and for correlative electrophysiologic, clinical, and imaging studies, but it has not been used in a formal trial setting.\textsuperscript{158} The enhancement pattern in the optic nerve is similar to that in the brain and spinal cord, although enhancement may affect the full thickness of the nerve or be more perineural than central.\textsuperscript{159}

**EFFECT OF TREATMENT ON ENHANCING LESIONS**

The results of clinical trials with multiple pharmaceutical agents are discussed in detail elsewhere in this book. The use of enhancing lesions, apart from being relatively simple, reproducible measures of disease activity, has become the standard in phase II and phase III trials, in part as a result of the success of several interventions that include anti-
inflammatory properties. While the list of agents showing this effect is increasing, the next generation of neuroprotective agents may have less of an effect on the inflammatory aspects of the disease, and their effect on enhancing lesions may be inconsequential in some cases despite important impact downstream of the inflammatory events in MS.

The three major interventions to date with predominantly anti-inflammatory effects, the so-called ABC drugs, have been the subject of extensive study, yet their specific mechanisms of action (including their interaction at the level of the blood-brain barrier) are not well understood. The beta-interferon products show a consistent effect in decreasing enhancing lesion frequency and the percentage of positive scans, evident in monthly MRI studies, and effects that can be seen within weeks after initiating therapy. The biological wash-out period has been evaluated in a pilot study using monthly MRI scans, and it appears to be on the order of about 6–10 months, since baseline MRI activity was restored over this interval in a study of two patients using interferon beta-1b. Suggestions of wash-out effects have also been seen in phase II studies of alpha interferon. Glatiramer acetate also suppresses enhancing lesions, but with a different pattern than that of the beta interferons. The effect demonstrated using monthly MRI is delayed for several months, then increases to maximum benefit after an interval of about 4–6 months. The beta interferon products are believed to influence the integrity of the blood-brain barrier and indirectly enhancing lesions by way of mechanisms that include peripheral down-regulation of T-cell activation, down-regulation of adhesion molecule expression on endothelial cells, and inhibition of proinflammatory cytokine and matrix metalloproteinase secretion. Many of these effects may be similar to those of corticosteroids.

Other immune-suppressing agents may have strong and sustained effects on enhancing lesions, and counts of enhancing lesions provide a convenient measure of the magnitude and duration of effect. A note of caution. In theory, with profound immune cell suppression it is possible that the typical imaging features of enhancement may be masked, despite continued injury. Consequently, reliance on enhancing lesion rates alone as a measure of efficacy may fail to provide a reliable measure of disease activity.

The corticosteroids penetrate the blood-brain barrier and achieve high concentrations in the cerebrospinal fluid within about 6 hours. The response to corticosteroids alone may occur within minutes to hours of administration. In one study, the blood-brain barrier was shown to be restored within 8 hours of treatment. Consequently, the interval between corticosteroid administration and acquisition of an enhanced MRI scan is an important factor in MS trials and one that can influence results. The effects of corticosteroids on enhancing lesions can be sustained over weeks and months although the effect on individual lesions may be transient, over days. Interestingly, while corticosteroids either alone or in combination with other therapy have transiently decreased enhancing lesions, they do not prevent some of the natural sequelae of enhancing lesions such as their T2 footprints. However, it can be shown using magnetization transfer ratio measurements that corticosteroids reduce tissue damage and promote lesion recovery. As with the beta interferon preparations, corticosteroids may close the blood-brain barrier by down-regulating adhesion molecule expression and inhibiting proinflammatory cytokine and matrix metalloproteinase secretion.
THE FUTURE
Counts of enhancing lesions are now well-established, verified outcome measures for MS clinical trials. Their success has been in part a fortuitous result of a prominent impact on enhancement by established MS treatments, trials of which have demonstrated that counts of enhancing lesions can provide direct, quantitative, and objective evidence for pharmacologic reduction in the inflammatory activity in the CNS. Enhancing lesion measures are likely to remain important in screening studies and definitive phase III trials, and they may become standard safety measures in phase I and phase II trials. It is important to recall, however, that absence of a significant effect on enhancement does not provide evidence that a pharmacologic intervention is ineffective in MS. This scenario would be anticipated in trials of neuroprotective agents, for example. Equally important, a significant effect on enhancement alone does not establish efficacy, although to date discordance between effect on enhancing lesions and other indicators of benefit have been rare. In the future, more sophisticated imaging techniques that provide improved imaging of the inflammatory processes in MS may prove complementary and will provide incremental information relative to the simple enhanced lesion methodologies described here. In order for us to benefit from these emerging technologies, studies are needed that will address specific pathophysiologic mechanisms that underlie enhancement, the details of the blood-brain barrier at cellular and molecular levels, and factors bridging these events that link the inflammatory enhancing lesion and the ultimate clinical outcome.

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Measures of magnetization transfer in multiple sclerosis

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INTRODUCTION

Although conventional T2-weighted magnetic resonance imaging (MRI) is very sensitive for the detection of multiple sclerosis (MS) lesions, it is not without relevant limitations. First, MRI lacks specificity with regard to the heterogeneous pathological substrates of individual lesions\textsuperscript{[1]} and, as a consequence, does not allow the characterization and quantification of tissue damage—specifically, edema, inflammation, demyelination, remyelination, gliosis, and axonal loss, all lead to a similar appearance of hyperintensity on T2-weighted images.\textsuperscript{[2]} Secondly, T2-weighted images do not delineate tissue damage in the gray matter and in the normal-appearing white matter (NAWM), which usually represents a large portion of the brain tissue from MS patients and which is known to be damaged in MS.\textsuperscript{[3]}

These limitations are only partially overcome by the use of postcontrast T1-weighted scans. Gadolinium-enhanced T1-weighted images allow active lesions to be distinguished from inactive lesions\textsuperscript{[4,5]} since enhancement occurs as a result of increased blood-brain barrier permeability\textsuperscript{[6]} and corresponds to areas with ongoing inflammation.\textsuperscript{[7]} However, the activity of the lesions as demonstrated on postcontrast T1-weighted imaging still does not provide information on tissue damage. Chronically hypointense areas on T1-weighted images correspond to areas where severe tissue disruption has occurred,\textsuperscript{[8]} and their extent is correlated with the clinical severity of the disease and its evolution over time.\textsuperscript{[9,10]} Even so, the extent of T1-hypointense lesions may not correspond to the severity of intrinsic pathology in the lesions and provides no information about damage to the NAWM and the gray matter. Finally, the definition of what constitutes a hypointense area is highly subjective.

Recently, several non-conventional MRI techniques have been developed and applied in efforts to improve our understanding of the evolution of MS.\textsuperscript{[11]} These techniques, including magnetization transfer (MT)-MRI, may provide quantitative information about MS microscopic and macroscopic lesion burdens with a higher pathological specificity for the most destructive aspects of MS (i.e. severe demyelination and axonal loss) than conventional MRI. This chapter outlines the major contributions made by the application of MT-MRI in the assessment of patients with MS.
PHYISICAL BASIS OF MT-MRI

All MRI techniques exploit the enhanced absorption of energy experienced by certain nuclei when exposed to radiofrequency energy at a particular (resonance) frequency. The rapid success of MRI in clinical use is based on the earlier observation that the recovery to equilibrium of such ‘excited’ spins can be described by two relaxation times, T1 and T2.[12] Thus, a tissue of, for example, water protons being investigated with MRI can be characterized in terms of nuclear spin density, T1 and T2, and images can be produced that reflect primarily one or the other of these variables. Such conventional MRI techniques incorporate the assumption that a region of tissue may be fully described using only those three variables, and thus, for example, a region of hyperintensity on T2-weighted imaging may be attributed to relatively longer T2. Since conventional MRI does not typically offer absolute quantitation of intensity, a region may be described as hyperintense without any conclusions being drawn about the magnitude of the change in T2 that was responsible for the observation.

MT techniques in MRI are based on an assumption that more than one relaxation time may influence the characteristics of a region seen on MRI. As such, tissue is treated as a more complicated structure that includes non-water protons associated with proteins and other large molecules. These non-water protons cannot be detected directly, but MT theory holds that they may be probed via their effects on the water protons. This hypothesis, confirmed in part by experimental work, forms the basis of current MT-MRI techniques.

The premise of MT-MRI is that proton spins, having well-known relaxation properties, can exchange spin magnetization with protons of much larger molecules, such as myelin or other proteins. The consequence of these exchange processes in MRI is that observed proton relaxation times may reflect the characteristics of the macromolecular environment. Additionally, MRI acquisition techniques have been devised to provide contrast that reflects the magnitude of the transfer effect. In these studies the exchange process is relied on to transfer magnetic saturation into the water proton spins, reducing or destroying the signal from affected spins. Quantification in these MT-MRI studies arises from the ability to compare images that reflect the exchange of magnetization with those obtained as controls. Thus, MT techniques can provide quantitative information, a potential advantage over conventional methodology. More importantly, MT analysis may represent a window into the structure of tissue.

A two-site exchange model for MT

In biological tissue, water protons constitute the bulk of nuclei visible on MRI. These water protons are characterized by relatively long T1 and T2 values. The relaxation environment for protons attached to macromolecules is, by comparison, more solid-like, with correspondingly short transverse relaxation (T2) times. Direct observation of these spins is not currently feasible since the signal decay is too fast for observation and the frequency of the signal is very close to that of the overwhelmingly larger water signal. A two-site model demonstrating the exchange possibilities and characteristic variables is
shown in Fig. 7.1. It is assumed that each compartment has associated with it intrinsic relaxation times T1 and T2. These intrinsic relaxation times should be distinguished from observed relaxation times that are measured with standard techniques. With the addition of a rate constant $k$ and a molecular ratio $f$, the exchange characteristics of the two-site system can be completely described using six variables. More complex models are possible, but clinical applications to date have not required the incorporation of more than two sites.

**Selective saturation**

A fundamental requirement for detecting the effects of one type of spin (macromolecular spin) as opposed to those of another (water spin) is the ability to perform a magnetic resonance study that is selective with respect to the spin of interest. Saturation of spin magnetization is perhaps the most straightforward method for this purpose, and it was first used in the ‘double resonance’ experiments of Forsen and Hoffman\textsuperscript{[13–15]} using a system of two chemically exchanging substances where the resonance frequencies differed in the two spin systems. Briefly, saturating radiofrequency excitation was applied at each spin resonance in turn while the magnetization of

![Diagram](image)

**Fig. 7.1** A two-site model for MT, demonstrating the six variables that are required for full characterization. The free spin environment corresponds to water, and the bound environment corresponds to large molecules, symbolized as a proton attached to the rest (R) of the molecule.
the opposite spin resonance was measured. The data obtained allowed the full characterization of the system. Subsequent MT-MRI studies performed in vivo were based on selective inversion of the water spins, dubbed ‘selective hydration inversion’. The first MT images used continuous off-resonance saturation, the efficacy of which can be demonstrated using Bloch’s equations. Modern techniques exploiting MT may use either inversion or, more frequently, saturation of the macromolecular spins with pulsed off-resonance or on-resonance saturation methods. As in the pioneering methods cited above, two studies are performed and compared in order to associate quantitative information with each point or region of the image. This information is typically a number that represents the amount of saturation effect measured in the water protons, often expressed as the MT ratio (MTR).

PATHOLOGICAL BASIS OF MT-MRI CHANGES IN MS

As discussed above, a low MTR indicates a reduced capacity of the molecules in the brain tissue matrix to exchange magnetization with the surrounding (MRI-visible) water molecules. Although in MS lesions this may be caused either by a reduction in the integrity of macromolecular matrix reflecting damage to the myelin or to the axonal membrane or by a dilution of the macromolecules caused by inflammatory edema, studies with animal models reported that MTR reduces only slightly with edema but more strongly with severe demyelination and axonal loss. A marked reduction in MTR has been found in a primate model of lysolecithine-induced demyelination, in a feline model of wallerian degeneration, and in regions with pathologically proven axonal damage following experimental brain trauma in pigs. Markedly reduced MTR values are also measured in the ‘pure’ demyelinating lesions of patients with progressive multifocal leukoencephalopathy or central pontine myelinolysis and in the affected optic nerves of patients with optic neuritis, where this was correlated with an increased latency of the visual evoked potentials, which is in turn correlated to the extent and severity of demyelination. Follow-up studies in primates affected by relapsing experimental allergic encephalomyelitis demonstrated that, after MTR reduction in the acute phase of lesion development, it is possible to observe recoveries of MTR. This MTR temporal profile might be correlated with demyelination and remyelination during lesion development and resolution. The influence of remyelination on MTR values is confirmed by a study of the corpus callosum of rats with lysophosphatidylcholine-induced demyelination, which is known to remyelinate spontaneously. In this study, the recovery of MTR values after their initial decrease was significantly associated with an increasing number of remyelinating axons. The relationship between reduced MTR values and axonal loss is suggested by the strong correlation found in MS lesions between MTR and N-acetylaspartate (NAA) levels (NAA being an MR spectroscopy marker of axonal dysfunction), signal intensity on T1-weighted images, and mean diffusivity. An association between MTR and axonal density is also indirectly confirmed by the demonstration of markedly reduced MTR values in the optic nerves of patients with Leber’s hereditary optic neuropathy. The most compelling evidence that marked MTR reduction corresponds to severe tissue damage comes from a recent post mortem study of lesions and NAWM from
patients with MS. In this study, strong correlations were found between MTR and the percentage of residual axons (Figs 7.2 and 7.3) and the degree of demyelination (Figs 7.4 and 7.5).

ANALYSIS OF MT-MR IMAGES

The first step in the quantitative analysis of MT-MRI scans is the creation of calculated MT images or MTR maps, which are derived from two MRI scans acquired without and with an off-resonance saturation pulse. MTR maps are derived, on a pixel-by-pixel basis, according to the following equation:

\[
MTR = (1 - \frac{M_s}{M_0}) \times 100\%
\]

where \(M_0\) is the intensity of a given pixel without the saturation pulse and \(M_s\) is the intensity of the same pixel when the saturation pulse is applied (Fig. 7.6).

Thus, the MTR represents the fraction of signal loss that is due to the complete or partial

![Fig. 7.2 Scatterplot showing the correlation between MTR and axonal density in MS lesions and NA WM. Courtesy of Dr JH van Waesberghe and Dr F Barkhof, Dutch MR-MS Centre and Department of Radiology, Vu Medical Centre, Amsterdam, The Netherlands.](image-url)
**Fig. 7.3** An illustrative case of three MS lesions (arrows) showing that the MTR is lower when the density of residual axons is reduced. Courtesy of Dr JH vanWaesberghe and Dr F Barkhof.
Fig. 7.4 Medians and percentile distributions of the MTR values of MS lesions and NAWM according to their degree of inflammatory and demyelinating activity (on the x axis, the inflammatory and demyelinating activity has been scored from 0 to 4, with 0 representing the lowest and 4 the highest activity score). The rectangles represent the 75th, 50th, and 25th percentiles; the upper and lower bars represent the 90th and 10th percentiles, respectively. The MTR values decrease with increasing severity of inflammatory and demyelinating activity. Courtesy of Dr JH van Waesberghe and Dr F Barkhof.
**Fig. 7.5** An illustrative case of one MS lesion (arrow) showing that its MTR and myelin density are both very low. Courtesy of Dr JH van Waesberghe and Dr F Barkhof.

**Fig. 7.6** Axial gradient-echo images of the brain (a) without and (b) with the MT pulse applied. (c) The corresponding MTR map obtained from the two previous images.
Fig. 7.7 Axial slice from an MTR calculated set of images (MTR map) from a patient with MS, showing MTR values of different brain tissues. MS lesions have highly variable MTR values.

saturation of the bound proton pool, and ranges from near zero in the cerebrospinal fluid to about 50% in tissue that contains a high proportion of bound water molecules (Fig. 7.7). MS lesions, which usually have a lower MTR than NAWM,\cite{3} appear as areas of hypointensity on MTR maps (see Fig. 7.7). The degree of hypointensity (i.e. the degree of MTR decrease) is related to the amount of tissue destruction in the examined area.

Several approaches can be adopted to analyse MS-related abnormalities on MTR maps:

1 Region-of-interest analysis of specific tissues. This approach allows the study of individual MS lesions and discrete areas of the NAWM and gray matter.
2 Analysis of the average MTR of T2-visible lesions. This approach enables information to be obtained about the severity of tissue damage in the overall lesion population. The average lesion MTR can be calculated as follows:
\[ \text{Average lesion MTR} = \frac{\sum A_i \times \text{MTR}_i}{\sum A_i}, \]

where \( A_i \) is the area of lesion \( i \), and \( \text{MTR}_i \) is the average MTR within that lesion. Thus the contribution that each lesion makes to the average is weighted by the size of the lesion.

3 Measurement of the load of the lesions visible as hypointense areas on the MTR maps. This approach provides information about the extent of lesions with more severe tissue damage.

4 Contour plotting of MTR. This approach involves displaying the MTR values as an overlay on MRIs. In this way, it is possible to detect gradients and boundaries of abnormal MTR that are too subtle to be detected by conventional reading of the MTR maps (Fig. 7.8).

5 Histogram analysis of large portions of brain tissue. This strategy encompasses both microscopic and macroscopic lesion burdens in the examined tissue. The first step in the creation of the histogram is a preliminary manual or semiautomated image segmentation aimed at excluding all the non-cerebral tissues. Secondly, to reduce the effects of image noise and also cerebrospinal fluid signal, all the pixels with very low MTR (i.e. from zero to 5–10%) are also excluded from the analysis. Then, the data set of MTR values is displayed as a histogram, which is usually normalized to the total number of brain pixels to allow comparisons of histograms from subjects with different brain volumes. For each histogram, several parameters can be calculated. These include the height and position of the histogram peak (i.e. the most common MTR value in the brain), the average MTR, and the MTR corresponding to the 25th, 50th and 75th percentiles of the histogram (referred to as MTR\(_{25}\), MTR\(_{50}\) and MTR\(_{75}\)), which indicate the MTR at which the integral of the histogram is 25%, 50% and 75% of the total, respectively (Fig. 7.9). MTR histograms can be obtained for the whole brain or for specific regions (e.g. frontal lobe, cerebellum, and brainstem), which can be segmented according to standard neuroanatomical references. MTR histogram analysis is a highly automated technique and, as a consequence, intrarater, interrater and scan-rescan variability of MTR histogram-derived measurements are low.
Fig. 7.8 (a) An example of an MT image in MS with focal lesions in the periventricular white matter. (b) An MT contour plot demonstrating the gradation of MTR values from the low MTR center of the large focal lesion (black arrow) to the NAWM. The contours are drawn at 2, 4, and 6 standard deviations (SD) below normal values as obtained from age-matched control subjects. A smaller lesion on the contralateral side is shown to be asymmetrical with regard to MTR. (c) In another patient, a small focal MS lesion is demonstrated to be 6 SD below normal (white arrow) but also to be extended into the NAWM by MT contours at 2 SD below normal.
Fig. 7.9 Average MTR histogram of the brain from 20 healthy controls, showing some of the metrics that can be derived and that are generally used in the study of MS.

**USE OF MT-MRI TO ASSESS TISSUE DAMAGE WITHIN MACROSCOPIC MS WHITE MATTER LESIONS**

Although conventional T2-weighted scans play a major role in the assessment of MS lesion burden,\[1,43,44\] cross-sectional\[45\] and longitudinal studies\[46,47\] have found that the magnitude of the correlation between clinical disability and brain T2-weighted lesion load is only modest. The paucity of such a correlation is probably due, at least partially, to the extremely variable extent of the intrinsic tissue damage of MS white matter lesions visible on conventional MRI scans. Using MTR, it is possible to grade the extent of intrinsic tissue damage of individual MS lesions and, as a consequence, of aggregates of MS lesions. Monitoring individual lesion evolution may be relevant for the understanding of MS pathophysiology and also as a new approach for assessing treatment efficacy. In preliminary trials, this approach might indeed give information in relatively short periods of time about the efficacy of experimental treatment in preventing severe tissue destruction.

Two approaches have been used to obtain estimates of the severity of intrinsic tissue damage of aggregates of macroscopic white matter lesions from individual MS patients or groups of MS patients—measurement of the load of the lesions visible as hypointense areas on the MTR maps (MT-MRI lesion load) and the analysis of the average MTR of T2-visible lesions (average lesion MTR).
MT-MRI changes in active MS lesions

In MS, lesions that enhance on MRI scans after gadolinium injection represent areas with a damaged blood-brain barrier and ongoing inflammation,[6,7] and virtually all ‘active’ MS lesions enhance during the early phases of their formation.[48,49] However, ‘active’ MS lesions may have different patterns (homogeneous or ring-like) or different durations of enhancement,[6] or they may enhance only when highly sensitive approaches, such as the administration of a triple dose of gadolinium, are used.[50] This enhancement variability suggests that the pathological nature of MS enhancing lesions and the severity of the associated changes in the inflamed tissue may vary widely. MT-MRI studies of individual enhancing lesions confirm this perception. Homogeneously enhancing lesions, which may represent new active lesions, have significantly higher MTR values than ring-enhancing lesions,[51–54] which may represent old, reactivated lesions. In the latter type of lesion, the central portions, which probably represent the most damaged tissue, have the lowest MTR values.[54] A recent longitudinal study also confirmed that ring-like enhancing lesions had the lowest MTR, both at baseline and at follow-up, after enhancement ceased.[55]

The duration of enhancement is also associated with different degrees of MTR changes in new MS lesions: lesions enhancing on at least two consecutive monthly scans have lower MTR than those enhancing on a single scan.[56] This indicates that a longer enhancement in MS lesions may be related to more severe tissue damage. The fact that a less damaged blood-brain barrier is associated with milder tissue damage is also indicated by the demonstration that new lesions that enhance after the injection of a standard dose of gadolinium have significantly lower MTR values than those enhancing only after a triple dose[57] and that large enhancing lesions tend to have greater MTR reductions than smaller lesions.[51]

Using MT-MRI and variable frequencies of scanning, several authors have investigated the structural changes of new enhancing MS lesions for periods of time ranging from 3 months to 36 months.[51,55,57–64] The results of all these studies consistently show that, on average, MTR drops dramatically when the lesions start to enhance and may show a partial or complete recovery in the subsequent 1–6 months. However, only three of these studies[55,62,64] evaluated the evolution of individual lesions in an attempt to define the prevalence of lesions whose MTR values remain stable, improve, or worsen during the follow-up period. In a study of 11 patients with monthly MT-MRI scans, van Waesberghe et al. showed that 56 out of 126 enhancing lesions (44%) have a marked MTR increase and that 6 out of 126 lesions (5%) had a marked MTR decrease over a 6-month follow-up period, although the major changes were seen in the first 2 months.[55] The remaining 64 lesions (i.e. the 51% of the enhancing lesions studied) had either a modest increase or decrease in the MTR. In a study of 15 enhancing lesions from four patients followed for 9–12 months with MT-MRI scans every month or every three months, Dousset et al. showed that five (33%) lesions had a recovery of their MTR values which was close to the MTR of NAWM, eight (54%) had an incomplete MTR recovery and two (13%) had a continuous worsening of their MTR.[62] Filippi et al. evaluated the prevalence and evolution of early MTR changes in 42 individual enhancing lesions from 10 patients with early relapsing-remitting MS, followed with monthly MRI...
scans on four separate occasions. The lesion MTR on each scanning session was normalized to the corresponding NAWM-MTR. At the end of the follow-up period, 16 lesions (38%) were classified as ‘increasing MTR’ lesions, 21 (50%) as ‘stable MTR’ lesions, and five (12%) as ‘decreasing MTR’ lesions. The classification of the lesions after the first month of follow-up strongly predicted the classification at the end of the follow-up period. This suggests that only a minority of the enhancing lesions from patients with early relapsing-remitting MS have progressive structural damage soon after their formation. New lesions that enhance only after the injection of a triple dose of gadolinium and that are known to have significantly a higher MTR than those that enhance on a standard dose at the time of their appearance have a similar short-term recovery profile. However, at each time point of the follow-up, MTR in triple-dose-enhancing lesions is significantly higher than in standard dose lesions. This again confirms the relative mildness of tissue damage in those lesions with less severe disruption to the blood-brain barrier.

The most likely pathological mechanisms underlying the short-term changes in the MTR of newly enhancing MS lesions might be demyelination and remyelination. Several lines of evidence indicate that demyelination, either alone or associated with axonal loss, produces a marked reduction in MTR. The relatively good preservation of axons that is usual in acute MS lesions and the rapid and marked increase in the MTR are consistent with demyelination and remyelination but not with axonal loss. Nevertheless, edema and its subsequent resolution may also give rise to the observed pattern of MTR behavior, owing to the diluting effect of extra-tissue water. However, it seems unlikely that edema alone is sufficient to explain these findings, since previous studies in humans and experimental animals showed that edema in the absence of demyelination results in only modest MTR reductions. Currently, the effect of gliosis on MT values is not known. However, it seems unlikely that gliosis could play a major role over short periods of time, as is also suggested by animal studies of remyelinating lesions. Regardless of the underlying pathological changes, short-term MTR changes in newly formed MS lesions can be detected by image combination methods using serial MT-MRI scans as areas of ‘pseudo-enhancement’, thus providing information about the acute events in MS that is usually derived from postcontrast T1-weighted images.

These results suggest that the balance between damaging and reparative mechanisms may be highly variable during the early phases of MS lesion formation. Different proportions of lesions with different degrees of structural changes may, therefore, contribute to the evolution of the disease and may explain why previous studies found poor correlations between the number of enhancing lesions and the long-term evolution of disease. At present, however, there are few data supporting such a concept. In a patient at presentation with an isolated lesion of the type seen in MS, it has been shown that there is a strict relationship between the MTR recovery in this newly formed lesion located in the internal capsule and the corresponding recovery of the contralateral sensory-motor deficit. A recent 3-year follow-up study showed that newly enhancing lesions from patients with secondary progressive MS had a lower MTR at the time of their appearance and presented a more severe and significant MTR reduction during the follow-up period than those in patients with relapsing-remitting MS.
The vast majority of enhancing MS lesions leave T2-visible abnormalities, and a significant proportion of them may appear hypointense on T1-weighted scans. MTR values for MS lesions that are visible on T2-weighted scans are significantly lower than MTR values for NAWM, for lesions in elderly patients or in patients with small-vessel disease, or for systemic immune-mediated diseases (including systemic lupus erythematosus, Wegener’s granulomatosis, Behçet’s disease, and antiphospholipid antibody syndrome), HIV encephalitis, central nervous system tuberculosis, traumatic

**Fig. 7.10** (a) Proton-density weighted image showing several MS lesions. (b) Corresponding postcontrast T1-weighted image showing that one of these lesions is enhancing. (c) MTR image obtained by an image combination method using follow-up MT-MRI scans (without gadolinium administration), showing that the enhancing lesion visible in (b) can be detected as an area of ‘pseudoenhancement’.
Fig. 7.11 Mean MTR values of newly enhancing lesions from patients with relapsing-remitting MS (gray bars) and secondary progressive MS (black bars) on baseline and follow-up scans. A significant progressive reduction of MTR values during the follow-up was observed for newly enhancing lesions from patients with secondary progressive MS (p < 0.0005) but not for those from patients with relapsing-remitting MS.

Brain injury,\textsuperscript{[39]} and migraine,\textsuperscript{[77]} In contrast, reductions in MTR values with a magnitude comparable to that seen in MS lesions have been found in white matter lesions of patients with vascular dementia,\textsuperscript{[78]} amyotrophic lateral sclerosis,\textsuperscript{[79]} progressive multifocal leukoencephalopathy,\textsuperscript{[26,27]} central pontine myelinolysis,\textsuperscript{[28]} cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy,\textsuperscript{[80]} Leber’s hereditary optic neuropathy,\textsuperscript{[36]} and acute disseminated encephalomyelitis.\textsuperscript{[81]} Nevertheless, regardless of the average lesion MTR values found in all these conditions, the lesions of MS tend to have a greater variability in their MTR values (see Fig. 7.7), perhaps as a consequence of their more marked temporal and pathological heterogeneity.

Lower MTR values have been reported in hypointense lesions than in lesions that are isointense to NAWM on T1-weighted scans,\textsuperscript{[53–55]} and the MTR has been found to be inversely correlated with the degree of hypointensity.\textsuperscript{[53,82]} In a longitudinal study with monthly MT-MRI and T1-weighted scans, van Waesberghe et al. found that MS lesions that changed from hypointense to isointense when gadolinium enhancement ceased also
had a significant increase in MTR, whereas a strongly decreased MTR at the time of initial enhancement was predictive of a persistent T1-weighted hypointensity and lower MTR after 6 months. On the basis of these results and of a post mortem study, it may be argued that ‘fixed’ MS lesions with a lower MTR are expressions of more severe demyelination and axonal loss.

Decreased MTR values have also been found for areas of NAWM that are adjacent to focal T2-weighted MS lesions (see Fig. 7.8). MTR progressively increases with distance from MS lesions to the cortical gray matter, and the MTR was lower for patients with more disabling MS courses. These latter findings suggest that the actual size of MS lesions is greater than that visible on T2-weighted images and that the demyelinating ‘penumbra’ detected by MT-MRI might be relevant in determining disability.

**Use of MT-MRI to assess intrinsic tissue damage in aggregates of macroscopic MS lesions**

*MT-MRI lesion load*

With this approach, the total volume of tissue occupied by lesions that appear hypointense on MTR maps is measured. Several studies have shown that MT-MRI, T2-, and T1-weighted lesion loads differ considerably, and the measurement reproducibilities also differ. This is likely to be due to two main technical limitations of this approach. First, the identification of MS lesions on MT-MRI scans is subjective, albeit confirmed by the presence of corresponding abnormalities on T2-weighted images. Second, calculated MTR images have a poor contrast-to-noise ratio (CNR) and MS lesions with a low MTR may show varying degrees of hypointensity, whereas several areas of white matter that are isointense on T2-weighted images also have reduced MTR and, therefore, look relatively hypointense on MT-MRI scans. A ‘conservative’ approach leads to an MT-MRI lesion load that is lower than the corresponding T2-weighted lesion load, with a similar measurement repeatability. On the other hand, the inclusion of diffuse white matter abnormalities extending beyond the borders of focal lesions weakens the pathological specificity of MT-MRI findings, leading to an MT-MRI lesion load that is higher than the T2-weighted lesion load and also to poorer measurement reproducibility.

On the basis of these studies, the volume of hypointense lesions on MT-MRI scans would seem not to be a reliable measure of lesion burden in MS. The limitations of MT-MRI lesion load as an outcome measure in MS are reinforced by its modest correlations with clinical disability, which are similar to or even lower than those for T2-weighted lesion load.

*Average lesion MTR*

The analysis of average lesion MTR requires several postprocessing steps, including the preliminary identification of MS lesions on T2-weighted scans, the coregistration of T2-weighted and MTR scans, and the superimposition of T2-visible lesion outlines on to the coregistered MTR scans. Compared with the measurement of the MT-MRI lesion load, this approach has two major advantages. First, it bases the identification of lesions on T2-
weighted scans, which are characterized by a much better CNR than calculated MTR images. Second, it enables us to obtain a quantitative estimate (weighted by the size of individual lesions) of intrinsic tissue damage in the whole of the macroscopically diseased white matter. The suggestion that average lesion MTR may give additional information on MS tissue damage to those provided by other MRI measures of disease burden is strengthened by the weak correlations reported between average lesion MTR and lesion load or brain volume. This concept is also supported by the finding of moderate correlations between average lesion MTR and other measures of intrinsic lesion damage derived from diffusion tensor MRI and MRS, even though these correlations are stronger than those with MRI measures of macroscopic MS disease burden.

Even though the average lesion MTR has been found to be the best discriminant between patients with MS and those with central nervous system symptoms or signs of systemic immunemediated disorders, independently of the burden of MRI-visible lesions, the correlation between average lesion MTR and the clinical manifestations of MS are somewhat disappointing. Patients with cognitive impairment have a significantly lower average lesion MTR than those without, but average lesion MTR was found to explain only 35% of the total variation in neuropsychological test performance. Similar average lesion MTR values have been found in patients with secondary progressive and primary progressive MS, matched for the degree of disability. Consistent with their clinical evolution, patients with secondary progressive MS have a faster decline of their average MTR values than all the other clinical phenotypes of the disease. Average lesion MTR has been found to be lower in patients with relapsing-remitting MS than it is in patients presenting with clinically isolated syndromes suggestive of MS, but in the latter group of patients it does not predict subsequent disease evolution. Also, average lesion MTR was not found to differ significantly between patients with relapsing-remitting MS and those with benign MS or secondary progressive MS, or between patients with and without fatigue. The only partial correlation found between the degree of intrinsic lesion damage, measured using average lesion MTR, and the clinical manifestations of MS might be due, on the one hand, to the variable extent of tissue damage outside T2-visible lesions and, on the other hand, to the fact that intrinsic lesion damage can induce adaptive cortical changes (Fig. 7.12), which in turn have the potential to limit the clinical consequences of damage to subcortical white matter.

**USE OF MT-MRI TO ASSESS DAMAGE OF MS TISSUES THAT APPEAR NORMAL ON CONVENTIONAL MRI SCANS**

There is increasing evidence that irreversible tissue loss can occur in tissues that appear normal on conventional MRI scans, tissues that represent a large portion of the overall brain tissue even in those patients with high T2 lesion volumes. MTR analysis has been extensively used to achieve reliable in vivo estimates of the extent of tissue damage occurring outside T2-visible lesions in an attempt to increase our understanding of the mechanisms that lead to the progressive accumulation of irreversible disability in MS.
**NAWM and normal-appearing brain tissue**

Post mortem studies have shown that abnormalities can be detected in the NAWM from patients with MS.\textsuperscript{[104,105]} These abnormalities include diffuse astrocytic hyperplasia, patchy edema, and perivascular cellular infiltration. In addition, Arstila et al. described abnormally thin myelin in biopsies of NAWM of MS patients,\textsuperscript{[106]} and two recent post mortem studies also detected signs of axonal damage in MS NAWM.\textsuperscript{[102,103]} Such pathological abnormalities modify the relative proportions of mobile and immobile protons of the diseased tissue; therefore, it is not surprising that MT-MRI is able to show microscopic damage in the NAWM, which is not detected by conventional imaging.\textsuperscript{[11,69,70,72]}

Variable degrees of NAWM changes may precede new lesion formation in MS.\textsuperscript{[58,59,107]} Filippi et al. showed significant MTR reduction in the areas of NAWM that were subsequently involved by newly enhancing lesions compared with those that were not.\textsuperscript{[58]} These changes were detectable 3 months before the appearance of the lesions and

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**Fig. 7.12** (a) Relative cortical activation in right-handed relapsing-remitting MS patients during a simple motor task with their clinically unimpaired right hand compared with matched healthy volunteers. (b) Correlation between relative activation of the contralateral primary somatomotor cortex and average lesion MTR.
tended to become more evident on scans obtained closer to those where enhancement occurred. The degree of these changes was variable. The MTR variability was relatively large in areas of NAWM that subsequently enhanced compared with the very small variations seen in the white matter from controls or in the NAWM outside areas of future enhancement. These data have been confirmed by other studies using MT-MRI\textsuperscript{[59,107]} or diffusion-weighted MRI.\textsuperscript{[108,109]} Only one study did not confirm such observations.\textsuperscript{[51]} This study was, however, conducted in only three patients with heterogeneous disease courses. There are several possible pathological substrates that may contribute to the changes seen in NAWM before the appearance of new MS lesions; these substrates are not mutually exclusive. They include edema, marked astrocytic proliferation, perivascular inflammation, and demyelination. All of these processes may account for an increased amount of unbound water and, as a consequence, determine MTR changes.

Using region-of-interest analysis, several studies have shown that NAWM changes are invariably detected in all the major phenotypes of MS and are diffuse in several cerebral regions.\textsuperscript{[11,69,70,72]} Reduced MTR values have been found in several NAWM regions even in patients with clinically definite MS and no (or only very few) T2-visible lesions.\textsuperscript{[110]} These observations have indicated the need to obtain more accurate estimates of the overall extent of NAWM damage in MS (using region-of-interest analysis, tissue changes can be assessed in small portions of NAWM only) and, as a consequence, have led to the application of histogram analysis to all brain pixels classed as normal on conventional MRI.\textsuperscript{[111]} This approach requires the prior identification of macroscopic lesions on T2-weighted images, whose outlines are then superimposed onto the coregistered MTR maps and masked, thus obtaining MTR maps of normal-appearing brain tissue (NABT) (Fig. 7.13).\textsuperscript{[111]} Using such an approach, Tortorella et al. showed that NABT-MTR histogram abnormalities are present in all the main MS clinical phenotypes, and are more pronounced in patients with secondary progressive MS (Fig. 7.14).\textsuperscript{[111]} In patients with relapsing-remitting MS, average MTR of the NABT was found to be highly correlated with cognitive impairment\textsuperscript{[90]} but not with the severity of fatigue.\textsuperscript{[95]} Interestingly, a recent study of a large cohort of patients has shown that the NABT-MTR histogram characteristics of patients with primary progressive MS do not significantly differ from those of patients with secondary progressive MS who have similar levels of disability, even though patients with secondary progressive MS had higher T2-visible lesion burdens.\textsuperscript{[91]} A significant decline in NABT-MTR over time has been shown to occur at a faster pace in patients with secondary progressive MS than in patients with other clinical phenotypes.\textsuperscript{[92]} Reduced MTR values have also been detected in the NABT from patients at presentation with a clinically isolated syndrome, and the extent of these abnormalities has been found to be an independent predictor of subsequent disease evolution.\textsuperscript{[93]} These findings, however, have not been confirmed by other investigators using region-of-interest analysis\textsuperscript{[112]} or whole-brain histogram analysis.\textsuperscript{[113]}

More recently, subtle but significant NABT-MTR histogram changes have also been disclosed in first-degree relatives of patients with MS when compared with healthy controls from a general population.\textsuperscript{[114]} In MS patients, NABT-MTR values are only partially correlated with the extent of macroscopic lesions and the severity of intrinsic lesion damage, thus suggesting that NABT changes do not reflect only wallerian degeneration of axons transversing large focal abnormalities.\textsuperscript{[88,91,111]} On the contrary, a strong correlation has been found between NABT-MTR and brain volume, suggesting
that NABT damage is involved in determining irreversible tissue loss in MS. The correlation between MT-MRI-derived and diffusion tensor MRI-derived metrics thought to reflect NAWM or NABT damage has been found to be of weak to moderate strength. This suggests that brain damage occurring in the absence of conventional MRI-

**Fig. 7.13** This figures illustrates the strategy that the authors have developed to segment the NABT from patients with MS. (a) First, macroscopic MS lesions are identified on the proton-density-weighted image. (b) They are then segmented using a semiautomated local technique based on local thresholding. (c) Then, the segmented lesions are superimposed automatically on to the coregistered, scalp-stripped MTR map. (d) Finally, the areas on the MTR map corresponding to the segmented
lesions are nulled out. In this way, only pixels belonging to NABT remain and MTR histograms can be produced.

Fig. 7.14 Mean MTR histogram-derived metrics of the NABT from patients with relapsing-remitting MS, secondary progressive MS, benign MS, and primary progressive MS. The MTR histogram from patients with relapsing-remitting MS has the lowest average MTR and peak position and the highest peak height compared with those from all the other MS phenotypes. This suggests that small, discrete lesions beyond the resolution of conventional scanning are the most likely change occurring in a relatively large portion of the NABT. Compared with findings in relapsing-remitting MS, patients with secondary progressive MS had a dramatically reduced MTR histogram peak height. This suggests that, among other factors, a progressive reduction of cerebral tissue with truly normal MTR may be responsible for the evolution from relapsing-remitting to secondary progressive MS. Patients with primary
progressive MS have a lower peak height than those from all the other MS phenotypes, whereas the average histogram MTR and peak position are similar to those from control subjects. This suggests that the amount of residual normal brain tissue is much lower in primary progressive MS and suggests widespread but mild changes as the most likely underlying pathology.

detectable abnormalities is the result of a complex relationship between destructive and reparative mechanisms, which may have variable effects on findings from MT-MRI and diffusion tensor MRI. More recently, in patients with relapsing-remitting MS\textsuperscript{[96]} and primary progressive MS,\textsuperscript{[100]} moderate to strong correlations have also been found between the severity of structural changes of the NABT (as measured using MT-MRI) and the relative activations of several cortical areas located in a widespread network for sensory-motor and multimodal integration, measured using functional MRI (Fig. 7.15). This suggests that not only macroscopic MS lesions but also subtle NABT changes can cause adaptive cortical reorganization, with the potential to limit the functional consequences of MS-related structural damage.

All the above-mentioned studies are based on NABT histogram analysis. This means that it is not possible to define the relative contributions of NAWM and gray matter pathology to the observed NABT-MTR histogram changes. Nevertheless, NAWM represents the largest part of the NABT included in MTR histograms and, as a consequence, it is likely that the major contribution to the reported histographic changes comes from subtle white matter abnormalities rather than from abnormalities in the gray matter. Consistent with this, preliminary data coming from histogram analysis of NAWM taken in isolation confirm data obtained from the analysis of the NABT.\textsuperscript{[115]}
Fig. 7.15 (a) Relative cortical activation in right-handed patients with primary progressive MS during a simple motor task with their clinically unimpaired right hand as compared to matched healthy volunteers. (b) Correlation between relative activation of the ipsilateral primary somato-motor cortex and average NABT-MTR.

The role of NAWM-MTR changes in the diagnostic work-up of patients suspected of having MS remains to be elucidated, but it is likely to be modest, since MTR changes of NABT and NAWM are not disease-specific. Indeed, reduced NAWM-MTR values can also be found in patients with other neurological conditions associated with non-specific white matter lesions on T2-weighted images, such as neurological systemic lupus erythematosus,[75] cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy,[80] progressive multifocal leukoencephalopathy,[26] HIV encephalitis,[26] Leber’s hereditary optic neuritis,[36] and head trauma.[39] Nevertheless, it might be worth noting that MTR changes of the NAWM have not been found in patients with other conditions, such as migraine and multiple T2 lesions,[77] Devic’s neuromyelitis optica,[116] and acute disseminating encephalomyelitis,[81] which can also be considered in the differential diagnosis of patients with MS.
Gray matter

Post mortem studies have shown that MS pathology does not spare cerebral gray matter.\cite{117-120} Consistent with this, recent studies have shown reduced MTR values in the gray matter of patients with MS, using region-of-interest analysis\cite{115} or histogram analysis.\cite{115,121} Interestingly, in one study,\cite{115} the average percentage reduction of the peak height of the gray matter MTR histogram from MS patients was of the same magnitude (about 20%) as the average percentage reduction of the peak height of the cortical gray matter MTR histograms from patients with Alzheimer’s disease,\cite{122} and in another study,\cite{121} the peak height of the gray matter MTR histogram was inversely correlated with the severity of clinical disability (r = −0.65). Cortical and subcortical brain tissue MTR,\cite{123} but not basal ganglia MTR,\cite{124} was found to differ significantly between MS patients and healthy controls and to correlate strongly with MS cognitive impairment.\cite{123} However, gray matter MTR histograms did not differ between patients with and without fatigue.\cite{125} Significant correlations have also been reported between gray matter MTR histographic changes and T2 lesion volume.\cite{115,121} This fits with the notion that at least part of gray matter pathology in MS is secondary to retrograde degeneration of fibers transversing white matter lesions.

USE OF MT-MRI TO ASSESS OVERALL BRAIN TISSUE DAMAGE IN MS

As reviewed in the previous paragraphs, there is evidence that the extent and nature of the damage of T2-visible abnormalities, NAWM, and gray matter all contribute to the accumulation of irreversible neurological disability in MS. Consistent with this view, there has been an increasing use of magnetic resonance metrics with the potential to provide a complete assessment of MS pathology in the brain. Such magnetic resonance metrics would be of particular interest in the context of clinical trials, where it would be unrealistic to monitor treatment efficacy by measuring the extent of tissue damage from several structures and tissues.

One of the simplest and most robust approaches to generate magnetic resonance metrics that can assess and grade overall tissue damage in MS is the production of MTR histograms of the whole of the brain tissue. However, this approach is not without limitations. First, by constructing an MTR histogram, one gives up spatial information present in an image and instead looks at the distribution of MTR values. Second, the cerebral atrophy that occurs in MS\cite{126-128} can lead to an increase in the contamination of the signal from parenchyma by signal from the cerebrospinal fluid. This is particularly difficult to account for, since a simple intensity cut-off to remove the cerebrospinal fluid signal will ameliorate the problem, but partial volume effects mean that it is not possible to set the cut-off to remove the effect completely.

Owing to the presence of diffuse demyelination and axonal loss, MS patients typically have lower whole-brain average MTR, as well as lower peak height and position of the whole-brain MTR histogram, than normal subjects (Fig. 7.16).\cite{35,40,91,92,94,129,130} MTR histogram parameters also differ between the various clinical forms of MS;\cite{92,94,129,130}
typically, patients with secondary progressive MS have the lowest whole-brain MTR histogram-derived measures (see Fig. 7.16).\cite{91,94,129,130} In patients with secondary progressive MS, whole-brain MTR histogram metrics also appear to be particularly sensitive to disease changes over relatively short periods of time.\cite{92} This exquisite sensitivity could make these MTR-derived quantities appealing as outcome measures for assessing the efficacy of new experimental treatments in patients with secondary progressive MS. Recent preliminary work has also suggested a potential role of whole-brain MTR histograms in the diagnostic work-up of individual cases suspected of having MS, especially in the absence of ‘typical’ conventional MRI changes.\cite{131}

Correlations between MTR histogram parameters and clinical outcome have been widely tested,\cite{35,40,87,88,91,92,94,129,130,132,133} and van Buchem et al. demonstrated a relationship between disease duration and MTR histogram parameters (especially MTR25 and MTR50) in a cohort of 44 MS patients.\cite{132} The same study demonstrated that increasing physical disability is associated with an increased volume of brain with low MTR values and a decreasing amount of residual truly normal brain tissue.\cite{132} Moderate to strong correlations between various whole-brain MTR his-

![Fig. 7.16 Average MTR histograms of the whole-brain tissue from healthy volunteers (black line), patients with primary progressive MS (gray line), and patients with secondary progressive MS (dotted line).](image_url)
considered in isolation. Whole-brain MTR histogram metrics are also correlated with the presence of neuropsychological impairment in MS patients. These studies have assessed the impact of overall tissue damage of specific brain structures on the corresponding clinical manifestations. These studies have shown that MTR histogram parameters from the whole of the cerebellum and brainstem are strongly correlated with the impairment of the corresponding functional systems and that MTR histogram parameters of the whole of the frontal lobes are lower in patients with cognitive impairment that in those without. Several studies suggest that MTR histogram parameters in MS patients are not influenced only by the lesion burden in cerebral tissues, but also by the volume of brain parenchyma. van Buchem et al. found that the absolute MTR histogram peak height (not corrected for differences in brain volume between individual patients) is largely influenced by the total volume of pixels entering the analysis. In the same study, the relative MTR histogram peak height (normalized for brain volumes) was highly correlated with average brain MTR, MTR_25, and MTR_50 but not with MTR_75. This indicates that, in MS patients, a lowering of the relative histogram peak height reflects a decrease in the amount of brain tissue with truly normal MTR. The relationships among MTR histogram findings, the extent of T2-weighted MRI abnormalities, and brain atrophy in MS patients have been investigated by several studies. Phillips et al. found strong inverse correlations between MTR histogram peak height and both T2-weighted lesion volume (r=−0.73) and cerebrospinal fluid volume (r=−0.83), and a positive correlation between T2-weighted lesion volume and cerebrospinal fluid volume (r=0.73). In another MT-MRI study of 42 MS patients, significant correlations were found between T2-weighted lesion load and brain tissue MTR, histogram peak height, MTR_25 and MTR_50; and between T1-weighted lesion load and average lesion MTR, brain tissue MTR, MTR_25 and MTR_50. Brain volume was significantly correlated with many of the above-mentioned MT-MRI measures. Kalkers et al. selectively investigated the subgroup of MTR histogram parameters that are more closely related to partial volume averaging effects from enlarged cerebrospinal fluid spaces. They found that these so-called cerebrospinal fluid-related MTR variables (reflecting the lower left portion of brain MTR histograms) were better than parenchymal variables at differentiating secondary progressive MS patients from healthy controls and other MS phenotypes, underpinning the role played by brain atrophy in determining MS-related changes of brain MTR histograms. The fact that this role is probably especially relevant in the more disabling and advanced phases of MS is also suggested by the lack of significant correlations between brain volume and MTR histogram metrics found by Iannucci et al. in a sample of relapsing-remitting MS patients with mild disease severity.

**MT-MRI STUDIES OF THE CERVICAL CORD AND OPTIC NERVE IN MS**

MT-MRI of the cervical cord and optic nerve presents technical difficulties, mainly because of the sizes of these two structures and their tendency to move during imaging. Nevertheless, recent work has shown that it is possible to acquire good-quality MT
images of the cervical cord\textsuperscript{[136]} and optic nerve\textsuperscript{[29,137]} (Fig. 7.17). The cervical cord and optic nerves are attractive regions in which to study the pathophysiology of MS. Thus, the application of MT-MRI to the assessment of MS-related damage in these structures is likely to increase our understanding of the mechanisms that lead to the development of irreversible disability in MS.

Preliminary studies using region-of-interest analysis and small cohorts of patients found that the cervical cord of MS patients had lower MTR values than that of controls.\textsuperscript{[138,139]} More recently, the contribution made by the cervical cord to the clinical manifestations of MS has been studied in a group of 96 patients with different MS phenotypes using MTR histogram analysis.\textsuperscript{[140]} The entire cohort of patients with MS had a significantly lower average MTR of the overall cervical cord tissue than control subjects. Compared with control subjects, patients with relapsing-remitting MS had similar cervical cord MTR histogram-derived measures, whereas those with primary progressive MS had significantly lower average MTR and peak height. Patients with secondary progressive MS had lower MTR histogram peak height than those with relapsing-remitting MS. The peak height and position of the cervical cord MTR histogram were independent predictors of the probability of having locomotor disability (Fig. 7.18).

A more recent study has compared cervical cord MTR histogram metrics of patients with primary progressive MS and secondary progressive MS and found no significant difference between these two groups.\textsuperscript{[91]} In primary progressive MS, a model that included cord area and cord MTR histogram peak height was signifi-

\[\text{Fig. 7.17 Axial gradient-echo images of the cervical cord (a) without and (b) with the MT pulse applied. (c) The corresponding MTR map obtained from the two previous images.}\]
Fig. 7.18 MTR histogram-derived metrics of the cervical cord from MS patients with locomotor disability (EDSS≥4.0) and without locomotor disability (EDSS<4.0). All the MTR histogram-derived metrics are lower in patients with locomotor disability.

cantly, albeit modestly, associated with the level of disability. No correlations or only moderate correlations have been found between brain T2 lesion load or average brain MTR cervical cord MTR histogram metrics and this suggests that MS pathology in the cord is not a mere reflection of brain pathology (as is the case for other conditions, such as cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and, as a consequence, measuring cord pathology in MS might be a rewarding exercise in terms of strengthening clinical-MRI correlations. Another study found no significant difference between any of the cervical cord MTR histogram metrics of patients with MS and Devic’s neuromyelitis optica (Fig. 7.19), despite the fact that the macroscopic lesions in the cervical cord of patients with Devic’s neuromyelitis optica were longer and had a conventional MRI appearance suggesting more severe intrinsic damage than those of MS. This again suggests the relevance of subtle changes in the NAWM of patients with MS.

Thorpe et al. measured MTR of the optic nerves of 20 MS patients with optic neuritis. They found significant differences in MTR between affected nerves and both unaffected nerves and controls. In the affected nerves, MTR correlated with the length of the lesions on T2-weighted scans and with latency of the visual
evoked potential, but not with visual acuity and color vision. Boorstein et al. also reported a reduction of MTR values in the affected nerve of patients with acute unilateral optic neuritis, independently of the presence of T2-visible lesions. The asymptomatic nerves had MTR values similar to those from control subjects. More recently, Inglese et al. have shown that MTR of the optic nerves from MS patients with incomplete or no recovery from a previous episode of acute optic neuritis is significantly lower than the corresponding quantities of the optic nerves from MS patients with complete functional recovery after an episode of acute optic neuritis, but that it is not different from those of the optic nerves from patients with Leber’s hereditary optic neuritis (Fig. 7.20). In contrast, MTR values of the affected optic nerves from patients with recovery did not differ from the corresponding quantities in clinically unaffected optic nerves, which had MTR values similar to those of the optic nerves from healthy volunteers (see Fig. 7.20). At present, these data are the strongest in vivo evidence that, in patients with MS, neurodegeneration is associated with functional deficits secondary to incomplete recovery from relapses.

**Fig. 7.19** Average MTR histograms of the cervical cord from healthy volunteers (black line), patients with Devic’s neuromyelitis optica (gray line), and patients with secondary progressive MS (dotted line).

**MT-MRI AND CLINICAL TRIALS OF MS**

The limited ability of conventional MRI to characterize and quantify the features of pathology in
Fig. 7.20 Mean MTR values of the optic nerves (ON) from patients with MS, patients with Leber’s hereditary optic neuropathy (LHON), and healthy controls. The MTR values of the affected optic nerves from MS patients without recovery from visual impairment were similar to those of the optic nerves from patients with Leber’s hereditary optic neuritis and much lower than those of affected optic nerve from MS patients with visual recovery, unaffected optic nerves from MS patients, and optic nerves from controls.

MS has prompted the neuroimaging community to define more sensitive and more specific MRI measures for use in the monitoring of MS clinical trials. At present, none of the available MR techniques is able to provide metrics that fulfill all the requisites for being considered the dominant surrogate of MS pathology.\textsuperscript{[144]} Nevertheless, MT-MRI holds substantial promise for the following reasons. First, MT-MRI can provide quantitative metrics with some specificity to MS-related irreversible tissue loss. Second, it enables us to assess the entire brain, an important aspect considering that MS is a widespread disease affecting all the central nervous system tissues. Third, quantities derived from MT-MRI are reproducible, correlated with the degree of disability and cognitive impairment, sensitive to disease changes, and relatively cost-effective (high quality MTR data can be obtained with scanning time of less than 10 minutes). Finally, MT-MRI is likely to be easier to implement than other quantitative magnetic resonance methods across the many centers that typically are involved in large-scale clinical trials of MS.
Only preliminary data have been published regarding the effects of available disease-modifying treatments for MS on MT-MRI-derived parameters.\textsuperscript{145–147} All of these studies were conducted in small sample sizes and with a base-line-versus-treatment design. Two of the studies have shown that treatment with interferon beta-1b\textsuperscript{146} or interferon beta-1a\textsuperscript{147} favorably modifies the recovery of MTR values that follows the cessation of gadolinium enhancement in newly formed lesions from patients with relapsing-remitting MS. These findings suggest that, in addition to its effects in reducing the formation of new lesions, interferon might also act by reducing tissue damage and promoting remyelination within those lesions that are still formed during therapy. In contrast, Richert et al. did not find any significant difference in the MTR values of NAWM regions-of-interest before and during interferon beta-1b therapy\textsuperscript{146} or in the parameters derived from whole brain MTR histograms\textsuperscript{145} in a larger cohort of patients with relapsing-remitting MS receiving this treatment. In the latter study, month-to-month fluctuations of the histogram peak height persisted during the treatment period despite the almost complete suppression of contrast-enhanced MRI activity. Taken together, these preliminary findings confirm that MT-MRI has the potential to improve our ability to investigate the mechanisms of action of experimental treatments on the different aspects of MS pathology.

Several recent MS clinical trials have incorporated MT-MRI, with a view to assessing the impact of treatment on demyelination and axonal loss. To the authors’ knowledge, MT-MRI has been used in phase II and phase III trials for relapsing-remitting MS (injectable and oral interferon beta-1a, interferon beta-1b, and oral glatiramer acetate) and secondary progressive MS (interferon beta-1b and immunoglobulins). As already mentioned, some of these studies were conducted at single centers with small numbers of patients\textsuperscript{145–147} and, as a consequence, they were not confronted with problems of standardization of MT acquisition and postprocessing. In multicenter trials, MT-MRI acquisition has been limited to highly specialized magnetic resonance centers and only subgroups of patients (about 50–100 per trial) have been studied using MT. Although the results from these MT studies have yet to be published (and it is therefore difficult to comment on the advantages and limitations of MT-derived endpoints in multicenter trials), it is likely that the use of MT-MRI in MS trials will increase in the near future. A recent international consensus conference of the White Matter Study Group of the International Society for Magnetic Resonance in Medicine has indeed recommended the use of MT-MRI in the context of large-scale MS trials as an adjunctive measure to monitor disease evolution\textsuperscript{148} and, as a consequence, ad hoc guidelines are in preparation (MA Horsfield and M Filippi, personal communication).

**CONCLUSIONS**

Conventional MRI has markedly increased our ability to detect the macroscopic abnormalities of the brain and spinal cord associated with MS. New quantitative MR approaches with increased sensitivity to subtle NAWM changes and increased specificity to the heterogeneous pathological substrates of MS lesions give complementary information to conventional MRI. MT-MRI offers the possibility of obtaining information about tissue structure in a non-invasive manner. MTR histograms provide a
means of estimating the relative volumes of tissues characterized by specific ranges of MTR, and allow conclusions to be drawn about both focal and diffuse aspects of the disease. This indicates the potential of MT-MRI for detecting relevant changes of lesion pathology during experimental treatment of MS patients. Refinements in the techniques and equipment used for acquisition of MT-MR images should result in more precise measures of the MT effect and, eventually, in more specific techniques for non-invasive MR-based evaluation of MS patients. Nevertheless, other quantitative techniques, such as MRS and diffusion tensor MRI, are also contributing significantly to improve our understanding of MS pathophysiology. Since MT-MRI and diffusion tensor MRI have the potential to provide relevant and complementary information on the structural changes occurring within and outside T2-visible lesions, and since MRS could add information on the biochemical nature of such changes, multiparametric MRI studies are now warranted to give a better understanding of the nature of the pathological damage in MS and, it is hoped, to evaluate the efficacy of experimental treatment in preventing the formation of ‘disabling’ pathology.

ACKNOWLEDGMENT


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Measures of T1 and T2 relaxation in multiple sclerosis
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INTRODUCTION

In the past decade magnetic resonance (MR) technology has evolved rapidly, leading to new insights in the pathology of multiple sclerosis (MS). Magnetic resonance imaging (MRI) shows abnormalities in more than 95% of patients with clinically definite MS.[1] In patients with suspected MS who present with clinically isolated symptoms, an abnormal brain MR scan has a positive predictive value of 88% for conversion to clinically definite MS after a follow-up of 14 years.[2] On the other hand, a normal MR scan of the brain and spinal cord can exclude the diagnosis of MS in nearly all cases.[3] Therefore, MRI is highly sensitive for visualizing the pathology of MS and has a high negative predictive value in the diagnosis of MS.

Certain specific features on brain magnetic resonance images make the diagnosis of MS more likely. MS lesions often have an irregular and confluent shape and are located in the periventricular region, especially around the frontal, occipital, and temporal horn. Involvement of the corpus callosum, including subcallosal lesions and corpus callosum atrophy, is a common feature. Further, cortical and subcortical lesions can also be found in addition to lesions scattered in periventricular white matter. With improvements of MRI techniques, MR imaging of the spinal cord has become common practice showing focal and diffuse abnormalities.[4]

Magnetic resonance criteria for the diagnosis of MS have been defined. According to Paty et al., the presence of four or more lesions on brain MRI scans or three lesions with one located in the periventricular region, carries a sensitivity of 94% for MS but a specificity of only 57%.[1] The specificity is markedly improved if the brain MRI shows three or more lesions with at least two of the following features: a lesion ≥6 mm in size; one or more lesions abutting the ventricular bodies; or a lesion in the brain stem or cerebellum.[5] The criteria of Barkhof et al. also include gadolinium-enhancing lesions, or a juxtacortical lesion; these features increase the specificity to 78% for the diagnosis of MS in patients who present with a clinically isolated syndrome.[6] The international panel on MS diagnosis has recently revised the diagnostic criteria, facilitating the diagnosis of MS in patients with a variety of presentations, leading to three possible outcomes: ‘MS’, ‘possible MS’ (at risk of MS), and ‘not MS’. In addition to brain lesions, these revised criteria also include spinal cord lesions for MS diagnosis, especially in patients with insidious neurological progression suggestive of MS.[7]
CONVENTIONAL PULSE SEQUENCES IN MS

The most commonly used magnetic resonance pulse sequence in the diagnosis of MS is the spin-echo (SE) pulse sequence. In the SE sequence (Fig. 8.1), the magnetically aligned spins are brought to resonance with a 90° radiofrequency pulse. Dephasing of the spins, owing to magnetic field inhomogeneity and spin-spin interactions, leads to a gradual decay of the signal. This can be partially reversed by a rephasing 180° pulse, which produces a signal regain (or SE) after a time delay TE—the echo time. This pulse sequence (exciting 90° followed by a rephasing 180°) is repeated with a delay time TR—the repetition time—to collect sufficient information to create a high-resolution MRI.

In SE imaging, image contrast is dependent on the TE and TR used, as well as on the inherent tissue parameters proton density (N[H]), T1 and T2 relaxation times. The T1 relaxation time is the time constant that describes the transfer of energy from spins to their environment—the longitudinal or spin-lattice relaxation rate. The T2 relaxation time is the time constant that describes the transverse or spin-spin relaxation rate, a process that depends on spin-spin interactions and that induces dephasing of the magnetic resonance signal. In biological tissues, typical T1 values range from about 50 ms to a few seconds. In general, the T2 relaxation time is shorter than the T1 relaxation time and ranges in biological tissues from a few microseconds in solids to a few seconds in liquids. The ability of MRI to create high-contrast images of the brain depends on the differences in T1 and T2 relaxation times of brain structures (Table 8.1).

Apart from these inherent tissue parameters, magnetic resonance contrast can be influenced by the user-selectable parameters TR and TE. Image contrast can be made T1-dominated (‘T1-weighted’) by using a short time interval between consecutive excitation pulses (short TR images). On the other hand, image contrast can be made T2-weighted
(accentuating differences in T2 relaxation time) by allowing sufficient loss of phase coherence to occur before a refocusing pulse is applied to produce an echo (long TE images). To avoid T1 effects in the T2-weighted images, the TR should be long; therefore T2-weighted images have long TRs and long TEs. Proton density (PD)-weighted images are obtained by choosing TR and TE so that T1 and T2 contrast effects are minimized; this is done by choosing long TRs and short TEs. In addition one can add an extra inversion (180°) pulse to ‘prepare’ the magnetization before imaging. The time duration between this inversion pulse and the excitation pulse (the inversion time (TI)) determines the image contrast; e.g. in Short TI Inversion Recovery (STIR) imaging the TI is very short, resulting in fat suppression.

MS lesions appear as areas of increased T1 and T2 relaxation times relative to white matter of the brain. On PD-weighted images the signal from cerebrospinal fluid (CSF) is suppressed, but T2 contrast is still preserved. Periventricular MS plaques can therefore easily be distinguished from adjacent CSF spaces because of greater signal intensity (Fig. 8.2a). On T2-weighted SE images, MS lesions and CSF are both displayed as very high-signal intensity (bright); therefore periventricular plaques can easily be obscured by partial volume effects (see Fig. 8.2b).

Fluid-attenuated inversion recovery (FLAIR) sequences produce heavily T2-weighted images with suppression of the CSF signal by applying a long inversion time to produce nulling of CSF signal at the time of imaging. With introduction of fast-FLAIR, which is a more rapid imaging technique resulting in reduction of acquisition times, this sequence is increasingly used for MS diagnosis and monitoring. Fast-FLAIR is particularly helpful in detecting juxtacortical lesions (Fig. 8.3), while lesions in the posterior fossa and spinal cord are more difficult to detect than with conventional SE imaging. This may be related

<table>
<thead>
<tr>
<th>Tissue</th>
<th>T1 (ms)</th>
<th>T2 (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter</td>
<td>521–718</td>
<td>63–67</td>
</tr>
<tr>
<td>Gray matter</td>
<td>858–1080</td>
<td>65–103</td>
</tr>
<tr>
<td>Putamen</td>
<td>826–1027</td>
<td>63–67</td>
</tr>
<tr>
<td>Thalamus</td>
<td>763–950</td>
<td>66–71</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>555–700</td>
<td>61–77</td>
</tr>
<tr>
<td>CSF</td>
<td>2441–2610</td>
<td>345</td>
</tr>
</tbody>
</table>

Data from Stevenson et al., Grant Steen et al., Breger et al., Kjaer and Henriksen, Darwin et al., Tong and Prato, and Georgiades et al.
Fig. 8.2 Proton density (PD)-weighted (a) and T2-weighted (b) spin-echo MR images of a patient with MS. On the PD-weighted MR the periventricular MS lesions (bright signal) are clearly distinguishable from the ventricles because of suppression of signal from CSF (dark signal). On the corresponding T2-weighted MR, CSF has a high signal, which hampers the distinction between the border of the ventricle and the border of the lesion.
Fig. 8.3 Fluid-attenuated inversion recovery (FLAIR) (a) and T2-weighted (b) MR images of a patient with MS. Owing to the reduced gray-white matter contrast on FLAIR images, and the low signal of CSF, cortical and subcortical lesions are more apparent than on the corresponding T2-weighted MRI.

to CSF pulsations (incomplete CSF signal suppression), the inherent considerable T1 weighting of this sequence (acting antagonistically to the T2 contrast), or to a difference in composition of lesions in the posterior fossa and spinal cord (resulting in a different imaging appearance). Stevenson et al. showed that posterior fossa lesions are characterized by relatively short T1 and T2 relaxation times, which overlap with the T1 and T2 of normal appearing white matter (NAWM), resulting in reduced contrast—and therefore reduced conspicuity—between posterior fossa lesions and background NAWM.\[9\]

On heavily T1-weighted images, obtained with an inversion recovery sequence, MS lesions are visualized as areas of reduced signal intensity, owing to increased T1 relaxation times, compared with normal white matter. In general, inversion-recovery sequences take more time to acquire for a given spatial resolution and signal-to-noise ratio, and lesions may be less conspicuous than on SE images, particularly when close to CSF spaces or gray matter. More commonly, moderately T1-weighted images (short TR and short TE) are used in MS patients, to show contrast enhancement after the administration of gadolinium-DTPA in active lesions, indicating disruption of the blood-brain barrier in the presence of inflammation. In part of the MS lesions, prolongation of
T1 relaxation time is sufficiently long to reduce signal intensity on T1-weighted MRIs. These lesions are commonly known as hypointense T1 lesions or ‘black holes’ (Fig. 8.4), and their use in monitoring disease progression in MS has been established.
CONVENTIONAL SE MRI IN MS: WHERE DO WE STAND?

T2-weighted SE MR images

The most commonly used measure for disease burden in MS is the assessment of brain lesion load on unenhanced T2-weighted images. The quantification of lesion volumes can be performed by manual tracing of lesion outlines, but it is more often performed by semiautomatic lesion detection, which provides an objective and reproducible measure of the amount of diseased brain tissue. Several studies have compared the extent of disease on the MR scan with the degree of clinical severity measured with the expanded disability status scale (EDSS) score. Overall, the correlation between T2-weighted lesion number or load and disability is statistically significant but weak.\[10\] There is evidence that the strength of the relationship may be relatively good early in the disease,\[3\] but that it declines in later (progressive) phases.\[11\]

Many factors may contribute to the weak relationship between the clinical and MRI features. First, brain lesions that appear hyperintense on T2-weighted images are histopathologically heterogeneous, consisting of edema, inflammation, mild and severe demyelination, remyelination, gliosis, and axonal loss. Although severe demyelination and axonal loss are probably the main factors that contribute to functional impairment, they have the same appearance as lesions that consist of edema, mild demyelination, and gliosis. Second, the EDSS is a subjective, non-linear scale that mainly represents spinal cord disease. Small lesions in the spinal cord may therefore be more important in determining disability than large lesions in the brain. Brain MRI lesions may correlate better with cognitive functioning than with physical functioning, as has been shown using the Multiple Sclerosis Functional Composite (MSFC) scale,\[12\] a multidimensional quantitative measure that measures three dimensions: ambulation and leg function, arm and hand function, and cognition. Third, microscopic pathology in the NAWM may contribute to disability but may not be discernible on conventional T2-weighted scans or may not be included in lesion load measurements. These microscopic abnormalities may appear as diffuse abnormalities (poorly demarcated, high-signal areas) on both PD and T2 images, an MRI feature that has been shown to occur typically in primary progressive MS.\[4\] In addition to the number and volume of T2 lesions, quantification of diffuse abnormalities may also be important in accurately assessing disease burden in MS patients.

At present, brain MRI lesion load is used as a secondary outcome measure in definitive clinical trials, while clinical assessments of disability or relapse rate are accepted primary outcome measures.\[13\] New MRI parameters have been analysed to improve the correlation with clinical disability or to improve the histopathological specificity. Apart from magnetization transfer imaging, MR spectroscopy, diffusion-weighted MRI and brain and spinal cord atrophy, hypointense T1 lesions have been shown to improve the association with clinical disability and to improve histopathologic specificity.
Hypointense lesions on mildly T1-weighted SE MR images

Hypointense T1 lesions were first described by Uhlenbrock et al.,[14] who noted that hypointense lesions are common in the cerebrum of MS patients but occur less frequently in patients with subcortical arteriosclerotic encephalopathy. Hypointense lesions occur less frequently in the brainstem and in the cerebellum of MS patients, and are only rarely observed in the spinal cord.[15] Uhlenbrock et al. suggested that these lesions represent chronic MS plaques in which astrocyte growth and scarring is present.[14] Autopsy[16,17] and biopsy[18] studies have confirmed this hypothesis. The degree of hypointensity on T1-weighted SE images correlates strongly with the degree of matrix destruction (widening of the extracellular space) and loss of axons. Follow-up studies show better correlations between an increase in hypointense T1 lesion load and worsening of clinical disability in relapsing-remitting and secondary progressive MS than is seen with an increase in T2 lesion load.[19–21] In secondary progressive MS especially, the relative increase in hypointense T1 lesion load relates to disease progression. Cross-sectional studies typically show slightly higher correlations between the volume of the T1 lesions and EDSS than between the volume of the T2 lesions and clinical disability (Table 8.2).[4,20–25] Further, infratentorial hypointense lesions are often seen in MS patients with chronic cerebellar ataxia, and these lesions correlate strongly (r=0.89) with EDSS in these patients,[26] whereas T1 signal intensity of the spinal cord (at C2 level) also correlates with EDSS in MS patients not selected on clinical grounds.[27] Progressive cerebral atrophy, reflecting a global decrease in axonal density, correlates with increase in hypointense lesion volume, both having a significant association with disability.[21]

These clinical and histopathologic studies indicated that hypointense T1 lesions may be used as surrogate markers for disease progression in MS and have led to the inclusion of hypointense T1 lesions—in addition to T2 lesions—as secondary outcome measures in clinical trials.[28] Several clinical efficacy studies have since been conducted. Interferon beta-1b and glatiramer acetate, therapies that effectively reduce the number of active lesions in MS, also reduce the development of hypointense lesions, indicating a beneficial effect on the occurrence of axonal damage in MS lesions.[29,30] In contrast, the antibody CAMPATH-1H does not have a significant effect on the accumulation of hypointense T1 lesions.[31] Hypointense lesions have also been shown to correlate with cognitive

Table 8.2 Correlation between expanded disability status score and T2 and T1 lesions

<table>
<thead>
<tr>
<th>Study</th>
<th>T1 lesion volume</th>
<th>T2 lesion volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sailor et al.[21]</td>
<td>0.47</td>
<td>0.34</td>
</tr>
<tr>
<td>Rovaris et al.[22]</td>
<td>0.60</td>
<td>0.49</td>
</tr>
<tr>
<td>van Walderveen et al.[23]</td>
<td>0.58</td>
<td>0.49</td>
</tr>
<tr>
<td>Truyen et al.[20]</td>
<td>0.46</td>
<td>0.33</td>
</tr>
<tr>
<td>Lycklama a Nijeholt et al.[4]</td>
<td>0.43</td>
<td>0.33</td>
</tr>
<tr>
<td>Ianucci et al.[24]</td>
<td>0.52</td>
<td>0.42</td>
</tr>
<tr>
<td>Adams et al.[25]</td>
<td>0.40</td>
<td>0.35</td>
</tr>
</tbody>
</table>
impairment, as measured by the MSFC.\cite{12} The ratio of frontal T1 to T2 lesion volume relates better to cognitive impairment in demented MS patients than in non-demented MS patients.\cite{32} Similarly, correlations with depression are present since more parietal hypointense lesions are present in MS patient with dementia than in non-demented patients.\cite{33} Furthermore, hypointense lesions in the parietal lobe are significantly associated with MS quality of life measures such as emotional dysfunction and impaired overall mental health.\cite{34}

Although hypointense lesions serve as a secondary outcome parameter in clinical trials, some problems are still left unresolved. First, short TR, short TE images are usually referred to as mildly T1-weighted, although the degree of T1 weighting is variable and highly sequence-dependent. On T1-weighted SE images, only part of the lesions will appear hypointense, whereas most lesions will appear dark on heavily T1-weighted images (such as with inversion recovery sequences). Apparently, T1 prolongation must be quite strong to result in the appearance of ‘black holes’ on short TR, short TE SE images. More generally, the amount of hypointense T1 lesion load depends on the settings used to obtain the images. For example, at 1.5 Tesla the maximum contrast is attained for repetition times between 600 and 700 ms; at lower field strengths the TR needs to be decreased accordingly.\cite{35} Second, the degree of hypointensity on T1 weighted MRIs varies between lesions. Some lesions have the same signal intensity as CSF (dark), while other lesions are closer to gray matter. These differences probably relate to variable degrees of tissue destruction. Obviously, defining objective criteria for the identification of hypointense lesions is mandatory. Further, the hypointense signal of CSF may obscure identification of adjacent hypointense T1 lesions, and similarly, gray holes close to gray matter may go undetected. Although hypointense lesions are used as secondary outcome criteria in phase III trials, standardization of acquisition parameters and a clear definition of what constitutes black (and gray) holes is lacking so far.

One way of standardizing the measurement of black holes is to use precise relaxation time measurements. Before this technically complex matter can be discussed, the methodology used to measure T1 and T2 relaxation times must first be described.

T1 AND T2 RELAXATION TIMES

Methodological considerations in T1 and T2 measurement

The measurement of T1 relaxation times can be performed using several magnetic resonance techniques. Difference in T1 dependence in successive images of the brain can be obtained by varying the TR (saturation recovery method), the TI (inversion recovery method), or the flip angle of the exciting radiofrequency pulse. In general, inversion recovery methods are preferred over saturation recovery techniques. A saturation recovery sequence requires a \( TR \leq T1 \), in which case the slice profile becomes very distorted, and accurate measurements of T1 relaxation times are impossible. Inversion recovery methods can be run at long TRs, so that the slice relaxes completely between subsequent inversion pulses. Since T1 measurements obtained from images with different TI or TR values may be influenced by different transmitter and receiver gains of the
scanner, these parameters should be kept constant during the whole measurement. Until recently, T1 relaxation time measurements suffered from one major disadvantage: acquisition times tended to be very long, which limits the application in the clinical setting. Since more rapid acquisition techniques have become available, this problem may be circumvented. Echoplanar imaging (EPI), for example, is the most rapid imaging technique at present and provides complete spatial encoding of an MR image after a single 90° excitation pulse. The combination of rapidly switching magnetic field gradients and a high speed data acquisition system allows a reduced examination time, typically to the order of a few minutes for the whole brain. Using EPI, T1 relaxation times can be measured by applying a 180° inversion pulse with varying inversion times to introduce a wide range of T1-dependent contrast in successive images. Although EPI has some artifacts (susceptibility artifacts near the skull base and paranasal sinuses, geometric distortions due to B0 inhomogeneity, and limited spatial resolution), it allows multiple-slice T1 relaxation time measurements within a reasonable time period. Further, high-quality T1 images within a clinically reasonable time frame can be obtained by the simultaneous acquisition of an SE and a phase-shifted stimulated echo (phase acquisition of composite echoes (PACE)), as has been shown by Ropele et al. Since T1 relaxation times are field strength-dependent (although not linearly), differences in field strength should be taken into account when comparing acquisition methods and results.

T2 relaxation time measurements can be performed by using SEs at varying echo times. Most commonly, the Carr-Purcell-Meiboom-Gill (CPMG) sequence is used in which any number of echoes may be collected by applying additional consecutive rephasing 180° pulses after an initial 90° pulse. The CPMG sequence is usually run in a single-slice mode since this allows the use of non-selective 180° pulses, which produce more accurate refocusing of the magnetization in the selected slice.

**Interpretation**

In vivo measurement of T1 and T2 relaxation times of protons provides information about the tissue water environment. Using gravimetric analysis of operative samples from patients with brain tumors, a linear correlation was shown between total water content and T1 relaxation time. Further, relaxation time measurement gives information about the existence of separate water compartments, where a bi- or multiexponential decay curve can be plotted. The possibility of a multicomponent relaxation in the brain must always be considered when measuring T1 and T2. Only when a monoexponential curve provides a better fit for the measured data than a bi- or multiexponential curve can one assume that only one water compartment is present. In normal brain tissue, a longitudinal relaxation decay curve follows a monoexponential function. Also, transverse relaxation of gray matter in the normal brain is monoexponential although biexponential decay curves can be found in cases of partial volume effects with CSF. In contrast, T2 of white matter is usually multicomponent in nature and different T2 times correspond to three different water reservoirs: a minor fraction with a short T2 between 10 and 50 ms, caused by water compartmentalized in myelin membranes, so called myelin water; a major fraction (approximately 80% of the water in normal brain) with T2 between 70 and 95 ms, caused by water in cytoplasmatic and extracellular spaces; and a small fraction with T2 values of 1 s or more, consistent with CSF (for example in perivascular spaces).
In experimental studies, correlations have been found between changes in T1 and T2 relaxation times (and their ratio) and histopathology. Triethyltin-induced cerebral edema affects the brain white matter diffusely, without enlargement of the extracellular space or astrocyte swelling. T1 and T2 values lengthen with increasing water content of the edematous white matter, and at all stages the percentage increase in T2 is almost twice that in T1. In vasogenic edema, the extracellular space enlarges and protein-rich fluid accumulates as a result of damage to blood vessels. This results in increased relaxation time values, but T2 increases in the same proportion as T1. Further, the T2 decay follows a biexponential function (Fig. 8.5) comprising a short (intracellular water) and long (edematous fluid) T2 component. The biexponential T2 decay in case of enlargement of the extracellular space is of interest, since this also occurs—apart from in vasogenic edema—in cases of axonal loss. This contrasts with findings in experimental gliosis in cats, where T1 relaxation time is increased without a corresponding increase in T2 relaxation time and the T2 magnetization decay remains monoexponential.

Several quantitative magnetic resonance studies have been performed on animals with experimental allergic encephalomyelitis (EAE). The general conclusion to be drawn from these studies is that in the EAE lesion, prolongation of T1 and T2 relaxation times is particularly related to edema. Further, changes in relaxation time values can often be observed before the onset of clinical symptoms or pathologic changes. In primate EAE, prolonged T1 and T2 values are associated with the presence of inflammation, demyelination and hemorrhagic necrosis. In guinea pigs, prolongation of T1 was observed during meningeal and perivascular inflammation, while T2 increased with demyelination. Stewart et al. performed a multiexponential analysis of T2 data from EAE lesions in the spinal cord and brain of guinea pigs. They found a short T2 component, assigned to myelin water, which was smaller or absent in demyelinated lesions. Gareau et al. showed a reduction in the short T2 component in EAE NAWM compared with normal white matter, suggesting a significant loss of myelin in NAWM; this reduction in the short T2 component was not influenced by modulations in inflammation caused by antibody treatment. Interestingly, reductions in the magnetization transfer ratio (MTR) were prevented or reversed with suppression of inflammation, indicating that MTR is sensitive to changes to myelin influenced by inflammation, while the short T2 component is a more specific indicator of myelin content in tissue. Although these studies provide insights into the histopathologic characteristics of changes in relaxation parameters, the results are often hampered by partial volume effects caused by the small size of lesions and by difficulties relating the in vivo magnetic resonance measurements and in vitro histologic examination.
Fig. 8.5 Example of a T2 decay curve, which is fitted by a biexponential function (consisting of T2 long and T2 short components) according to the formula:

\[ M_{xy}(t) = M_1 \cdot e^{-t/T2\text{long}} + M_5 \cdot e^{-t/T2\text{short}} \]

, in which \( M_1 \) represents the magnetization of the T2 long component and \( M_5 \) represents the magnetization of the short T2 component.

Measurement of relaxation time in NAWM

Lacomis et al. showed in 1986 that in MS patients, T1 relaxation time of NAWM was prolonged compared with control white matter and that this increase was most evident in patients with longer disease duration.\(^{[49]}\) This finding was confirmed by Haughton et al., who also observed that T1 of NAWM increased progressively with increasing disability, although the correlation was only marginally significant.\(^{[50]}\) In other studies, consistent findings of increased T1 and T2 relaxation times in NAWM of MS patients have been found. One study showed that throughout the NAWM discrete areas of abnormal T1 and T2 values are present, which often consist of only one or two pixels.\(^{[51]}\) Barbosa et al. hypothesized that these discrete areas may represent small areas of reactive astrocytes, edema, and perivascular cellular infiltration, which have also been described pathoanatomically.\(^{[51]}\) These studies show that there are white matter abnormalities that do not appear as discrete foci of abnormal signal intensity on conventional MRI. Since this ‘invisible’ lesion load may constitute a significant proportion of the total lesion load,
an estimate of the disease burden might be more accurate if it were based on T1 and T2 calculations of white matter, in addition to the number and volume of plaques.

**Measurement of relaxation time in focal MS lesions**

Measurement of relaxation time within MS lesions generally shows increased T1 and T2 values. Larsson et al. examined a group of patients with stable but severe disease. T1 relaxation was found to be monoexponential in all MS lesions, but in seven of 33 lesions T2 relaxation curves were found to fit a biexponential function better than a monoexponential function. This study was extended to include patients suffering from an acute attack of MS. A large overlap was shown between T1 and T2 values obtained in acute and chronic plaques. In acute plaques the T1 relaxation time was monoexponential during the course, and a decrease in T1 was present with time. In contrast, a biexponential T2 relaxation process was observed after a time period of 23–187 days, which reversed to monoexponential decay curve in some cases. Larsson et al. suggested that, in the acute lesions, increased numbers of inflammatory cells and increased intercellular water probably accounted for the simultaneous increase in T1 and T2. The biexponential T2 decay curve would represent myelin loss, which is replaced by water (high monoexponential T2 values) and gliosis (accounting for the T2 fast component). After resorption of edema, only one component (gliosis) could be detected. Armspach et al. also showed that a biexponential T2 decay curve can usually be observed in lesions of MS patients, of which the short T2 component probably reflects remaining myelinated fibers. The long T2 values were spread out over a wide range, probably characterizing different pathologic processes such as edema, demyelination, and gliosis. MacKay et al. analysed T2 decay curves in MS lesions and focused on the short T2 component between 10 and 55 ms, the myelin water component. In four MS cases, the average myelin water content in lesions was significantly reduced compared with that of normal white matter. MacKay et al. therefore noted that increased proton density and elevated (overall) T2 relaxation time of a lesion do not necessarily relate to the state of myelination. The additional use of myelin maps (representations of the very short T2 component) may therefore provide additional information on the myelinated state of lesions. Kidd et al. postulated that T2 decay curve analysis may provide insight into the pathologic characteristics of lesions. A monoexponential decay with a relatively short T2 would indicate lesions that predominantly consist of gliosis, while a biexponential decay or a monoexponential decay with a long T2 may relate to an expanded extracellular space caused by loss of tissue structure (including axonal loss).

**Measurement of T1 relaxation time in chronic hypointense MS lesions**

In an autopsy study, hypointense lesions were shown to consist of axonal loss and matrix destruction. In a more extensive histopathologic sample, 109 lesions were selected and examined using post mortem MRI and histopathology. Contrast ratio measurements on T1-weighted MR images and MTR measurements were used as in vivo magnetic resonance indices for tissue destruction and demyelination, respectively. Histopathologic outcome parameters were axonal density, degree of matrix destruction, and degree of lesional activity (classification based on the presence of different myelin breakdown
products, which reflect various stages of lesion development). In this large sample, a strong correlation was shown between the MTR and T1 contrast ratio measurements and histopathologic outcome parameters. The strong correlation with axonal loss indicates that quantification of T1 and MTR may provide an in vivo tool to monitor irreversible deficit in MS lesions and may be used as a surrogate outcome measure in clinical trials. Since the MTR is a complex function of the magnetization transfer rate and the native relaxation time of water protons (‘T1-free’), both of which display different behavior in NAWM (showing normal ‘T1-free’ values), diffuse abnormalities and among MS lesions, an even closer correlation with histopathology may be achieved by analysing these magnetization transfer mechanisms separately.[56]

In vivo T1 relaxation time measurements in chronic hypointense T1 lesions support the hypothesis of using T1 relaxation time measurements as an in vivo tool to monitor irreversible deficit in MS patients. In a group of 14 MS patients, chronic hypointense lesions that were more than 6 months old were selected on previous T2-weighted images, and T1 relaxation time measurements were performed using multislice inversion recovery EPI. Further, magnetic resonance spectroscopy was performed to assess metabolite concentrations within the lesions.[57] Highest T1 relaxation time values were found for severely (‘black’) hypointense T1 lesions compared with isointense and mildly hypointense (‘grey’) lesions. Prolongation of T1 relaxation times in severely hypointense lesions was paralleled by a decrease in the concentration of N-acetyl aspartate (NAA), a brain metabolite that occurs exclusively in neurons and axons. This correlation was present for MS lesions, but remained significant after inclusion of NAWM in the analysis. Remarkably similar results were obtained by Brex et al., showing a correlation coefficient of $r = -0.9$ between increase in T1 relaxation time and decrease in NAA.[58] In contrast to the short T2 component, which is an indicator of myelin content in tissue, prolongation of T1 relaxation time in hypointense lesions is probably an indirect consequence of loss of axonal structure, and the decrease in signal intensity results from an increase of free water in the extracellular space, with subsequent enlargement of the extracellular space.

More recent data show that multislice T1 relaxation time measurements with inversion recovery EPI enables the calculation of histograms based on T1 relaxation time values.[59] In normal volunteers, such a whole-brain T1 histogram (Fig. 8.6) is composed of a sharp peak centered around T1 values of white matter (range 679–765 ms) with a broad shoulder on the right side compatible with T1 values of gray matter. This broad shoulder gradually extends into a large tail of higher T1 values, compatible with T1 values of CSF. Preliminary results in 38 MS patients have shown differences in T1 histogram shape compared with normal volunteers, with a lower (normal-appearing) white matter peak for MS patients that is centered around higher T1 values (range 700–957 ms). Further, close correlations were present between T1 histogram parameters, such as relative white matter peak height and T1 value with the highest incidence, and conventional magnetic resonance measures of disease burden in MS patients, such as T1 lesion volume and measures of atrophy. Considering the close correlation between T1 relaxation times and NAA levels, these preliminary results indicate that T1 histogram analysis may provide a global measure to monitor disease progression in MS patients.
Fig. 8.6 Example of a whole-brain histogram of a normal volunteer based on $T_1$ relaxation times. A sharp peak is centered around $T_1$ values of normal white matter (see also Table 8.1) with a broad shoulder on the right side (compatible with $T_1$ values of gray matter). The ‘tail’ of long $T_1$ values represents CSF.

Can we predict axonal loss in individual MS lesions?

Axonal loss is the irreversible end-stage in the development of MS lesions and the main contributor to progressive neurologic deterioration. Although axonal loss was thought to occur mainly in chronic MS, studies have shown that in acute (inflammatory) lesions, damage to axons also occurs.\textsuperscript{[60–62]} Trapp et al.\textsuperscript{[60]} showed that axonal transection is an abundant feature in active and chronic active lesions from patients with duration of clinical disease ranging from 2 weeks to 27 years.\textsuperscript{[60]} Further, the greatest degree of axonal transection occurred in areas of active demyelination and inflammation. In addition, Bitsch et al. showed that axonal damage occurs in active demyelinating but also in remyelinating and inactive demyelinated lesions, whereas a correlation was shown with the number of macrophages and CD8-positive T lymphocytes.\textsuperscript{[62]} This result shows that axonal injury is—in part—indepedent of demyelinating activity.

Bruck et al. found various reductions in axonal density (ranging from 35% to 81% compared with periplaque white matter) in lesions that showed massive gadolinium-DTPA enhancement.\textsuperscript{[18]} These enhancing lesions appear hypointense on unenhanced T1-weighted images, and the degree of hypointensity was shown to be affected mainly by
two factors—the extent of axonal reduction and the amount of extracellular edema. This result is supported by an in vivo study, which showed that most (80%) enhancing lesions appear hypointense on unenhanced T1-weighted images, these lesions are also known

![Image of T1-weighted MR images showing a hypointense T1 lesion.](image)

**Fig. 8.7 Example of an acute (or ‘wet’) hypointense T1 lesion. On the precontrast T1-weighted MR image (a) the lesion appears as hypointense, whereas on the postcontrast T1-weighted MR image (b) ring-enhancement is visible after the administration of gadolinium-DTPA.**

Approximately 55% of these acute hypointense lesions reverse to isointensity at follow-up, while 45% will remain hypointense. Factors that predict the evolution of individual lesions are unknown. Hypointense appearance at 6 months of follow-up was in part determined by the MTR value at the time of initial enhancement and by the duration of enhancement. Also, ring-enhancing lesions were persistently hypointense in all cases, in contrast to nodular-enhancing lesions. The MTR value at the time of initial enhancement predicts the persistent hypointense appearance (indicating axonal loss) at follow-up, although in individual lesions this is difficult to predict, since MTR values are generally decreased during the phase of enhancement. However, in a large number of cases, they too tend to reverse to subnormal or normal values after enhancement ceases. This is similar to the observation of reversible decreases of NAA levels in acute lesions and decreases in T1 relaxation time at follow-up in acute lesions.

At this time, therefore, factors that predict black holes, indicating axonal loss, are largely undefined. Pattern and duration of enhancement, MTR, NAA concentration, and T1 relaxation time measurement may all play a role. Simon et al. showed that the
development of T1 hypointense lesions over a 2-year period is strongly influenced by prior inflammatory disease activity, as indicated by enhancing lesions. In contrast, results from a study covering approximately 4 years showed that the percentage of enhancing lesions that evolve into black holes relate only weakly to the rate of enhancing lesions, and more strongly to the hypointense lesion load at the initial scan. This is in concordance with results of histopathologically defined hypointense lesions, obtained from biopsy material. This study showed that the extent of hypointensity increased in initially demyelinated plaques and decreased in remyelinating lesions, but that the increase in hypointensity over time is determined by the initial axonal loss. Therefore, apart from the amount of new inflammatory activity, other factors, possibly genetic, appear to determine the development of axonal loss in MS lesions. Recent studies indeed indicate that in subgroups of MS patients demyelination and axonal destruction may follow different pathogenetic pathways with even interindivdual variability of axonal injury, with marked similarity among different lesions in the same patient.

**Measures of T1 and T2 relaxation: current perspectives**

At the present time, conventional T2-weighted SE MRI is the most sensitive method for visualizing abnormalities in the brain of patients with suspected MS, since all pathologic tissue alterations occurring in MS tissue will increase T2 relaxation time. Histopathologic heterogeneity probably accounts for the weak correlations between T2 lesion load and clinical disability measures. A stronger correlation with clinical disease parameters, including cognition, can be obtained with T1-weighted SE MRI. Chronic hypointense T1 lesions (‘black holes’) correlate histopathologically with irreversible tissue destruction, as indicated by matrix destruction and axonal loss. Experimental studies indicate that histopathologic characterisation of lesions may be improved using T1 and T2 relaxation time measurements. In MS lesions, a wide range of T1 and T2 relaxation times are observed, which probably reflects histopathologic heterogeneity. Many plaques show biexponential or multiexponential T2 relaxation, with the longer T2 component probably related to enlargement of the extracellular space. The short T2 component can be assigned to water bound to myelin membranes and may provide a quantitative in vivo measure of myelination (and remyelination). In vivo multislice T1 relaxation time measurements within a reasonable time frame have become possible using fast scan techniques, such as EPI. Considering the close correlation between T1 relaxation time, hypointensity on T1-weighted MRI, concentration of NAA, and axonal injury or loss, T1 relaxation time measurements may become an in vivo measure to monitor tissue destruction both in lesions and in NAWM of MS patients.

**REFERENCES**


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INTRODUCTION

Magnetic resonance imaging is a sensitive tool for measuring various aspects of multiple sclerosis (MS) pathology in vivo. Lesions on T2-weighted and contrast-enhanced T1-weighted magnetic resonance imaging (MRI) scans are used routinely as indicators of disease activity for diagnosis and in clinical trials of immunomodulatory agents. However, contrast-enhancing lesions and T2 lesions reflect pathologic processes that are potentially reversible and that indicate variable amounts of tissue injury (see chapters 6 and 8). Furthermore, lesion measurements fluctuate over time and do not account for diffuse pathology in the normal-appearing white matter (NAWM). These factors limit the usefulness of conventional lesion measurements. New MRI measures are sought as more reliable markers of MS disease progression (see chapters 7, 10 and 11). One straightforward approach is the estimation of atrophy of central nervous system (CNS) structures. In contrast to lesions, atrophy reflects the end result of irreversible and severely damaging pathologic processes caused by MS. Axonal damage and loss, chronic demyelination, and gliosis result in a reduction in CNS parenchymal tissue volume and a corresponding expansion of cerebrospinal fluid spaces. These gross morphologic changes can be accurately quantified using standard MRI acquisitions and various computer-aided image analysis approaches, even in the early stage of disease. The recent focus on axonal damage as a significant component of MS pathology and a major cause of progressive disability has led to widespread interest in the measurement of atrophy in MS patients. CNS atrophy is now widely regarded as an objective measure of global disease burden and an indirect measure of disease severity in MS.

As many groups have incorporated atrophy measurement into their image analysis protocols for MS, some questions regarding atrophy have been clarified, although others remain. What is the best way to measure atrophy? What are the specific pathologic processes that lead to atrophy? Can the rate of atrophy be slowed by available treatments? Recent studies have described the different methods used for atrophy measurement, the characterization of atrophy in MS subtypes cross-sectionally and over time, the relationship of atrophy to other MRI measures of pathology, and the use of atrophy as an outcome measure in clinical trials.
METHODS FOR ESTIMATION OF ATROPHY

Methods currently used to estimate atrophy vary considerably according to level of automation, the scale, and the conceptual approach. For example, the level of automation—or degree of operator interaction required to perform the measurements—ranges from completely subjective rating scales to fully automated volumetric calculations. The scale of atrophy measurements ranges from highly localized measurements of third ventricular width (of the order of 3 mm) to global measurements of whole brain volume (of the order of 1000 ml). Methods also differ significantly according to conceptual approach, from the estimation of total atrophy since disease onset on the basis of a single image, to the precise determination of the shift in the edges of a structure between serially acquired images.

Important considerations for any methodology are measurement reliability and sensitivity to change. Reliability is expressed in terms of accuracy or reproducibility. Reproducibility is especially important for techniques that are to be used in longitudinal studies. The coefficient of variation (CV) between repeated measurements is often used to report reproducibility. Repeated measurements performed on scan-rescan data simulate conditions in serial studies and provide a better estimate of measurement variability than repeated measurements on the same image data. Ideally, the measurement variability should be small in relation to the size of the changes, which is less than 1.0% a year for whole brain volume in MS patients.

Manual methods

Subjective rating of atrophy on an ordinal scale\(^1,2\) is a semi-quantitative approach that can be applied without specialized software or equipment. This technique has been used recently by comparing patient images to images of an age-and sex-matched control from a large normative database and rating each as normal or mildly, moderately, or severely atrophic.\(^2\) Reassessment of a subset of 27 images by two observers demonstrated very good intraobserver agreement (\(\kappa=0.9\)) and moderate to very good interobserver agreement (\(\kappa=0.8\)) (the kappa coefficient (\(\kappa\)) is a commonly used measure of intraobserver agreement where \(\kappa=1\) indicates perfect agreement)). The ordinal rating scale approach is limited in terms of sensitivity and is therefore not very useful in detecting changes over time. Another technique that does not require specialized software is the measurement (using graded calipers) of distance between anatomic landmarks on films. Recent use of this approach for estimation of ventricular enlargement demonstrated good agreement with volumetric digital image analysis method (\(r^2=0.84, p=0.009\)); however it can be applied only to images with consistent patient positioning in the MRI unit.\(^3\)

The use of image analysis software allows for quantitative estimation of widths, areas, and volumes of CNS structures directly from digital images. The calculation of distances between manually selected anatomic landmarks is readily available on reading consoles and can be used to estimate the sizes of particular structures, such as the third ventricle width, lateral ventricle width, and brain width.\(^4,5\) Intrarater variability calculated from reanalysis of 10 image sets ranges from 1% (CV for brain width) to 7% (CV for third
ventricle width). Stereology is an approach used to calculate areas and volumes based on
the Cavalieri principle (i.e. a grid is randomly overlayed on an image and the number of
grid intersection points contained within the structure of interest are counted) (Fig. 9.1).
Stereology has been applied to measure the area of the corpus callosum and the volumes
of the brain stem, cerebellum, upper cervical cord, gray matter, white matter, cerebral
hemispheres, and ventricles. Intraoperator variability of this method, based on
reassessment of a subset of images, has been reported to be 2.8% for cerebral volume and
6.9% for ventricular volume. Many image analysis packages also include tracing tools
that can be used to delineate structures of interest manually so that volumes can be
calculated by simply multiplying the sum of voxels included in the region by the voxel
size. Manual tracing by an expert observer yields accurate segmentation, but it is also
the most time-consuming approach, and measurement variability is relatively high.

Semiautomated and automated methods

Semiautomated and automated segmentation programs offer more rapid assessment of
areas and volumes. These methods are commonly used to calculate spinal cord cross-
sectional area, lateral ventricle volume, cerebrospinal fluid volume, and whole or partial brain volumes. Atrophy can be estimated as the differences between
groups of patients and matched controls in cross-sectional studies, or as the change in
size over time in longitudinal studies. There are many different site-specific segmentation
algorithms and programs currently in use for MS applications.

A semiautomated thresholding algorithm has been developed for measurement of spinal
cord cross-sectional area. An operator selects regions of interest, which are used to
determine an intensity threshold midway between cerebrospinal fluid and spinal cord
tissue. To minimize axial repositioning errors, the cord is segmented in five adjacent
image slices and the area is determined as the mean cross-sectional area. Scan-rescan
tests resulted in mean CVs of between 0.79% and 1.6%. A similar thresholdbased
approach has been applied for semiautomated segmentation of the lateral ventricles in
T1-weighted images. First, the mean intensity of brain parenchyma is determined
from automated segmentation or operator-selected regions of interest, and then the
threshold is determined as 60% of the brain intensity (Fig. 9.2). The intrarater CV for this
technique is 0.13% and the intraclass correlation coefficient is 0.99.
In general, segmentation of brain parenchyma consists of two basic steps: first, separation of tissue from cerebrospinal fluid and background, usually by intensity thresholding, and secondly, separation of the brain tissue from other cranial structures, usually by use of connectivity, morphologic operations, or knowledge-based anatomic operations. One example of a semiautomated algorithm allows the user an interactive choice of low and high thresholds that cover the intensity range of brain parenchyma; the user can then select a seed point within the parenchyma on a slice-by-slice basis.\textsuperscript{25} A region is automatically grown around the seed point that includes all connected pixels within the given range of intensities. Boundaries are drawn manually when necessary to prevent the region from growing outside the brain and into other structures. The intraobserver CV for this technique calculated from re-segmentation of 10 images is 1.9\% for whole brain volume.

Another approach is to perform the same steps automatically (Fig. 9.3). First, determine the optimal threshold for separation of parenchyma
Fig. 9.2 Segmentation of the lateral ventricles by thresholding. (a) Slice from the original T1-weighted image with a user-selected region of interest (ROI) in the normal-appearing white matter. Mean intensity in ROI is 447. (b) Calculation and application of the ventricle threshold as 60% of the white matter ROI mean intensity. The threshold is 268. (c) Boundaries of the final segmentation superimposed on the original image. The number of pixels inside the lateral ventricles on this slice is 2085.
Fig. 9.3 Generic automated brain segmentation algorithm: (a) Slice from the original proton density/T2-weighted dual echo image (early echo minus late echo). (b) Optimal thresholding to separate tissue from background and cerebrospinal fluid. (c) Morphological erosion with a $5 \times 5 \times 5$ diamond-shaped kernel to disconnect connected structures. (d) Identification of the largest connected component, the brain parenchyma. (e) Morphological dilation with a $5 \times 5 \times 5$ diamond-shaped kernel to recover the original shape. (f) Boundaries of final segmentation superimposed on the original image. The whole brain volume for this example is 946.4 ml.
and cerebrospinal fluid on the basis of histogram analysis in images with good
differentiation between parenchyma and cerebrospinal fluid (e.g. T1-weighted or fluid attenuated inversion recovery (FLAIR) images) or, in the case of multiple input images (e.g. T1-, T2 and proton density-weighted images or PD images), assign each voxel to the tissue class of highest probability using multispectral classification. Second, apply morphologic operations to erode small connections between the brain and other cranial structures. Finally, use connectivity principles to find the largest connected component within the image, the brain.

Variations on these steps have been implemented by several groups to generate an initial segmentation of the brain. However, in general, after the final step, there are still some non-brain structures included in the segmentation, and additional processing is required. In one variation on this approach, the segmentation is restricted to a central 20 mm thick slab of tissue selected by the radiologist (Fig. 9.4). Manual editing is performed after automated segmentation, if necessary. Limiting the segmentation to the central slices helps to avoid excessive manual editing, speeds up the processing, and increases sensitivity to change by focusing on the region in the brain around the ventricles. The CV is 0.56%, as determined by a scan-rescan test. The same basic approach has also been applied to whole brain segmentation and implemented either as semiautomated programs (with only minor editing requirements) or as fully automated programs. Measurement variability with these techniques is consistently below 1%.

An important distinction between volumetric methods of atrophy measurements is whether the structure size is reported as the actual volume (e.g. in milliliters) or as a normalized volume. Normalized measures of whole brain atrophy are calculated as the brain parenchymal volume divided by an estimate of the intracranial volume, in order to correct for head size. One way to accomplish head-size normalization is to determine the total volume of the intracranial contents (ICC, including cerebrospinal fluid, white matter, gray matter, and lesion volumes) in addition to the volume of brain parenchymal tissue (BP, including only white matter, gray matter, and lesion volumes) and then calculate normalized brain volume as:

\[
\frac{\text{BP volume}}{\text{ICC volume}}
\]

Normalized brain volume calculated in this way is referred to as the brain to intracranial cavity volume ratio (BICVR), the percent brain parenchyma volume (PBV), the brain parenchymal fraction (BPF), the brain to intracranial cavity ratio (BICCR) or the parenchymal fraction (PF). Calculation of these quantities usually involves independent segmentation of the cerebrospinal fluid (CSF), in which case, normalized brain volume can be calculated as (Fig. 9.5):

\[
\frac{\text{BP volume}}{\text{(BP volume + CSF volume)}}
\]

CVs for normalized brain volume range from 0.2% to 2%, depending on the level of automation in the segmentation. A method used to calculate BPF that does not require segmentation of the cerebrospinal fluid has also been developed. In this
technique, the volume of brain parenchyma is normalized by the total volume within a smoothed outer surface of the brain, which is generated in an intermediate step of the brain segmentation algorithm. The scan-rescan CV for BPF is 0.2%.

Head-size normalization is particularly important in cross-sectional studies, in which normal biological variation in head size can easily obscure subtle disease-related volume differences. In normal healthy controls, normalized brain volume is fairly consistent between the ages of 20 and 55 years.\textsuperscript{[31]} Therefore, normalized brain volumes also provide a means of estimating the total amount of atrophy that has occurred up to the time of the scan, by comparison with an age-

![Fig. 9.4 Example of the central slab approach for 5 mm slice thickness. (a) Four contiguous slices are selected from the T1-weighted image set, with the most caudal at the level of the velum interpositum cerebri.](image)

![Fig. 9.4 (b) The generic automated brain segmentation algorithm (see Fig. 9.3) is applied to segment the brain parenchymal tissue in each slice. Here, the boundaries of the segmented region are superimposed on the original image. The four-slice volume for this example is 270.3 ml.](image)
matched healthy control group. Normalization is also important in placebo-controlled longitudinal trials in which it is necessary to establish that two groups of patients are comparable at baseline. Using absolute brain volumes, it is not possible to ensure that the placebo group and the treated groups do not have different amounts of atrophy at the start of a trial.

Another type of atrophy estimation calculates brain atrophy directly from images acquired serially over time.\textsuperscript{[32,33]} The technique involves registration of the images followed by subtraction. Atrophy is calculated by determining the amount of lateral motion of the edges of the brain and ventricles using an intensity-based calculation called the brain boundary shift integral (BBSI) (Fig. 9.6). The mean error in atrophy measurement using this semiautomated technique is 0.16\%.\textsuperscript{[32]} Error was calculated as the mean difference in boundary shifts when the same eight pairs of images were reanalysed. A fully automated variation on this method uses a full affine registration (including three rotations, three translations, three scales, and three skews) to correct for variations in pixel size by aligning the skull in the two images, and then calculates the shift in brain edges using an edge-based method instead of an intensity-based method.\textsuperscript{[33]} The median atrophy error is similar, 0.2\%, as calculated by rescanning 16 normal volunteers and determining the percentage brain volume change.
Fig. 9.5 Example of calculation of normalized brain volume. (a) Slice from original proton density-weighted image. (b) Slice from original T2-weighted image. (c) Segmented brain parenchymal volume. Volume that is calculated by multiplying number of segmented voxels by the voxel size is 1262.9 ml. (d) Segmented intracranial contents (brain parenchyma plus cerebrospinal fluid); volume is 1633.9 ml. The normalized brain volume for this example is 0.773.
Fig. 9.6 Example of the registration and subtraction approach. (a) Slice from baseline image. (b) Slice from image acquired 1 year later, after three-dimensional registration. (c) Subtraction image. Bright regions indicate tissue loss. Whole brain net volume loss is 52.2 ml (4.4%).

Confounding issues

Regardless of the method used, atrophy measurements from MRI scans can be affected by technical and biological factors, which may complicate interpretation of the results. Technical factors include patient positioning, scanner hardware and software upgrades, partial volume effects, motion artifacts, dental artifacts, voxel size calibration, intensity inhomogeneities, and protocol or sequence variations. Some effects can be minimized by the choice of measurement strategy. For example, one- and two-dimensional measures can be difficult to use in longitudinal studies, owing to the requirements for precise repositioning of the patient and careful selection of landmarks. Three-dimensional (or volumetric) measures and techniques that utilize image registration can reduce the effects of patient repositioning on atrophy measurements. Scanner upgrades and voxel size drift can be partially corrected by using phantoms and consistent calibration procedures throughout the course of longitudinal studies, or by using normalized measures of atrophy. Partial volume effects can be minimized by decreasing slice thickness or by accounting for partial volume effects in volume calculations.

Atrophy measurements may also be affected by biological factors, such as normal aging, alcoholism, anorexia, dehydration, cerebral vascular disease, and steroid treatment. Care should be taken to ensure age matching and proper exclusion criteria for atrophy studies.
ATROPHY IN MS

Natural history

Recent studies have shown that atrophy begins early in MS and progresses throughout the course of the disease. Axonal transection and severe damage occur in early inflammatory lesions.\[34\] Magnetic resonance spectroscopy of patients with less than 5 years’ disease duration demonstrates reduced N-acetylaspartate indicative of axonal damage or loss (see chapter 10).\[35\] MRI atrophy findings in very early MS are consistent with these studies. In a longitudinal study of patients with clinically isolated syndromes suggestive of MS, ventricular enlargement was significantly higher in the patients who had progressed to clinically definite MS after 1 year than in the patients who did not develop MS.\[13\] Similarly, brain atrophy was also detected in six out of 15 patients with early relapsing-remitting MS within 18 months of diagnosis.\[27\] In both studies reporting atrophy in very early MS, the mean rate of change in ventricular volume was approximately 20% a year.

In patients with relapsing-remitting MS of longer duration, normalized volumes and, in some studies, absolute volumes of CNS structures have been shown to be significantly lower than in age-matched healthy controls.\[6,9–14,24,30,36–38\] Atrophy is not confined to particular CNS structures, even at this stage of disease. Significant differences between relapsing-remitting MS and controls have been found in the whole brain,\[14,24,30,37\] central slab volume,\[36\] ventricular volume,\[14\] corpus callosum,\[36\] brainstem,\[6,9\] cerebellum,\[6\] and upper cervical cord.\[6\] The differences are primarily due to a decrease in white matter volume in relapsing-remitting MS,\[6,38\] since there is no significant difference in gray matter fractions between patients and healthy controls. Longitudinally, the rate of atrophy in relapsing-remitting MS patients has been compared to that in age-matched normal healthy controls.\[25,32,39\] The rate of decrease in cord cross-sectional area\[39\] and whole brain net volume loss\[25,32\] over 1 year are significantly higher in relapsing-remitting MS. For whole brain atrophy measurements, the mean rate of atrophy in relapsing-remitting MS is approximately 0.6–1.5% a year,\[25,30,32,37\] but it is highly variable between patients (Table 9.1).

Most longitudinal studies of patients with secondary progressive MS indicate that brain atrophy continues to progress at about the same rate as in relapsing-remitting MS, if subgroups of patients are compared directly.\[32,37,40,41\] However, some researchers have found significantly lower rates of atrophy in secondary progressive MS.\[42\] The rate of spinal cord atrophy may also be less in secondary progressive MS than in relapsing-remitting MS.\[39\] The comparative reports to date have included small numbers of patients; rates of atrophy in patients with relapsing-remitting MS patients have been compared with rates in separate patient groups with secondary progressive MS in these studies. Further investigation is needed to determine the kinetics of atrophy over the entire course of MS.

Brain and spinal cord atrophy are also evident in patients with primary progressive MS.\[10,14,32,39,40,42–44\] In Cross-sectional studies that compare atrophy across MS subtypes, patients with primary progressive MS appear to have approximately the same amount of brain atrophy as patients with secondary progressive
### Table 9.1 Annualized percentage decrease in brain volume measurements

<table>
<thead>
<tr>
<th>Study</th>
<th>Atrophy measure</th>
<th>Relapsing-remitting MS</th>
<th>Secondary progressive MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losseff et al. [18]</td>
<td>Four-slice volume</td>
<td>1.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=13)</td>
<td>(n=16)</td>
<td></td>
</tr>
<tr>
<td>Rudick et al. [30]</td>
<td>Brain parenchymal fraction</td>
<td>0.61</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ge et al. [37]</td>
<td>Whole brain volume</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(n=27)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Fox et al. [32]*</td>
<td>Net brain volume loss</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=6)</td>
<td></td>
</tr>
<tr>
<td>Rovaris et al. [25]†</td>
<td>Whole brain volume</td>
<td>1.3</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(n=50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molyneux et al. [41]</td>
<td>Four-slice volume</td>
<td>–</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>(n=46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saindane et al. [49]</td>
<td>Percent brain parenchymal volume</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zivadinov et al. [51]</td>
<td>Whole brain volume</td>
<td>1.2</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(n=42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rovaris et al. [46]</td>
<td>Seven-slice volume</td>
<td>0.9</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(n=114)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Annual atrophy rate in 26 normal controls was 0.3%; in nine primary progressive patients, it was 0.9%.
†Annual atrophy rate in five normal controls was 0.07%.
Study involved both relapsing-remitting and secondary progressive patients.

MS of the same duration or similar disability levels, despite the significantly lower lesion load in primary progressive MS. So far, only a limited amount of information is available on the rate of atrophy in primary progressive MS measured longitudinally. However, it appears that spinal cord atrophy may progress at a faster rate in primary progressive MS than in other MS subgroups, whereas brain atrophy may progress at a rate similar to that of secondary progressive and relapsing-remitting MS.
Correlations between atrophy and MRI pathology

The major pathologic substrates of atrophy in MS are believed to be demyelination and axonal loss; therefore, it is reasonable to hypothesize that the amount of tissue loss is related to other MRI markers of pathology, including lesions visible on T2-weighted, T1-weighted, or contrast-enhanced MRI, and magnetization transfer ratio (MTR). However, results from correlational analyses have been inconsistent across studies, particularly with regard to the relationship between enhancing lesions and atrophy.

Gadolinium-enhancing lesions on T1-weighted MRI scans indicate acute inflammatory activity accompanied by a breakdown in the blood-brain barrier (see chapter 6). Enhancing lesions have been implicated as the initiating events that lead to severe tissue damage and atrophy in MS. This hypothesis is supported by evidence that the presence, number, or volume of enhancing lesions at baseline are predictive of subsequent atrophy. In a phase III clinical trial of interferon beta-1a in relapsing-remitting MS, the number of enhancing lesions at baseline was the only significant predictor of change in third ventricle width over 2 years ($r^2=0.19$). Similarly, in a trial of glatiramer acetate in relapsing-remitting MS, there was a modest correlation between the number of enhancing lesions at baseline and the change in brain volume over 9 months in the placebo group ($r=-0.34, p=0.0002$). However, other studies have failed to find a relationship between enhancing lesions and atrophy. The discrepancies in findings may be due to several factors. One explanation is that a reduction in brain volume or an enlargement of the ventricles following active inflammation may be due in part to the resolution of inflammation and reduction in edema. This may lead to a variable effect on atrophy measurements, depending on the degree of associated edema. Another possibility is that enhancing lesions represent a range of underlying lesion types, and different studies may have a different mix of destructive and non-destructive lesions included in the counts of enhancing lesions. Patients with higher counts of enhancing lesions typically have a higher relapse rate and, therefore, a greater number of steroid treatments, which may have an effect on atrophy measurements. It has also been hypothesized that atrophy may stem from disease processes that are not linked to inflammation, such as diffuse, primary axonal damage. On the other hand, it could be that inflammation is truly a precursor of the tissue damage that causes atrophy, but that a single snapshot is an insufficient measure of disease activity because changes in the permeability of the blood-brain barrier are relatively rapid. Furthermore, if atrophy is the final step in a pathologic cascade initiated by inflammation, then the optimal time to compare inflammation and atrophy would be dependent on the time course of these processes, which is not yet known and may be highly variable. The relationship between inflammation and atrophy may also vary over the course of disease. These issues are important questions for ongoing research.

Lesions on T2-weighted scans are non-specific markers of MS pathology and may be due to one or more of edema, inflammation, demyelination, axonal loss, or gliosis. Correlations between T2 lesions and atrophy have been demonstrated, despite the lack of pathologic specificity. An explanation for these findings may be that, to some extent, T2 lesion volume represents the sum of current and previous focal tissue damage, whereas atrophy is the sum of all previous damage. Significant correlations with
concurrent atrophy measures range from \(-0.24\) (between central slab volume and T2 lesion volume)\(^{[46]}\) to \(-0.75\) (between PBV and T2 lesion volume).\(^{[24]}\) In several longitudinal studies of patients with relapsing-remitting MS, T2 lesions and changes in T2 lesions are correlated to subsequent atrophy,\(^{[4,30,46]}\) possibly reflecting the evolution from focal tissue damage to atrophy.

It would be expected that T1 hypointense lesions (‘black holes’), which represent regions of severe tissue damage and axonal loss,\(^{[52]}\) would correlate more strongly with atrophy than non-specific T2 lesions would. However, the relationship between T1 lesions and atrophy appears to be very similar to that between T2 lesions and atrophy in most studies.\(^{[14,36,46,50,51]}\) In the CAMPATH-1H study,\(^{[48,53]}\) change in T1 lesion volume was significantly correlated to change in brain volume \((r=0.49, \ p=0.006)\), but change in T2 lesion volume was not.

The relationship between whole brain MTR and atrophy has not been as extensively studied as that between atrophy and lesions. Decreased MTR is mainly due to demyelination, axonal loss, and diffuse abnormalities in the NAWM,\(^{[54]}\) which are the same factors believed to be responsible for atrophy. Various MTR parameters, including mean MTR, histogram peak height, and first, second, and third MTR histogram quartiles, have been shown to be significantly correlated to central slab volume \((r=0.4–0.5)\).\(^{[54]}\) In preliminary reports, correlations between mean whole brain MTR and normalized brain volume measures are also relatively strong \((r=0.6–0.7)\).\(^{[56,57]}\) Brain atrophy appears to be more strongly correlated with whole brain MTR than with lesions, which is consistent with the hypothesis that both measures are sensitive to diffuse damage in normal-appearing tissue and possibly have common pathologic substrates.

**Correlations between atrophy and disability**

Measures of atrophy are more closely related to neurologic disability in MS patients than conventional lesion measurements (Table 9.2). The strength of the correlations depends on the type of atrophy measure, the type of disability measure, and possibly, the type of MS. Cross-sectionally, correlations between the expanded disability status score (EDSS) and brain atrophy are typically modest \((r=0.2–0.5)\).\(^{[16,14,30,36,37,41,43]}\) while correlations between the EDSS and spinal cord atrophy are stronger \((r=0.5–0.7)\).\(^{[10,12,43]}\) This may be related to characteristics of the EDSS, which is primarily a measure of ambulation. Correlations between brain atrophy and the MS Functional Composite (MSFC)\(^{[58]}\) are stronger than the correlations between brain atrophy and EDSS.\(^{[14,59]}\) The MSFC consists of a walking score (timed 25-minute walk), an arm function score (nine-hole peg test), and a cognitive score (paced serial addition test, or PASAT) (see chapter 2).

By comparison of results across studies, normalized atrophy measures, which correct for head size, appear to be more strongly correlated to disability than absolute volume measurements. Several longitudinal studies indicate that patients with greater rates of atrophy are more likely to worsen clinically\(^{[18,41,59]}\) and vice versa\(^{[60]}\). In an 8-year follow-up study of 172 patients originally enrolled in the phase III trial of interferon beta-1a in relapsing-remitting MS, 52% of patients in the quartile with the highest rate of atrophy in the first 2 years had reached an EDSS score of 6 or more at the 8-year follow-up. In contrast, only 12% of patients in the quartile with the lowest rate of atrophy in the first 2 years had reached an EDSS score of 6 or more at the time of follow-up.\(^{[61]}\) As with the
relationships between atrophy and lesions, the relationship between atrophy and disability may be complicated by a possible time lag between when tissue injury occurs and when this injury is detectable as atrophy on MRI. Furthermore, the brain may be able to compensate for tissue injury early in the disease when there is still sufficient functional reserve and capacity for tissue repair, leading to a dissociation between atrophy and disability. Data demonstrating higher atrophy-disability correlations later in the disease or in secondary progressive MS compared with relapsing-remitting MS support this hypothesis.\[37,59\]

Table 9.2 Correlations between atrophy and disability

<table>
<thead>
<tr>
<th>Study</th>
<th>Atrophy measure</th>
<th>Subjects</th>
<th>Disability measure</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losseff et al.[10]</td>
<td>Cord area</td>
<td>30 RR 15 SP 15 PP</td>
<td>EDSS</td>
<td>−0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stevenson et al.[39]</td>
<td>Cord area</td>
<td>10 RR 6 SP 12 PP</td>
<td>EDSS</td>
<td>−0.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Lycklama a Nijeholt et al.[12]</td>
<td>Cord area</td>
<td>28 RR 32 SP 31 PP</td>
<td>EDSS</td>
<td>−0.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Stevenson et al.[43]</td>
<td>Cord area</td>
<td>158 PP 33 TP</td>
<td>EDSS</td>
<td>−0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liu et al.[6]</td>
<td>Cord area</td>
<td>20 RR 20 SP</td>
<td>EDSS</td>
<td>−0.37</td>
<td>0.023</td>
</tr>
<tr>
<td>Lycklama à Nijeholt et al.[12]</td>
<td>Ventricle volume</td>
<td>28 RR 32 SP 31 PP</td>
<td>EDSS</td>
<td>No correlation</td>
<td></td>
</tr>
<tr>
<td>Losseff et al.[18]</td>
<td>Four-slice volume</td>
<td>13 RR 16 SP</td>
<td>EDSS</td>
<td>No correlation</td>
<td></td>
</tr>
<tr>
<td>Stevenson et al.[43]</td>
<td>Four-slice volume</td>
<td>158 PP 33 TP 33 Timed walk</td>
<td>EDSS</td>
<td>−0.20</td>
<td>0.006</td>
</tr>
<tr>
<td>Molyneux et al.[47]</td>
<td>Four-slice volume</td>
<td>95 SP EDSS</td>
<td>EDSS</td>
<td>0.18</td>
<td>0.018</td>
</tr>
<tr>
<td>Liu et al.[6]</td>
<td>Cerebral white matter</td>
<td>20 RR 20 SP</td>
<td>EDSS</td>
<td>−0.37</td>
<td>0.018</td>
</tr>
<tr>
<td>Filippi et al.[40]</td>
<td>Whole brain volume</td>
<td>11 RR 4 SP</td>
<td>EDSS</td>
<td>No correlation</td>
<td></td>
</tr>
<tr>
<td>Fox et al.[32]</td>
<td>Net brain volume loss</td>
<td>6 RR 6 9 PP</td>
<td>EDSS</td>
<td>No correlation</td>
<td></td>
</tr>
<tr>
<td>Ge et al.[37]</td>
<td>Percent brain parenchymal volume</td>
<td>27 RR EDSS</td>
<td>EDSS</td>
<td>No correlation</td>
<td></td>
</tr>
<tr>
<td>Ge et al.[37]</td>
<td>Percent brain parenchymal volume</td>
<td>9 SP EDSS</td>
<td>EDSS</td>
<td>−0.69</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Fisher et al.\cite{59}  
Brain parenchymal fraction  
134 RR EDSS  
-0.29 to -0.42 <0.001  
MSFC  
0.42 to <0.0001  
0.50  

Paolillo et al.\cite{36}  
Infratentorial-supratentorial ratio  
52 RR EDSS  
-0.49 0.004  

Kalkers et al.\cite{14}  
PF and VF  
80 RR 36 EDSS  
SP 21 PP  
MSFC  
0.36 to <0.01  
-0.40

RR, relapsing-remitting; SP, secondary progressive; TP, transitional progressive; PP, primary progressive; EDSS, Expanded Disability Status Score; MSFC, Multiple Sclerosis Functional Composite; PF, parenchymal fraction; VF, ventricular fraction.

Brain atrophy has also been shown to be related to cognitive impairment\cite{1,7,20} and quality of life\cite{2,60} in MS patients. An early study of chronic progressive MS patients demonstrated that performance on memory and intelligence tests was correlated to the degree of ventricle enlargement.\cite{1} In patients followed over 1 year, cognitive change was related to baseline normalized brain atrophy measures.\cite{20}

**ATROPHY AS AN OUTCOME MEASURE IN CLINICAL TRIALS**

The effects of MS treatments on atrophy have been investigated in several clinical trials, including those for interferon beta-1a (Avonex), CAMPATH-1H, cladribine, linomide, glatiramer acetate, interferon beta-1b, pulsed intravenous methylprednisolone, and interferon beta-1a (Rebif) (Table 9.3). Many

<table>
<thead>
<tr>
<th>Study</th>
<th>Atrophy measure</th>
<th>Subjects</th>
<th>Duration</th>
<th>Study design</th>
<th>Atrophy results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudick et al.\cite{30}</td>
<td>Brain parenchymal fraction</td>
<td>140 RR</td>
<td>24 months</td>
<td>Double-blind, placebo controlled</td>
<td>Treatment effect on atrophy in year 2 (p=0.03)</td>
</tr>
<tr>
<td>Ge et al.\cite{62}</td>
<td>Whole brain volume</td>
<td>27 RR</td>
<td>24 months</td>
<td>Double-blind, placebo controlled</td>
<td>Treatment effect on atrophy</td>
</tr>
<tr>
<td>Rovaris et al.\cite{46}</td>
<td>Seven-slice volume</td>
<td>227 RR</td>
<td>18 months</td>
<td>9 months blind, placebo controlled; atrophy 9 months</td>
<td>No treatment effect on atrophy</td>
</tr>
</tbody>
</table>

Table 9.3 Atrophy outcomes in clinical trials
of these drugs have been shown to be effective in reducing the number of gadolinium-enhancing lesions, but their effects on atrophy are not well understood. A 2-year phase III trial of interferon beta-1a in relapsing-remitting MS demonstrated a significant treatment effect on atrophy in the second year of the trial.\(^{[30]}\) Similar rates of atrophy were observed
in the European dose comparison study of interferon beta-1a in relapsing-remitting MS, in which the brain atrophy rate in the second and third years was about half of that of the first year. The delay in effectiveness may be due to a continuation of destructive processes initiated by inflammatory activity before the trial. A treatment effect on brain volume change was also observed in a subset of 27 patients from the 2-year phase III trial of glatiramer acetate in relapsing-remitting MS, but not in the larger, but shorter-term European trial of glatiramer acetate. A 5-year study of pulsed intravenous methylprednisolone in relapsing-remitting MS resulted in a significantly reduced rate of atrophy in the treated group compared with a group who received steroids only for relapses. In a 3-year European trial of interferon beta-1b in secondary progressive MS, there was no treatment effect for the group overall, but stratification by the presence of gadolinium-enhancing lesions at baseline revealed that in the subgroup without enhancing lesions, the treated group had significantly less atrophy than the placebo group. Other trials have found no treatment effects on atrophy. Results are not easy to compare across trials because each trial used a different type of atrophy measure and studied patients with different baseline characteristics. The durations of the controlled trials also varied considerably, from 9 months to 5 years, and time may be an important factor in studies of brain tissue loss due to MS. Atrophy measurement is attractive as an outcome measure for MS treatment trials because it may provide a means of testing the ability of a particular therapy to halt tissue destruction.

**SUMMARY**

Various reliable techniques have been developed to estimate regional and global CNS atrophy. Although atrophy is not pathologically specific, it reflects irreversible tissue loss caused by MS, and it is therefore a valuable marker of disease severity. Brain atrophy can be detected very early in the course of MS, and it appears to progress almost from the time of disease onset. Current evidence suggests that atrophy correlates better with neurologic measures of disability than T2 lesions or gadolinium-enhancing brain lesions do. Both cross-sectional and longitudinal measurements of atrophy provide important information on disease severity and progression. For example, normalized measures of CNS atrophy provide an estimate of how far the disease has progressed until that point in time. Atrophy measurement over time in relapsing-remitting MS may reflect underlying tissue destruction ‘between relapses’ that is not expressed clinically, due to functional reserve capacity. Finally, atrophy measurement in the later stage of disease may reflect ongoing tissue destruction not necessarily related to inflammatory events at that stage of the disease. Atrophy measures are attractive components of a comprehensive MRI-based outcome assessment in MS clinical trials since they reflect diffuse pathologic processes that are not accounted for by lesion measurements. Important areas for future research include the time course of atrophy following tissue damage, the relationship between inflammation and tissue destruction, and the precise pathologic mechanisms of atrophy.
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Measures to quantify axonal damage in vivo based on magnetic resonance spectroscopy in multiple sclerosis
Douglas L Arnold and Paul M Matthews

INTRODUCTION

The clinical course of multiple sclerosis (MS) is highly variable, and the pathological changes of the disease are heterogeneous between individual patients. In recent years there has been increasing interest in developing approaches to characterizing the pathological substrates of disability in MS in the hope that quantitative indices of pathology in vivo would provide new insights into disease pathogenesis, as well as more specific and sensitive endpoints for treatment trials.

This chapter reviews magnetic resonance spectroscopy (MRS) studies of chemical pathology specific for axonal injury in vivo, and places these in context with respect to results from classical pathological investigations. It focuses on one of the most important of the hypotheses that have developed from magnetic resonance studies, namely that axonal damage may be the final common pathway causing disability in MS.

THE CASE FOR AXONAL INJURY IN MS

Demyelination cannot account for chronic functional impairments in MS

Compared with the inflammatory lesions of encephalitis or ischaemic infarction, microscopic examination of MS plaques shows demyelination with a relative preservation of axons. This observation, together with experiments demonstrating that acute demyelination leads to conduction block, led to an earlier focus on demyelination as an explanation for functional impairments in MS.[1] However, demyelination alone does not adequately explain the functional impairments in MS.[2] Conduction in segmentally demyelinated axons can recover.[3] For example, in patients with optic neuritis, although there may be early conduction block after acute inflammation, conduction recovers across chronically demyelinated regions of the optic nerve.[4] In the optic nerve of the myelin-deficient rat, action potential propagation is approximately five times slower than normal, but the action potential propagation is stable and has
frequency-following and refractory properties similar to those of myelinated axons in wild-type rats.\[5\]

One crucial distinction between responses to acute and chronic demyelination is that molecular adaptive changes are possible with the chronic condition. In an elegant experiment, Rivera-Quinones et al. have demonstrated that mice deficient in class I MHC (β-2-microglobulin-deficient-mice) that are infected with Theiler’s murine encephalomyelitis virus develop extensive demyelination without neurological deficits, whereas class II MHC-deficient mice develop demyelination and severe paralysis leading to early death.\[6\] A potentially important difference in the response of these two mice to inflammatory demyelination was that the class I MHC-deficient mice showed increased axon sodium channel density after demyelination, whereas class II MHC-deficient mice did not. Adaptations in the axon such as increased expression of new sodium channels\[7\] can contribute to maintenance of axonal function with chronic demyelination.

**Mechanisms of acute conduction block are distinct from mechanisms for chronic functional impairment**

It thus is important to distinguish the phenomena of acute and chronic impairment of axonal function. In fact, there are multiple mechanisms of acute conduction block that are different from the mechanisms causing chronic functional impairment. Experiments such as those by Rivera-Quinones et al.\[6\] suggest that conduction block occurs acutely after demyelination in part because of the relatively sparse distribution of sodium channels in the newly exposed, normal internodal axon membrane. With chronic demyelination, sodium channels can be up-regulated adaptively along the demyelinated axon to restore conduction.\[8\] There is some evidence that insertion of new sodium channels in demyelinated axons occurs in patients with MS, as demyelinated white matter has up to a four-fold increase in saxitoxin binding, a measure of sodium channel density.\[9\]

The inflammatory response itself also is probably responsible for additional mechanisms of acute conduction block in multiple sclerosis. Local inflammation can lead to injury or dysfunction of axons, even if axons are not the direct autoimmune target. Locally released inflammatory mediators including nitric oxide and other reactive oxygen species can cause metabolic dysfunction and conduction block.\[10,11\] If applied for shorted periods at lower concentrations, these effects are reversible, which could account for subacute functional recovery accompanying resolution of inflammation. Reversible dysfunction also could be mediated by local production of antineuronal antibodies. Production in the central nervous system of antibodies directed against a broad range of epitopes has been described in MS. Takigawa et al. have recently demonstrated that antibodies directed against GM1 gangliosides may suppress the axonal sodium current necessary for depolarization and cause conduction block, for example.\[12\] Waxman has suggested that relative selectivity of antibodies for different sodium channel subtypes might account for the apparent variability of conduction block between different classes of axons.\[13\]
The ‘axonal hypothesis’

Defining the pathological changes ultimately responsible for functional impairments in MS is critical for the optimal targeting of new therapies. Successful trials of anti-inflammatory therapies have highlighted an apparent dissociation between new inflammation and short-term progression of disability.\textsuperscript{[14]} In conjunction with evidence of the type cited above, such observations emphasize that demyelination cannot be the primary pathological substrate for disability. The authors therefore have proposed an ‘axonal hypothesis’ for chronic disability in MS: axonal damage or loss is required for chronic functional impairments and disability.

One prediction of this hypothesis is that irreversible axonal loss must be associated with chronic, irreversible disability. A second prediction is that reversible axonal injury should be associated with functional recovery after relapse. Evidence supporting both predictions has come from MRS studies,\textsuperscript{[15,16]} which allow quantitative and non-invasive assessment of axonal injury and loss in patients with MS, enabling dynamic correlations between pathology in vivo and disability.

EVIDENCE FROM MRS AND PATHOLOGICAL STUDIES FOR AXONAL INJURY IN MS

An overview of the proposed pathogenesis of axonal injury in MS and the associated changes in other tissue components of the brain is shown in Fig. 10.1. The primary attack in MS is presumed to be directed against myelin or oligodendrocytes. At least initially, axons (and other cells) are probably mainly injured as ‘innocent bystanders’ by local effects of inflammatory mechanisms. However, in the longer term, axons may also be injured by the development of immunity directed against axons or neurons, perhaps as a consequence of chronic tissue injury. If the injury to myelin or axons is sublethal, there may be partial recovery of conduction associated with remyelination or axonal adaptations such as the insertion of new sodium channels. Axons that are lethally injured and ‘transected’ undergo wallerian degeneration, during which the distal, disconnected axonal segments and their myelin degenerate and are eventually removed. This process may contribute to neuronal cell death.\textsuperscript{[17]}

Atrophy occurs in association with the loss of axons, myelin, and other cells, but not directly in parallel with this cell damage, since increases in extracellular space and gliosis also occur. White matter atrophy attenuates decreases in axonal density, whereas increases in extracellular space and gliosis attenuate atrophy and contribute to decreases in axonal density. It follows that a full quantification of the extent of axonal injury and loss require measurement of both decreases in axonal density in remaining brain tissue and estimation of the loss of axons associated with atrophy. We have proposed that this be done by the use of an axonal injury composite (AIC), which expresses the loss.

Introduction to MRS

A limitation of the use of conventional magnetic resonance imaging (MRI) to follow pathological changes is that image contrast is affected by too many factors to allow...
changes in contrast generally to be interpreted in terms of specific pathological processes. In contrast, MRS studies can

**Fig. 10.1 The bases of axonal damage in lesions and normal-appearing white matter of patients with MS.**

provide more specific information regarding pathological changes in and around lesions, particularly regarding axonal loss or injury. Although the low concentrations of intracellular metabolites mean that the spatial resolution of the spectroscopic methods is much lower (of the order of 1 ml) than that of conventional MRI, statistical inferences from the two types of studies performed together can be pathologically specific and sufficiently well-resolved to be useful.

Water-suppressed, localized proton magnetic resonance spectra of the human brain reveal major resonances from choline-containing phospholipids (Cho), creatine and phosphocreatine (Cr), N-acetyl groups (predominantly from N-acetylaspartate (NAA)), and (under appropriate observational conditions) from lactate and mobile lipids or macromolecules (Figs 10.2 and 10.3).[18] Minor resonances from amino acids such as glutamate and γ-aminobutyric acid (GABA) and sugars such as glucose and inositol also can be identified. Two factors primarily determine which resonances can be usefully studied by MRS in the brain: mobility and concentration. Only molecules that are freely mobile give rise to well-defined, discrete resonances, and only relatively abundant
molecules (with concentrations on the order of mmol/l) provide a sufficient signal-to-noise ratio.

Fig. 10.2 NAA in the normal-appearing white matter of a normal subject and in a lesion and the normal-appearing white matter of a patient with MS. (A) Conventional MRI from the normal subject showing the phase encoding grid for the MRS imaging. A sample spectrum from voxel 1 is also shown. (B) Conventional MRI from a patient with MS also showing the phase encoding grid for the MRS imaging. A sample spectrum from a voxel with the appearance of lesion on MRI (2) and another from a voxel in normal-appearing white matter (3) are also shown.
The $N$-acetyl group resonance has been particularly useful in studies of MS since it originates predominantly from NAA. NAA is found only in neurons and neuronal processes in the normal mature brain and therefore can be used as a specific marker of neurons and axons.\textsuperscript{[19–21]} Decreases in brain NAA in white matter reflect axonal pathology. Because magnetic resonance spectra report on the density of NAA (the amount in the volume ‘voxel’ of interest), decreases in the signal from NAA can occur as a result of decreased relative axonal density (volume per unit volume) in the voxel (caused by either axonal loss or by axonal atrophy), decreased concentration of NAA in axons (caused by axonal metabolic dysfunction) or, in acute lesions, dilution secondary to oedema. Observed decreases in NAA may be either reversible or irreversible, depending on the nature of the responsible pathology (i.e. axonal loss secondary to axonal transection and wallerian degeneration versus reversible metabolic dysfunction associated with sublethal injury or resolution of acute oedema).\textsuperscript{[22]}

**MRS demonstrates substantial axonal injury in MS**

The most striking observation made by the initial MRS studies of MS was that the brain NAA:Cr ratio was lower in patients with MS than in normal controls.\textsuperscript{[23]} As the Cr:Cho ratio was normal, it was concluded that brain NAA concentration must be reduced,
implying that there was substantial injury to axons throughout the white matter of patients with MS. The observation of a low NAA:Cr ratio was confirmed in numerous subsequent studies.[24–32] The decrease in NAA resonance intensity observed in normal-appearing white matter (NAWM) can approach 50%,[33] and the decrease of NAA in lesions can exceed 80%.[22] In large lesions, a gradient of axonal injury between the center of the lesion, its edge, and the surrounding NAWM can be demonstrated.[25] The relationship between decreases in NAA resonance intensities to decreases in axonal density in subacute lesions has been confirmed directly using stereotaxically obtained brain biopsy specimens.[34] This has also been confirmed in studies of spinal cords from MS patients.[35] Direct measurements of the absolute concentrations of these metabolites has confirmed that NAA concentrations are reduced relative to normal controls.[34,36] Recently, MRS-measured values of NAA within the cortical normal-appearing gray matter of MS patients have also been shown to be decreased relative to those in the cortical gray matter of normal control subjects.[18,37] A combined spectroscopic and histopathological view of the thalamus has provided evidence that neuronal loss could be responsible for at least a large proportion of the reduction of NAA in gray matter.[38]

**Histopathology also demonstrates substantial axonal damage in MS**

This MRI evidence is consistent with a careful reading of post mortem pathological studies. Despite the emphasis on understanding myelin and oligodendroglial cell damage for the last several decades, even early neuropathological studies recognized axonal injury and loss in and around the lesions of MS. What was to some extent ‘forgotten’ in more recent textbooks is that Charcot[39] and many subsequent pathologists emphasized only that there was a relative preservation of axons (contrasting MS with highly destructive inflammatory diseases such as encephalitis). Axonal transection and damage in or around MS plaques have been assessed elegantly in recent studies that have demonstrated that axons are damaged in acute, as well as in chronic lesions[40] and that axonal injury (as assessed from expression of amyloid precursor protein) is far more extensive than axonal transection.[41] Histopathology shows that loss of axons varies considerably between lesions.[42] Confirming results from MRS studies, quantitative histopathological studies have shown that axonal loss extends substantially into the ‘normal-appearing’ white matter. For example, axonal density was decreased by a mean of 35% outside of lesions in the corpus callosum of eight patients with MS.[43] In the same patients there was also a loss of corpus callosum volumes, implying total axonal loss of as much as 50% in this ‘normal-appearing’ white matter.

**Relationship between axonal damage, cerebral atrophy, and disability**

Thus, volume changes due to loss of myelin and axons are not fully compensated by gliosis in the white matter. Associated neuronal loss leads to gray matter volume loss, so progression of destructive and degenerative pathology in MS leads to decreases in volume across the whole brain. Easiest to appreciate is the accompanying ventricular enlargement because of their relatively small volume in the healthy brain. However, gray matter structures also can show substantial atrophy, although it is more challenging to
monitor because of its smaller absolute magnitude.\textsuperscript{44,45} As sensitive methods for detecting small volume changes from serially acquired structural brain (or spinal cord) images become more available\textsuperscript{46–49} it has become possible to quantify atrophy in MS, even early in the course of the disease.\textsuperscript{50} Although functional compensatory mechanisms may allow the dissociation of mild atrophy and disability early in the course of MS, measures of brain and spinal cord atrophy\textsuperscript{51,52} tend to correlate strongly with disability.

**RELATIONSHIP OF AXONAL DAMAGE TO DISABILITY IN MS**

**MRS measurements of NAA correlate with changes in disability**

The axonal hypothesis posits that axonal damage (however it may occur) is the major direct cause of chronic functional impairment in MS. If this is true, then there should be an inverse correlation between levels of brain NAA measured by MRS and disability both in cross-sectional and in longitudinal studies. One of the first MRS studies of MS suggested that this was indeed the case.\textsuperscript{23} Davie et al. later showed that MS patients with high cerebellar dysfunction scores had lower cerebellar NAA than those with low cerebellar dysfunction scores, and that healthy controls had higher cerebellar NAA concentrations than either patient group.\textsuperscript{53} More recent cross-sectional studies have shown strong negative correlations between concentrations of NAA in cerebral white matter and disability in patients with relapsing-remitting MS.\textsuperscript{33}

Two studies have reported that the MRS measurement of white matter NAA concentrations is sensitive to the increasing axonal damage expected from increasing disease burden with time. An informative early serial study of patients with MS in which single-volume spectra were taken from a volume centred on the corpus callosum demonstrated a progressive decrease in the relative NAA resonance intensity over 18 months.\textsuperscript{26} This was confirmed in a follow-up study with a larger group of patients, although the mean rate of decrease of NAA in the larger study was slower.\textsuperscript{54} These and other studies have emphasized that quantitative MRS studies are reproducible (certainly to within 5\% in serial measurements of relative NAA concentrations in usual MRS imaging voxels) and that small changes can be detected reliably.

**The importance of axonal damage in the ‘normal-appearing’ white matter**

The earliest MRS studies in MS showed substantial decreases in brain NAA, even though lesions occupied only a small fraction of the MRS imaging volume. This suggested that axonal loss in MS was not restricted to the lesions and was widespread. This has now been confirmed directly in post mortem studies\textsuperscript{43} as well as in vivo studies.\textsuperscript{34}

Because the NAWM constitutes the greatest bulk of white matter, even though axonal loss and damage are less severe overall than in individual lesions, axonal injury in the NAWM may be more significant than that in lesions for determining chronic, non-relapse-related disability. One of the earlier studies to suggest the potential importance of abnormalities of NAWM compared imaging and MRS changes in patients with relapsing-remitting MS and in a more disabled group with secondary progressive MS. The two
groups did not have a significant difference in total T2-weighted lesion volume. However, the average extent of axonal injury as assessed by central brain NAA:Cr ratio was significantly greater in the secondary progressive patients (who had the longer disease duration and the greater disability). Follow-up work showed that this difference was definitely due to relatively greater changes in the NAWM in the patients with secondary progressive disease, rather than to differences in the chemical pathology of the lesions themselves (see Fig. 10.2). The strong correlation of decreases of NAA in NAWM with disability have been confirmed more recently and extended with measurements of absolute concentrations of NAA.

In order to determine the relationship between progression of chronic disability and brain NAA, information from MRS imaging and conventional imaging studies have been combined using statistical models that allow precise correlations over time to be determined between the spatial distribution of chemical changes and changes on conventional MRI. In this way, the time course of NAA changes could be followed with respect to the spatial distribution of NAA across the brain and the presence or absence of T2-weighted lesions in the same areas. This approach confirmed earlier reports showing progressive decreases in NAA with time and the correlation between diffuse axonal damage in NAWM and progression of disability in patients with MS.

**Reversible axonal dysfunction and clinical remission in MS**

The remission of symptoms after exacerbations of MS is probably associated with multiple factors including restoration of conduction in persisting axons and cerebral adaptations to the injury. A striking and unexpected observation (which has since been confirmed by several research groups) has been that acute MS lesions (see Fig. 10.3) can be associated with reversible decreases in white matter NAA. These reversible decreases in NAA are strongly correlated with reversal of functional impairments in MS. In small series of cases, serial studies of individual MRS imaging voxels have shown NAA decreases of between 30% and 80% in the centre of lesions with variable recovery of NAA towards normal concentrations after the acute phase of the relapse. NAA recovery was most rapid over the first few months after relapse.

Only a proportion of the apparent recovery of NAA in these large lesions can be related to resolution of local oedema, since the relative volume changes in even large lesions are smaller than the proportional decrease in NAA. The decrease of NAA in lesions therefore must result from either axonal volume loss or decreases in axonal NAA concentration. Axons shrink in diameter with demyelination, at least in part because demyelination is associated with dephosphorylation of neurofilaments that help to maintain axonal diameter. Thus, MS lesions are characterized by axonal dystrophy and increased variability in axonal diameter. Increases in the diameter of reversibly atrophied axons can occur with remyelination. NAA recovery also could reflect reversible metabolic dysfunction in axons, possibly associated with reversible mitochondrial damage. Mitochondrial toxins have been shown to cause decreases in NAA, and in vitro studies of a neuronal cell line have demonstrated that decreases in NAA following serum deprivation can be reversed fully by further incubation in serum-containing medium. Consistent with this, other acute, resolving metabolic pathologies have been defined in which there are reversible changes in brain NAA.
INTEGRATION OF MULTIPLE MEASURES OF PATHOLOGY AND FUNCTIONAL IMPAIRMENT

Recent pathological studies have emphasized heterogeneity in the pathology of MS. Defining this heterogeneity is important since it may be expected to contribute to the considerable clinical heterogeneity of MS. Lucchinetti et al., for example, have proposed that there are five distinct patterns of lesion pathology that can be discriminated in post mortem materials based on the nature of myelin, oligodendroglial cell, and axonal changes.[66] Just as the classical pathologist employs a range of cell and tissue markers in order to develop a composite picture of pathological changes in lesions, so those studying MS pathology by magnetic resonance should simultaneously apply and integrate information from multiple pulse sequences that generate complementary forms of contrast. Combined use of spectroscopic imaging and other imaging sequences (e.g. short T2 imaging[67] and quantitative MT imaging[68]) that are relatively more sensitive to distinct and specific aspects of pathological change can better define the pathological heterogeneity in lesions.

As measures of brain and spinal cord atrophy[51,52] and NAA density[35–54] all correlate strongly with disability, a combined index based on a combination of these metrics could provide a particularly sensitive and meaningful index of change.[46]

IMPLICATIONS OF MRS STUDIES FOR UNDERSTANDING THE NATURAL HISTORY AND TREATMENT OF MS

Evidence is accumulating that chronic, progressive changes in disability may directly reflect the chronic progressive damage to axons that now is appreciated as such a key feature of MS.[7,69] A principal conclusion of recent MRS studies has been that this damage is manifest throughout the white matter of the brain, not just in the focal lesions where the most prominent inflammatory changes occur.[33,36] Axonal metabolic dysfunction also seems likely to play a role in the acute, reversible functional impairments associated with relapses.[2] These effects can be both local to new inflammatory lesions and more widespread.[70]

These observations have important implications for the treatment of MS. First, they suggest that a given treatment strategy may not be equally efficacious for all patients, even with the same clinical syndrome (e.g. relapsing-remitting MS). If there is significant heterogeneity of pathological mechanisms between individual patients, it may be rational to tailor treatments for particular pathological subgroups. Magnetic resonance methods could provide a clinically practical way of stratifying patients for different treatments. There clearly is an urgent need to coordinate classical pathological studies and magnetic resonance studies in an effort to interpret the ‘in vivo pathology’ provided by the latter more precisely.

Second, new drugs or combinations of drugs that are targeted against multiple mechanisms responsible for the progression of the pathology need to be developed. Current approaches are directed primarily towards limiting the acute inflammatory responses. Modulation of mechanisms underlying acute and chronic axonal injury or enhancing functional re-organization of the brain may clearly be important in addition.
The lack of enthusiasm for axonal potassium channel blockade by aminopyridines may be tempered by the recognition that effects may only be expected for a limited period in lesion evolution (e.g. during the period of acute conduction block). Further development of strategies based on the use of neurotrophins and other neuronal survival factors may be important for enhancing axonal survival and recovery potential in the longer term. Efforts to control specific mechanisms of axonal injury, such as those that might be mediated by anti-sodium channel antibodies, also need to be explored.

A third major conclusion from the work reviewed in this chapter arises from the observation that axonal injury occurs even in acute lesions. With this in mind, the rationale for reducing relapse rate and treating acute relapses changes from that of short-term enhancement of the quality of life to preventing the accumulation of later, more severe axonal loss and associated disability. The sensitivity of clinical measures in short trials for detecting such changes is understandably limited, suggesting that use of potentially more sensitive surrogate markers (e.g. a composite index of brain NAA and atrophy) may provide a practical approach to rapidly identifying new drugs that could limit the progression of axonal damage. Appreciation for the role of axonal injury in chronic disability progression and the mechanisms by which inflammation leads to axonal injury should enhance enthusiasm for early treatment of patients to reduce inflammation.

Ultimately, the development of multiple, complementary methods for definition of the pathological changes of MS may contribute to rational approaches towards preparation of in vivo strategies for simultaneous targeting of multiple pathological stages with combined therapy. Such approaches also should allow improved trial designs, not only by increasing the precision with which trial endpoints based on such surrogate markers can be reached, but also by providing pathological specificity to allow trials of new agents, even in populations being treated with agents that target other stages in the pathological progression of the disease.

**SUMMARY**

Recent MRS techniques have focused the attention of the MS research community on the importance of axonal injury in this primarily demyelinating disease. Early axonal injury most likely results mainly from ‘innocent bystander’ damage to axons associated with the inflammatory response directed against myelin. However, as axons depend on glia for trophic and other support, accumulating glial damage also may lead to later axonal atrophy or dysfunction. MRS studies have emphasized that axonal damage in MS can be substantial and that it begins early on in the course of the disease. The dynamic observations of axonal pathology that are possible with MRS have demonstrated direct correlations between measures of axonal injury and disability. These observations suggest that MRS may play an important role in the assessment of new treatments for MS that are directed towards limitation of damage in the central nervous system axons or the salvage of injured axons.
DLA is grateful for support from the Medical Research Council of Canada and the Multiple Sclerosis Society of Canada. PMM acknowledges support from the Medical Research Council of Great Britain and the Multiple Sclerosis Society of Great Britain and Northern Ireland.

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Functional imaging in multiple sclerosis
Nancy L Sicotte

INTRODUCTION
The use of imaging technologies in the past decade has revolutionized clinical trials of potential therapies for multiple sclerosis (MS). In vivo imaging of brain structure using magnetic resonance imaging (MRI) is routinely used to evaluate the effectiveness of new MS therapies and has led to important insights into the disease process. The recognition that inflammatory activity occurs at high rates even in clinically stable patients[1] and the discovery that widespread abnormalities are present in seemingly normal white matter regions[2–4] are just two of the significant findings gleaned through the use of structural MRI. The application of newer MRI techniques, such as magnetization transfer imaging (MTI), diffusion weighted imaging, and spectroscopy, described in detail elsewhere, will help to characterize the neuropathologic heterogeneity of MS plaque as seen on a standard T2-weighted image.

While structural imaging has provided important insights, lesion burdens as determined on T2-weighted images are not well correlated with measures of neurologic disability.[5] Understanding how structural changes in the white matter are related to brain activity in the gray matter of cortical and subcortical regions may unravel some of the mystery of the dissociation between MRI and disability. Unlike standard structural MRI studies, functional imaging has not been used routinely in clinical trials of MS therapies, but these approaches will be increasingly important in the future as therapies focus on secondary progressive disease, cognitive impairment, and the role of plasticity and adaptation. Newer therapeutic approaches, such as remyelination or neuroprotective strategies, will require a new magnetic resonance ‘readout’ in addition to traditional T1 or T2 scans. Functional imaging techniques will play an increasingly important role in evaluating these new therapies. In addition, the use of functional imaging techniques will add to our understanding of the MS disease process and may reveal novel therapeutic targets.

While structural imaging gives details of the changes in white matter that occur in MS, functional imaging techniques can reveal the consequences of these lesions on cortical and subcortical activity. In some cases, small strategically placed lesions can cause disconnection or diaschisis, leading to widespread alterations in cortical activity and abnormal behavior.[6,7] Plaques near the gray-white junction may have profound effects on cortical activity.[8,9] In addition to the well known changes seen in white matter, pathologic and structural imaging studies have demonstrated significant involvement of gray matter regions in MS,[10–14] which may be reflected in altered brain functional
measures. Over time, the functional consequences of these various disease processes may change, causing disconnection, reconnection, or adaptation. Relating these dynamic processes to clinical measures is a challenging task.

This chapter provides a brief overview of the functional imaging techniques currently used, the approaches used to analyse the results of these procedures, and the special considerations for the use of functional imaging in MS patients. The results of functional imaging studies of MS patients carried out to date are reviewed. Finally, future applications of conventional and newer imaging techniques are discussed.

**GENERAL PRINCIPLES**

Several methods are currently available to assess human brain function. These include measures of glucose metabolism, cerebral blood flow, and receptor binding. The most commonly used techniques for human studies are positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). The ability of any functional imaging study to reveal brain activity accurately is limited by the spatial and temporal resolution of the particular technique, the type of scanner used, and the parameters chosen for an individual scan. It is important to emphasize that none of the techniques currently used in humans is a direct measure of neuronal activity; rather, they are measures of processes that are related to neuronal activity, such as blood flow and glucose metabolism.

**Positron emission tomography**

PET uses radioactive biological tracers that can be localized within the brain using tomographic methods. The behavior of very small amounts of biologically active tracers can be used to calculate the rate of ongoing physiologic processes. This technique can be used to quantify glucose metabolism, cerebral blood flow, receptor binding, and even gene expression. The principle is the same regardless of the particular application. A radioactive agent that emits positrons is attached to the tracer of choice. The tracer is introduced into the body by injection or inhalation. The radiolabeled material is then distributed throughout the body and into the brain according to the kinetics of the particular agent. As the radioactive material decays, a positron is emitted which then collides with a nearby electron and is annihilated, producing two $\gamma$-rays, 180° apart. These high-energy photons escape the body and are detected by a ring of externally placed detectors. Simultaneous detector ‘hits’ on opposite sides of the head signal the decay of a single positron, which can be localized to a particular spot within the brain using tomographic techniques. Over time, as multiple counts are collected, an image of the tracer activity is created. By sampling the amount of tracer in the blood, it is also possible to calculate the tracer kinetics and quantify the functional activity. The spatial resolution of modern PET scanners is approximately 5 mm.

Fluorine-18 is a positron emitter with a half-life of 110 minutes. When attached to a modified form of glucose, deoxyglucose, it forms 2-fluoro-2-deoxyglucose (FDG). When FDG is injected into the bloodstream, it is transported across the blood-brain barrier and taken up by cells in proportion to their metabolic demands. The modified glucose
molecule is metabolized only in a single step and it then remains fixed within the cell. The resulting images reflect the cumulative brain activity that took place during the 30-minute uptake period, weighted toward the moment of injection. It is possible to calculate an absolute cerebral metabolic rate for glucose (CMRglu) with concomitant sampling of arterial blood levels.[16] Measures of metabolic activity can be calculated on a global or regional level. Rates of glucose use are highest in brain areas that are most active, but with a temporal resolution of 30 minutes it is not possible to assess transient changes in cerebral activity using FDG as a tracer.

Oxygen-15-labeled water (H$_2^{15}$O) is another PET tracer that has been designed for use in activation studies. Because water can freely diffuse through the blood-brain barrier, the amount of tracer in the brain is determined by blood flow. With a half-life of 2 minutes, H$_2^{15}$O can be used for repeated studies in the same patient during the same imaging session. This allows for trial averaging to increase signal-to-noise ratios and for the use of control versus activation trial designs that are more statistically powerful. Regional cerebral blood flow (rCBF) can be calculated using the appropriate kinetic models.[26] The measurements determined can be quantitative—by sampling arterial blood—or relative, using a normalization approach.[18]

Positron emitters have also been attached to agents that bind specific receptors within the brain. These include dopamine receptors,[27] benzodiazepine receptors,[22] and opiate receptors.[23] Using a carbon-11-labeled peripheral benzodiazepine binding site agent, researchers have quantified activated microglia in animals with experimentally allergic encephalomyelitis and in the brains of MS patients post mortem.[28] Recently, this tracer was used in vivo to evaluate activated microglia in patients with dementia.[29] The possibilities for the use of PET appear to be endless. The newest application, currently in animals only, is the monitoring of gene transcription.[19]

Single photon emission computed tomography

SPECT uses principles that are similar to PET. Radiopharmaceuticals that emit single photons, usually γ-rays, are used. These include xenon-133, which can be inhaled, as well as iodine-123 and technesium-99m (99mTc) that are injected intravenously. The compound 99mTc-hexamethyl propyleneamine oxime (99mTc HMPAO) was developed specifically for use in SPECT studies. Because it is a lipophilic substance with flow-dependent uptake into the brain and little redistribution,[30] it is ideal for measuring brain perfusion and blood volume. Recent applications include receptor binding studies.[31] One limitation of SPECT is that it is not possible to quantify absolute measures of brain activity, only relative measures. In addition, the spatial resolution (approximately 9 mm) is lower and non-uniform relative to other techniques.

Functional MRI

Magnetic resonance imaging (MRI) uses strong magnetic fields and radiofrequency energy to produce images of the human body. The rate of magnetic resonance signal decay, or T2*, is slightly faster for deoxygenated hemoglobin than for oxygenated hemoglobin. fMRI uses imaging parameters that are optimized to detect these slight differences. When the brain is active, metabolic demands increase and blood flow
increases, delivering increased amounts of oxygenated blood. This causes a relative decrease in deoxygenated hemoglobin concentrations, resulting in a slightly slower rate of signal loss, so that relative to the preactivation state, the signal detected is increased. This technique, known as blood oxygen level dependent (BOLD) fMRI has many advantages over other functional imaging techniques. It does not require the use of radioactive materials so that repeated studies can be obtained safely and easily. It has superior spatial resolution, of approximately 1–3 mm³. Structural studies can be acquired at the same time, simplifying the process of localizing activated areas within the brain. Many activation paradigms are possible, including event-related and block design. The limitations are that scan quality is highly dependent on subject co-operation and that image quality is severely compromised by inadvertent movements. In addition, patients with implanted devices such as pacemakers are precluded from scanning. As with other measures of blood flow, BOLD imaging is not a direct measure of neuronal activity. In most cases, increases in local cerebral blood flow are tightly linked to neuronal firing, but recent studies have demonstrated that there are certain pathological conditions in which this relationship can break down.

**IMAGE PROCESSING AND STATISTICS**

Imaging data are a series of slices or volumes that consist of individual picture elements (pixels, for two-dimensional data) or volume elements (voxels, for three-dimensional data). When PET or SPECT images, which have low signal-to-noise ratios, are analysed, the data is typically smoothed before analysis and groups of voxels are assessed on a global and regional basis. In addition, the activity within specific regions of interest can be determined and then compared between groups. Biases are possible with this approach, especially if the investigator determines the region of interest directly from the functional image. To avoid this, many investigators have used standard structural atlases to guide the process of region identification. Subsequently, techniques have been developed to coregister PET directly with structural MRI studies.

fMRI measures the hemodynamic response to increased neuronal activity that is time-locked to the performance of a specific task. A typical MRI study of motor activity using a block design consists of alternating rest and movement blocks that last several seconds each. The hemodynamic response lags behind neuronal firing by about 4–5 seconds. There are many possible ways of estimating the significance of the signal change detected. One commonly used approach is statistical parametric mapping (SPM). Because the statistics are done on each individual voxel, it is important to use stringent corrections for multiple comparisons to avoid false-positive results. On an individual basis, fMRI can be registered directly onto a structural MRI obtained during the same imaging session. However, most studies involve the use of group statistics. The study of groups of subjects using functional imaging is complicated by the inherent variability of the human brain. Differences in brain size and shape make it difficult to determine if the same region is activated across individual subjects.

This problem has been addressed by the use of standardized ‘atlases’ that use a common reference system applied consistently across individual subjects and laboratories. The most commonly used system is that of Talairach and Tournoux.
single hemisphere from a middle-aged French woman is the basis of this common co-
ordinate system. Individual anatomical scans are aligned to the atlas by identifying the
line connecting the anterior commissure to the posterior commissure. The brain is then
rescaled along three axes to fit the atlas dimensions. The advantage of this system is the
use of a standard co-ordinate system that allows the comparison of activation sites across
studies. The shortcoming is that while subcortical structures are relatively well aligned
using this technique, highly variable cortical regions can be misaligned by as much as 2
cm.[41] In addition, any atlas-based approach must take into account diseasespecific
changes in brain size and shape that will occur only in the patient group. When these
individual patients are placed into the atlas co-ordinate system, large misregistration
errors may occur. When these patients are then compared to a control group with normal
brain volumes, spurious significant differences in activation patterns between the groups
could result. This may be particularly true when studying patients with degenerative
diseases such as MS. The limitations of the Talairach and Tournoux approach are being
addressed by the use of non-linear warping techniques,[42] the creation of a large
probabilistic atlas based on hundreds of scans,[43] and the use of disease-specific atlases
(Fig. 11.1).[44–46]

FACTORS SPECIFIC TO MS POPULATIONS

Special concerns exist regarding the use and interpretation of functional imaging studies
in MS populations. The varied locations and wide distribution of lesion burdens among
patients makes it difficult to compare groups. Factors such as lesion location and severity
may be critical in determining functional consequences. Recovery processes such as
remyelination and functional adaptation may cause changes in activation patterns over
time. Cerebral blood flow can be affected by disease-modifying agents such as
interferons,[47] and the specific central neurological effects of medications used to treat
MS symptoms are largely unknown. Some radioactive tracers may be preferentially taken
up by inflammatory cells.[48] Choosing the proper control group becomes difficult, and
combining groups of subjects for statistical analyses using the standard atlas approach is
potentially problematic, as discussed above. When changes in activation extent and
location over time are monitored, it is important to factor in structural changes such as
atrophy that may confound the interpretation of functional imaging results.

STUDIES TO DATE

Global measures of brain activity have consistently demonstrated abnormalities in MS
patients. For the most part these are measures of the gray matter, although functional
measures can be determined in white matter as well. In one of the earliest functional
imaging studies of MS patients, Brooks et al. measured rCBF and oxygen extraction rate
(rOER) in a resting state with PET scanning using inhaled carbon dioxide-15 and
oxygen-15 (\(^{15}\)O\(_2\)) in a group of 15 MS patients.[49] The study was done in part to address
the role of ischemia in MS plaques as a cause of neurologic dysfunction. Hyperbaric
oxygen therapy was considered a potential therapy for MS at that time.[50] Absolute
Fig. 11.1 MRI atlas created from T1-weighted images of 35 MS patients with secondary progressive disease. Signs of atrophy, including enlarged ventricles and widened sulcal spaces, are clearly seen. Disease-specific atlases such as this can be used as registration targets for group analyses of functional imaging data.

measures of regional cerebral metabolic rate of oxygen utilization (rCMRO2) were calculated using arterial measures of $^{15}$O$_2$. The MS patients demonstrated significantly decreased mean rCMRO$_2$ and rCBF both in white matter regions and in gray matter regions compared with a group of 13 age-matched controls. However, oxygen extraction rates were similar in both groups, indicating that there was no evidence of ischemia, one of the putative mechanisms by which hyperbaric O$_2$ therapy was felt to work. Those patients found to have atrophy by computed tomography (CT) scanning had decreased CMRO$_2$, but those with normal CT scans had normal values. In addition, decreased
CMRO$_2$ values were associated with declines in cognitive function, but not with locomotor dysfunction or disease duration. The authors concluded that the changes in oxygen utilization and cerebral blood flow seen in the MS patients were due to brain volume loss rather than altered function within the tissue itself. Decreases in rCBF and rCMRO$_2$ in both gray and white matter in MS patients compared with controls have been reported by others,$^{[51]}$ and rCMRO$_2$ was negatively correlated with expanded disability status score (EDSS) measures. Consistent with this, Lycke et al.,$^{[52]}$ using 99mTc HMPAO SPECT in patients with relapsing-remitting MS and in patients with secondary progressive MS found a relationship between decreased rCBF in the frontal gray matter and disability.

Global measures of glucose metabolism using FDG PET have also revealed widespread decreases in the cerebral metabolic rate for glucose (CMRglu) in MS patients (Fig. 11.2)$^{[53-57]}$ However, many of these studies found little or no correlation with the EDSS, although they were frequently limited to patients with mild to moderate disability. In a cross-sectional study of patients with relapsing-remitting MS, Blinkenberg et al.$^{[55]}$ found that decreased cortical and subcortical global CMRglu correlated with total lesion area (TLA) and cognitive dysfunction, but not with EDSS. In a serial study of relapsing-remitting MS patients, Blinkenberg et al.$^{[54]}$ measured changes in EDSS, TLA, and CMRglu. Over the course of 2 years, CMRglu decreased significantly in all of the MS patients studied. However, declining global CMRglu rates were not correlated with worsening of EDSS or TLA.
Fig. 11.2 FDG PET images from two slice locations in a normal control (top row) and a patient with MS (bottom row) displayed using the same scale. The MS patient’s scan demonstrates widespread reductions in cerebral glucose metabolism compared with the control subject’s scan. (From Bakshi et al.,[53] used with permission).
Deficits in global brain metabolism and blood flow can occur early in the disease process and may not be reflected in measures of physical disability such as the EDSS. However, regional hypometabolism and blood flow appear to be closely related to cognitive changes and depression. Paulesu et al. found that global CMRglu was decreased in MS patients, both those who were cognitively impaired and those who were not, compared with controls. However, the cognitively impaired patients had decreased regional CMRglu in the deep gray structures, including the thalamus and bilateral hippocampi. In addition, MS patients who were cognitively impaired had greater TLA than non-impaired patients, but the EDSS measures were similar. In addition, patients with evidence of frontal lobe dysfunction on neuropsychological testing had more widespread regional CMRglu deficits, including in the bilateral prefrontal areas and the basal ganglia. A SPECT study using 99mTc HMPAO to measure blood flow found decreases in bilateral frontal regions in cognitively impaired MS patients, while unimpaired MS patients had decreases in the right frontal lobe only. Of note, the cognitively impaired group had greater numbers of periventricular lesions and larger third ventricle width, suggesting that the global decline in frontal activity could be related to the effects of atrophy. Interestingly, atrophy of the corpus callosum has been associated with greater reductions in CMRglu rates in the left hemisphere than in the right hemisphere, a finding that is not due to greater lesion volumes in the left hemisphere.

Sabatini et al. found altered limbic system blood flow in depressed versus non-depressed MS patients who were well matched on cognitive measures and EDSS. Lesion burden and location were similar in the two groups. Alterations in cortical-subcortical patterns of activity are also seen in patients with unipolar depression. With treatment, the normal pattern of activity can be restored. No equivalent studies of depression treatment in MS patients have been reported.

Functional imaging offers an opportunity to evaluate the neurophysiology of particular symptoms such as fatigue, which is common in MS but poorly understood. Fatigue in MS has been associated with widespread decreases in CMRglu in several motor areas, including the premotor, supplementary motor, and basal ganglia areas. These decreases were not associated with EDSS or cerebral atrophy. Although the fatigued patients had higher scores on measures of depression, the pattern of brain activity seen was different from that seen typically with depression. Higher levels of glucose metabolism in patients with fatigue compared with non-fatigued patients were detected in the anterior cingulate gyri bilaterally and the cerebellar vermis. There were no significant differences in T2 lesion load or brain volume between the two patient groups. These differences in brain activity were seen even though the patients tested were not performing a specific task during the uptake period but were resting quietly.

Filippi et al. used fMRI to compare activation patterns in fatigued and non-fatigued patients performing flexion and extension of the right hand. Patients had minimal disability (EDSS≤2), and no motor impairments of the right hand. Compared with the normal controls, MS patients had larger areas of activation in the contralateral sensory motor cortex and supplementary motor cortex. Non-fatigued MS patients had larger ipsilateral cerebellar and contralateral thalamic activations compared to the fatigued patients. Fatigue severity scores were correlated with reductions in the activation of the contralateral thalamus and intraparietal sulcus and the ipsilateral operculum. Results from this and other studies implicate disruption in cortical-subcortical circuits as a possible...
cause of MS fatigue symptoms, but the results also demonstrate possible central neurological adaptations that can occur in the absence of demonstrable neurological deficits. Such adaptations include greater than normal activations to simple tasks, and more activity in attentional areas such as the anterior cingulate in MS patients.

**RECOVERY AND ADAPTATION**

The ability of the brain to adapt to ongoing insults is likely to play an important role in the recovery of function after relapse. Secondary progressive disease may result when this process of adaptation becomes unable to maintain function when a certain critical ‘threshold’ of tissue damage is crossed. A growing literature has examined adaptation and functional recovery after central nervous system injury following stroke and MS exacerbations using functional imaging techniques. On the basis of these studies there appear to be at least two ways that the brain can adapt.[65] One way is to recruit larger areas of cortex than is normally required to perform a particular task. This has been demonstrated after stroke and in the early stages of Alzheimer’s disease.[66,67] The other is to ‘unmask’ alternative pathways after injury. The latter theory has been supported by many studies of motor recovery that have found significant ipsilateral activity in the brain when the affected limb is used.[68] This does not appear to be due entirely to inadvertent ‘mirror movements’ of the non-affected limb. With recovery, these aberrant ipsilateral activations tend to disappear and the size of contralateral activations returns to more normal dimensions.[69] This same pattern was seen in the motor areas of an MS patient recovering from a severe relapse.[70]

In patients with established disability, these adaptative patterns can persist and progress. Lee et al. studied 12 MS patients using fMRI while the patients performed a finger flexion task.[71] The patients had significant disability, 11 of the 12 having an EDSS of 5 or more. Compared to controls, the patients had larger activations in the supplementary motor cortex and the ipsilateral sensorimotor cortex. The degree of activation of the contralateral sensorimotor cortex diminished with increasing impairment in limb function. The center of activation in the contralateral sensorimotor cortex was shifted posteriorly in the MS patients, and this shift increased with increasing lesion load in that hemisphere. In addition, the degree of ipsilateral sensorimotor cortex activation was correlated with the amount of lesion load in the contralateral hemispheres.

These types of compensatory changes may occur very early in the course of MS, even before neurologic abnormalities can be detected. Fillipi et al. studied early relapsing-remitting MS patients without motor deficits, using fMRI during flexion-extension of the right hand.[64] Compared with controls, MS patients had increased activation in multiple motor areas, including the contralateral sensorimotor cortex, bilateral supplementary motor cortex and the cingulate motor areas.

The process of adaptation after optic neuritis appears to be different from that seen for motor systems. fMRI activation patterns to flashing checkerboard stimuli were decreased in the calcarine cortex in patients with recovered optic neuritis when the affected eye was stimulated.[72] However, extrastriate visual areas appear to have increased levels of activity,[73] the magnitude of which is correlated with the degree of visual evoked response delay.
PUTTING IT ALL TOGETHER: STRUCTURE AND FUNCTION

The pathologic heterogeneity of lesions that appear bright on T2-weighted scans is frequently cited as a possible explanation for the poor correlation of lesion burden with clinical measures of disability. Newer structural measures such as magnetization transfer ratio, diffusion weighted imaging, N-acetylaspartate and ‘black holes’ have more neuropathologic specificity. Relating these measures to functional imaging results may be especially useful. Fillipi et al. found correlations between worsening magnetization transfer ratio values in the cervical cord and normal-appearing brain tissue in primary progressive MS patients and aberrant activation patterns on fMRI.\(^{[74]}\) In a study of nine patients, Reddy et al. correlated the increase in ipsilateral activity after hand flexion-extension seen using fMRI with N-acetylaspartate measures of central white matter.\(^{[75]}\) With lower values of N-acetylaspartate, consistent with worsening tissue integrity, the amount of aberrant ipsilateral activity increased. Combining functional imaging data with detailed white matter tract maps using diffusion weighted imaging is now feasible (Fig. 11.3).\(^{[76,77]}\) Future studies can monitor changes in both structure and function simultaneously, perhaps yielding important insights into the MS disease process.

SUMMARY AND CONCLUSIONS

Functional imaging studies are feasible in MS patients. The results to date reveal findings that are consistent with newer structural imaging and pathologic findings. Widespread abnormalities occur in brain function in MS patients. In general, these changes are poorly correlated with measures of ambulation, but are related to cognitive deficits and symptoms such as fatigue and depression. The relationship of functional abnormalities to specific lesion locations is unclear, but probably varies with location in the nervous system and the severity of tissue loss. Early functional changes are seen before measurable disability occurs, indicating the involvement of gray matter, either directly or indirectly, from disease onset. Adaptive changes do occur and can be measured. Exciting developments include the use of concomitant structural and functional imaging techniques that may help to match the severity of lesions with their functional consequences. Finally, functional imaging in MS patients offers a unique opportunity to study human brain plasticity. In the future, functional imaging will play a much larger role in clinical trials involving remyelination, cell grafts, neuroprotection, and secondary progressive disease.
**Fig. 11.3** Composite figure of fMRI activations during right hand finger opposition task (in color) overlaid on to fractional anisotropy (fA) map obtained with diffusion tensor imaging in a normal control. Highly organized white matter tracts have increased fA values and appear brighter on the structural image.

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INTRODUCTION

An examination of the costs, the benefits, and the effectiveness of therapeutic technologies is essential to the decision-making process surrounding which therapies to use in which types of patients. The clearest example is when two therapies or technologies are equivalent in terms of effectiveness but differ in terms of costs. The decision as to which therapy to use can then be based primarily on the cost. However, in reality, decisions are not so clear-cut. Therapies are rarely equivalent in terms of effectiveness. Cost analyses differ by the type of costs that are included (e.g. direct medical costs, direct non-medical costs, indirect costs, intangible costs), which costs are attributable to the given therapy, the perspective of the payer, and whether the researchers use cost-identification, cost-effectiveness, cost-utility, or cost-benefit analyses. This chapter helps clinical researchers to understand better the differences in cost analyses and identifies specific analyses that have been conducted for multiple sclerosis.

TYPES OF COSTS

Cost analyses may include various types of costs that can be assigned weights depending on the perspective of the payer. In general there are four types of costs that might be included in a cost analysis—direct medical costs, direct non-medical costs, indirect costs, and intangible costs.

Direct medical costs

Direct medical costs include the actual charges for resources associated with the therapy being examined, and they should be compared with those of the best therapeutic alternative. Such costs might include all clinical time, laboratory time, research and development, the need for ambulance services, visits to emergency rooms, hospital stays, radiologic procedures, medications, or durable medical equipment. Researchers can include downstream costs such as nursing home admissions, hospital readmissions, or other more expensive treatment. Direct costs reflect the value of the resources used to prevent, diagnose, treat, and rehabilitate patients.
Direct non-medical costs

Direct non-medical costs are costs that are direct in nature but are not medical. Some examples of direct non-medical costs are the costs to the criminal justice system and the costs of paying disability income, transportation, lodging, child care, family counseling, home aids, alterations to homes or vehicles, and clothing. For example, costs associated with adapting a vehicle for use with a wheelchair or with the installation of grab bars in a home bathroom qualify as direct non-medical costs. Costs of workplace modifications often fall on the employer rather than the patient, but they also fall into the category of direct non-medical costs.

A comprehensive examination of the costs of multiple sclerosis (MS) and the effect of particular therapies might want to determine if there are increases or decreases in the direct non-medical costs associated with the need for child care, transportation, home aids, and alterations to the family home or vehicle. A benefit of a therapy might be increasing a patient’s ability to return to work and no longer needing disability income or help with domestic chores. Researchers should be careful not to underestimate the value that such cost impacts might have for different payers. Direct non-medical costs are more difficult for clinical researchers to obtain because they often require in-depth surveys and the use of secondary data sources to estimate the costs. They can be incurred by many different parties, but they are an important source of total costs. A study of the cost of MS found that 57% of total costs (excluding intangible costs) could be attributed to direct non-medical costs and indirect costs.

Indirect costs

Indirect costs are those that are not actually paid and do not reflect the use of resources. Included in this category are losses that result from job absenteeism, decreased earning ability of the person who is disabled and possibly the person who is their primary caregiver, changes in occupation caused by illness or injury, the time costs of patient travel to appointments and waiting time in clinics, and informal caregiving. Indirect mortality costs due to premature deaths can be included in this category.

Intangible costs

Finally, intangible costs represent the value that those experiencing the illness, or society, place on the pain and suffering associated with a particular condition. Such losses are experienced as a result of a loss in the ability to perform activities of daily living and decreased social functioning. Economists have a variety of ways to estimate intangible costs. While the techniques are controversial, the ideas of comparative risk assessment or willingness to pay for some dimension of health have been used with some success to help to place a value on the loss of health. A study of intangible losses associated with MS showed that a person without MS would be willing to pay $US350,000–$US500,000 to avoid getting the disease, if this were possible, and those with MS would be willing to pay between $US375,000 and $US880,000. 


THE PERSPECTIVE OF THE DECISION MAKER

The perspective of the decision maker is essential in determining which types of costs are most important.

A health care provider is often primarily concerned with direct medical costs that specifically affect the budget of the provider’s organization. Providers will not ordinarily be concerned with direct non-medical, indirect, or intangible costs. However, social service providers would be interested in direct non-medical costs and possibly in indirect costs as a way of better understanding how to assist patients and how to justify the work that they perform.

The third-party payer is interested in the costs that pertain to reimbursement. Such a payer is very interested in medical expenses incurred or avoided as a result of a therapy. Some public third-party payers, such as Medicaid in the USA, may be interested in direct non-medical cost offsets because such payers may in fact pay for some social services such as transportation or case management. In addition, the US Federal Government may be paying disability income to people who qualify for Medicare and Medicaid by reason of disability. This type of payment is also considered a direct non-medical cost.

The patient and family are primarily interested in the amount of payments that are required of the family for medical care, alterations to the home and vehicle, lost work, informal caregiving, and intangible losses. Such decision makers are not as interested in direct medical costs unless they are uninsured or have to pay for them themselves.

Finally, the societal perspective should be the most comprehensive and complex perspective. Society at large should be interested in valuing each of the cost components for all diseases and disabilities.

TYPES OF COST ANALYSIS

Cost-identification analysis

Simple cost-identification analysis can be used when the effects of the therapeutic interventions being compared are observed to be minimal. In this case, costs can be added without a direct relationship to the effectiveness or benefits of the therapeutic interventions.

Cost-effectiveness analysis

In cost-effectiveness analyses, alternative interventions are compared in terms of cost per unit change in health outcome. All relevant costs \( C_i \) and benefits \( B_i \) are measured, and the ratio between the two \( C_i / B_i \) is calculated. All other things being equal, an alternative with a lower cost-benefit ratio is preferable to an alternative with a higher cost-benefit ratio. When interventions are quite different the issue may simply be whether the additional improvement in benefits is worth the cost. Examples of a unit of health outcome are the number of years of life saved, the decrease in the number of injuries,
clinical measures of disease progression, and functional status measures such as the Expanded Disability Status Scale (EDSS). The direct comparison of the cost to the increase or decrease in unit of effectiveness creates a cost-effectiveness ratio (CER). Such ratios are relevant only when compared to at least one other alternative therapeutic intervention. The great difficulty in comparing CERs is that (as seen by the preceding discussion) there exists a vast array of costs that may or may not be included in any particular analysis. One must be very careful that the same costs were included in the comparator CERs and that those costs were measured in the same way. One also must have comparable outcome measures to make inferences between studies.

The six basic steps in cost-effectiveness analysis (described in Sloan, and derived from DHHS 1992) are as follows:

1 Define the intervention. This includes specifying the nature of the intervention (e.g. provision of personalized cancer risk information), the types of people who will receive the intervention (e.g. patients, healthy adult volunteers, adolescents), and what alternative the intervention is replacing (e.g. usual care, less intensive administration of personalized risk information, current interventions used to achieve the same goal as the alternative intervention). In some cases, an intervention is compared to the natural history of a disease without any treatment; but more commonly, an intervention is compared to an alternative intervention that could be used.

2 Identify relevant costs. These usually include direct costs, such as paper for copying brochures and the purchase of computers, but may also include indirect costs, such as patient time spent in counseling, lost earnings, or other social costs associated with the intervention.

3 Identify relevant benefits. These include the net health benefits to the person receiving the intervention (after deducting any adverse side effects) but may also include indirect benefits such as greater productivity.

4 Measure costs. This requires attaching a monetary value to all components of costs, which entails placing a value on medical inputs and an individual’s time. In the case of costs that occur in the future, a discount rate is typically used to convert all costs into present-value terms.

5 Measure benefits. Convert all benefits into a single benefit. In the case of benefits that occur in the future, a discount rate is sometimes used to convert all benefits into present-value terms.

6 Account for uncertainties. This entails using sensitivity analysis, Monte Carlo simulations, or other methods to test the robustness of conclusions to uncertainties in the measurement of costs and benefits.

Cost-utility analysis

Cost-utility analyses are a particular form of cost-effectiveness analysis in which the measure of effectiveness is life years gained adjusted by a series of ‘utilities’ or quality-of-life weights to reflect the relative values or worth that individual patients place on different states of health. The outcome measure commonly used in cost-utility analyses is quality-adjusted life-years (QALYs). The cost-utility ratio is then expressed as the cost per QALY gained.
Cost-benefit analysis

Cost-benefit analyses attempt to place monetary values on the set of outcomes resulting from each alternative. The outcomes are translated into units of currency through approaches such as willingness to pay.

COST-OF-DISEASE STUDIES IN MS RESEARCH

There have been several cost-of-disease studies in MS across the world to date. The important findings from such studies that cover the USA, Canada, Sweden and Belgium are summarized here. First, the lifetime cost of MS is large no matter how it is measured because there are costs over a long period of time associated with the disease. Because MS strikes primarily younger adults, the lifetime earnings lost can be a large portion of the total cost of the disease.[1,5] Second, the costs are highly variable. This is true of health costs in general; a few people are extremely expensive and constitute a disproportionate share of direct medical costs in particular.[6,7] Third, costs are correlated with disease course,[1] level of disability, quality of life,[5] and level of functional limitation.[6,8]

Table 12.1 presents the most recent cost-of-disease studies in MS. All of these studies are able to address direct medical costs; a few studies include non-medical and indirect costs, and two estimate intangible losses. Estimates of annual direct medical costs vary from an equivalent of

<table>
<thead>
<tr>
<th>Study</th>
<th>Data and method</th>
<th>Direct costs</th>
<th>Indirect costs</th>
<th>Intangible loss</th>
<th>Direct plus indirect costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pope et al.[7]</td>
<td>US insurance</td>
<td>$7677</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>claims:</td>
<td>Private</td>
<td>Medicare</td>
<td>Medicaid</td>
<td>n=7477, n=5755, n=3681</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$13,048</td>
<td>$13,048</td>
<td>$7352</td>
<td>(95), (97), (93)</td>
</tr>
<tr>
<td>Henriksson et al.[5]</td>
<td>Survey in Sweden, 2000</td>
<td>296.5 MSEK ($30,473)</td>
<td>146 MSEK ($15,005)</td>
<td>270 MSEK ($27,749)</td>
<td>442.5 MSEK ($545,478)</td>
</tr>
<tr>
<td>Stolp-Smith et al.[6]</td>
<td>Provider-based US sample, n=155</td>
<td>$3499 (93) ($4178)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
$US1,945 to $US11,340. These figures differ by disease level, type of study, and location of study. Only one study has data recent enough to include direct cost data on the immunomodulating drugs, and the direct cost estimate from that study is much larger—$US30,473.\textsuperscript{[5]} Indirect costs range from very little from the study by Inman\textsuperscript{[8]} to $US24,352 in the study by Whetten-Goldstein et al.,\textsuperscript{[1]} which is the most complete estimate of these costs. Intangible losses are not comparable between the two studies. Henriksson et al. estimate an annual loss of $US27,770, which is comparable to their estimate of direct medical costs.\textsuperscript{[5]} Sloan et al. estimate lifetime intangible losses of $US350,000 to $US880,000.\textsuperscript{[2]}

Table 12.1 shows that the estimates are all made using different methodologies and data sources. Claims data are useful to document all utilization and costs that correspond to a certain payer, but additional services or data from other payers are often omitted from these studies. Surveys that rely on patient recall often bias utilization estimates upwards because people who participate in surveys about health are more likely to have used the health-care system. Other data are based on the patient population of a given provider or set of providers, so there is no randomization or completeness to the data. The size of the sample that the studies are based on also varies. Samples using national level claims data are the largest. Randomized surveys have smaller sample sizes and provider
specific samples tend to have the smallest samples. As with any type of study, care should be taken when interpreting findings from small samples.

**COST STUDIES TO EVALUATE THERAPIES AND TECHNOLOGIES IN RELATION TO MS**

Several recent studies have analysed the cost-effectiveness of treating MS with interferon beta; a summary is presented in Table 12.2. These studies generally show an increase in quality of life and a reduction in disease activity. However, the predominant finding has been that the use of interferon beta-1a and interferon beta-1b is quite expensive per effectiveness measure saved. The range is from $US39,250 per QALY saved, which is relatively low, to £GP37,845 (approximately $US56,768–1.5 is a reasonable conversion factor). Using cost-utility analysis of cost per QALY gained, the treatment is more expensive ranging from £GB276,466 to £GB1,485,499.

This is not an unusual finding for preventive therapies. Because of the ongoing nature of preventive care of any kind, it is often difficult to show a saving of direct medical costs. Most studies rely on short-term data collection for costs and a short time horizon for possible benefits. Cost-effectiveness studies do not estimate non-medical, indirect, or intangible benefits. While it is difficult to estimate the negative effect of side effects in these terms, it is likely that the sum of this type of benefit outweighs the costs. Cost-effectiveness analyses can be useful for comparing therapies, but care should be taken in determining the overall value of a therapy from these types of studies. These studies also show the varied outcomes and methods used for these types of analyses, which make it difficult to compare results between studies.

Two studies attempt to value the cost of treating acute exacerbations of MS in different settings. The first study analysed the costs of

**Table 12.2 Summary of cost-effectiveness studies of interferon beta**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kendrick[^12]</td>
<td>Published: UK 2000</td>
<td>RRMS patients; attempts to include long-term costs and benefits of disease</td>
<td>Cost-effectiveness per QALY after: 2 years treatment: $27,036; 20 years treatment: $37,845</td>
<td></td>
</tr>
<tr>
<td>Parkin[^13]</td>
<td>Published: UK 2000</td>
<td>102 RRMS patients; observe disease progression, cost estimates from 6 months of chart abstraction data and survey data; MSQOL and EQ5D measured</td>
<td>Cost effectiveness per QALY after 5 years: $28,700. Cost utility per QALY gained: $809,900</td>
<td></td>
</tr>
<tr>
<td>Forbes[^14]</td>
<td>Published: UK 1999</td>
<td>Cost-utility model with relative risk</td>
<td>Cost utility per QALY gained:</td>
<td></td>
</tr>
</tbody>
</table>
treated patients with intravenous methylprednisolone in inpatient, outpatient and home settings in Canada.\textsuperscript{[18]} Inpatient care was always found to be the most expensive. The relative cost savings of home care over outpatient care depended on assumptions about the overheads required to run the outpatient clinic. No clear, large, cost savings for home care over the outpatient setting was found. The second study found a savings of 86% for home treatment versus facility treatment in Israel.\textsuperscript{[19]} One can see that the studies are not directly comparable, and physicians need to interpret the results carefully. It is appropriate for the physician to think about the larger picture and the clinical needs of the patient as well as the preferences of the patient and family. In some cases, home care may be cost saving because transportation is difficult for the patient. In other cases, outpatient care would be more costly than inpatient care if a patient who did not tolerate the treatment well were in a setting without proper monitoring and care.

Mushlin et al. sought to determine the incremental cost-effectiveness of magnetic resonance imaging (MRI) and computed tomography (CT) in young adults presenting with equivocal neurological signs and symptoms.\textsuperscript{[20]} The researchers followed a decision analysis of long-term survival\textsuperscript{[21]} using accuracy data from a diagnostic technology assessment of MRI and CT in patients with suspected MS. It was found that in the baseline analysis, at 30% likelihood of an underlying neurological disease, the use of
MRI had an incremental cost of $US101,670 for each additional QALY saved compared with $US20,290 for CT. As the probability of neurological disease increased, researchers found that MRI was a cost-effective alternative, with the cost dropping to $US30,000 for each QALY saved. The researchers considered that if a negative MRI result provides reassurance, that the incremental costs of immediate MRI use decreased and fell below $US25,000 for each QALY saved regardless of the likelihood of disease. This study provides a very effective example of how such analyses can be used by providers and payers in the decisions over the type of care to provide to patients. MRI has become a standard diagnostic technique and is considered to be cost effective. In a 1981 study by Feigenson et al., the researchers examined the costs and the effectiveness of providing multidisciplinary inpatient rehabilitation to 20 patients with MS.\[22\] The researchers measured total direct medical costs of the intervention and a variety of functional status effectiveness measures: behavioral, cognitive, visual and perceptual, communication, sensation, muscle strength, spasticity, inco-ordination and involuntary movements, balance, functional status of upper and lower limbs, self-care activities, bowel and bladder incontinence, bed mobility, wheelchair transfers and management, ambulation status, homemaking, and performance in real-life activities. The researchers found that of the areas rated, intensive multidisciplinary therapy produced statistically significant improvements in balance, self-care activities, bladder control, bed mobility, wheelchair transfers, ambulatory transfers, homemaking, and ability to perform real-life activities. The average cost for rehabilitation was $US14,175. The cost of home aid services decreased from $US25,909 to $US8,680 following the intervention. It was concluded that such intensive therapy was cost-effective.

**CONCLUSIONS**

Cost analyses strengthen the ability of decision makers at different levels (e.g. providers, payers, family members) to determine which of a host of therapeutic interventions to engage. The comprehensive studies of the cost and burden of MS on society, providers, and families give researchers a base for the use of cost-effectiveness or cost-benefit analyses in their examination of new therapies. The new studies of interferon beta and other specific therapies are a step in further understanding cost and treatment of MS. The price of the drugs from the manufacturers ranges from $US10,000 to $US15,000 per patient per year. It is important that the drugs are shown to be effective before they are recommended for all patients with MS. The clinical benefits may not fully offset the costs, but indirect and intangible benefits, which are difficult to measure, can lead one to determine the treatment to be cost effective nonetheless. Drugs developed specifically for MS patients from research are generally expensive because they are protected by the Orphan Drug Act, which gives pharmaceutical companies additional incentives to develop drugs where the expected market is small. If better drugs are developed, we expect they still will be expensive.

MS is an expensive disease no matter how one looks at the data. It ranks among the top 20 diseases in total costs to society. Researchers use these numbers to help determine the research agenda and where research dollars should go. By all measures, MS is an important disease and deserves further research funding.
REFERENCES


13
Ethical considerations in multiple sclerosis clinical trials
William Pryse-Phillips

INTRODUCTION

Multiple sclerosis (MS) trials are challenged by the unpredictable course of the disease, imprecise measures of disease activity, and difficulties in maintaining patient participation in long trials. The three major ethical principles governing such trials and other studies have been summarized as: respect for people (autonomy), beneficence (the obligations to improve well-being and to do no harm), and justice (the risk of research participation must be less than the potential benefits).[1] These three principles have been expanded to seven.[2]

1 Value—enhancements of health or knowledge must be derived from the research (so clinical research with non-generalizable results and lack of publication of the results would each be unacceptable).
2 Scientific validity—the research must be methodologically rigorous.
3 Fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits should determine communities selected as study sites and the inclusion criteria for individual subjects.
4 Favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized and potential benefits enhanced. The potential benefits to individuals and knowledge gained for society must outweigh the risks.
5 Independent review—unaffiliated people must review the research and approve, amend, or terminate it.
6 Informed consent.
7 Respect for enrolled subjects—subjects should have their privacy protected and their well-being monitored and they should have the opportunity to withdraw.

Fulfillment of all these requirements is necessary to make clinical research ethical, although they must be adapted to the health, economic, cultural, and technological conditions in which the research is conducted. This chapter discusses some of these in the context of selected sections of the 2000 revision of the Declaration of Helsinki.[3]

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society

Clinicians have obligations to individual trial participants, whose rights in trials must be safeguarded, but also to society, because research improving the treatment of both present and future sufferers will only thus be facilitated. These loyalties conflict, but the
statement makes it clear that the Hippocratic dictum is to be followed. Yet while physicians have a primary duty to promote the welfare of their patients, they also have a duty that in the past has sometimes been considered to be at least equal to this—namely to effect improvement in the state of mankind, to which duty they should also, in discussion, encourage their patients to subscribe. Many more people stand to benefit from clinical practice that has been improved by strong evidence than stand to lose by receiving the less favored treatment in a clinical trial. ‘Medical ethics, we believe, will shift towards giving increasing weight to the value of therapeutic research vis-à-vis an individual’s right to choose a specific treatment. It is in the interests of most of us that medical science and therapeutics advance as rapidly as possible. Too much individual autonomy, both in the way in which doctors work and in the way in which patients choose will slow down progress.’[5]

**Even the best-proven prophylactic, diagnostic, and therapeutic methods must be challenged**

This laudable sentiment acknowledges that current best therapies have but a temporary status in that role and by extension that, for example, active control equivalence trials (ACETs) should be used in future studies. Unfortunately, ACETs are inefficient at showing whether a new drug is effective or not. The ability of a study to distinguish between active and control treatments (assay sensitivity) is weaker when a new drug is compared with an active comparator because the inherent imperfections of clinical trials ‘tend to reduce observable differences between treatment groups, promoting the conclusion that the two treatments are indistinguishable’. [6] Thus ACETs are often uninformative. Without placebo controls, the efficacy of a new drug cannot easily be assessed, while equivalent performance may reflect ‘simply a patient population that cannot distinguish between two active treatments that differ considerably from each other, or between active drug and placebo’. [7] Equivalence of the test drug to the active control might mean that neither is effective, and use of external data is required to allow the assumption that the active control is actually better than placebo. Temple and Ellenberg concluded that, for these reasons, ‘placebo-controlled trials may be ethically conducted even when effective therapy exists, as long as patients will not be harmed by participation and are fully informed about their alternatives’. [6]

**Medical research involving human subjects must conform to generally accepted scientific principles**

Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose as well as using resources that could have been better employed. Bryant and Clegg reviewed 17 studies of drugs affecting immune functions in MS and noted that these studies used different treatment regimens, patient groups, and outcome measures; that many were of small size and short duration; that there was often inadequate blinding to treatment allocation; and that the description of withdrawals and drop-outs was poor and the reporting of results incomplete. [8] Moreover, side effects were not well measured or reported.
There are other cautions that are relevant to the design of trials. Trial designs that cannot provide an answer able to alter clinical or collective equipoise are improper. Poorly designed trials of therapy waste time and money and may do harm to subjects both directly and by excluding the more established effective treatments.\[9\]

The question asked must never be trivial, especially if subjects are placed at any risk. Some studies appear to have been initiated to satisfy the marketing of the sponsoring company rather than any medical need. In many studies there has been imprecise determination of the number of relapses in the previous year, a problem that should in future be corrected by a year of observation before exhibition of the study drug. Most studies are initiated from MS clinics, where long-term data should be available, thus reducing the concern of sponsors that the time required for the trial will be excessive. Imprecise determination of the time at which the subject has been at his or her current expanded disability status score (EDSS) has been another failing.

There is also uncertainty about the appropriateness of different outcome measures. In the absence of any indication that magnetic resonance imaging (MRI) data predict the subsequent clinical course, it seems inappropriate to use this tangential surrogate measure in the future. Only the initial course of the disease, self-rated health, and the quality of life measured at baseline have been shown to predict change in disability measured by EDSS 1 year later. MRI indices seem not to be of value; ‘no statistically relevant association has been found between the number of gadolinium-enhancing lesions in the initial scan and worsening EDSS scores after 1–2 years.’\[10\] It would be helpful to add in a patient-derived global ‘perception of benefit’ tool to supplement objective external measures, as in dementia studies. Doctors and patients see things differently—doctors regard quality of life as a function of physical health status or disability levels, but patients consider that their mental health status, vitality, and general health are more relevant.\[11\] We must treat the patient rather than the MRI or the EDSS.

Undue primacy is given to intention to treat (ITT) (effectiveness) analyses of phase III trials.\[12\] Logically, the first scrutiny of trial results should be efficacy (‘per protocol’) rather than effectiveness because the former examines the basic pharmacological question in the ongoing drug discovery process: Does this molecule have a useful effect in modifying aspects of this disease? ITT analyses of effectiveness are applicable next, to provide a sociological answer about the average clinical benefit that can be expected when the drug is used by the average provider in the average community.

The rate of treatment failure in the placebo groups should reasonably be expected to approximate the rate of treatment failure consistent with the known natural history of MS and the behavior of patients treated with placebo in clinical trials.\[13\] If it does not do so, the trial is flawed and interpretations of it are inappropriate.

The apparent efficacy of a drug may be a product of unusual morbidity among the patients treated with placebo. Claims of efficacy have been made in the presence of unusually high rates of treatment failure in placebo-treated patients or when the response in the group treated with interferon beta is no better than that of similarly selected placebo-treated patients from comparable studies.\[13\]

Placebo-controlled trials in environments that disallow a new treatment for financial or political reasons (so that there is little chance of its becoming available in the population in which the study was done) are not ethical\[14\] although, in response to this statement, it has been pointed out that this means that investigators and study sponsors are being held
responsible for the inadequate health-care systems elsewhere\textsuperscript{[15]} and that ‘the incremental acquisition of resources to the presumed benefit of an individual may produce a decrement for society as a whole’.\textsuperscript{[16]} Placebo-controlled trials must be as efficient and expedient as possible but they must be of sufficient duration and sample size to test the study hypothesis adequately.\textsuperscript{[14]} Trials that are not adequate in these respects are mentioned because bad trials represent bad science, and bad science is bad ethics.

\textit{A specially appointed ethical review committee must be independent of the investigator and sponsor}

This now appears to be standard practice, although the in-house regulation of ethical matters in private research organizations would be a concern, as would the existence of for-profit independent ethics organizations.

\textit{Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results}

Rules for stopping are mandatory in view of the potential for harm to the subject,\textsuperscript{[17]} but the identification of important unwanted events is not difficult. The main problem here is how to justify the continuation of a trial that has shown early benefit. The Mayo Clinic/Canadian Sulfasalazine Trial,\textsuperscript{[18]} for example, showed early important benefit but 2 years later the same patients were worse. In this case, premature termination would have exposed patients to useless therapy, but the benefits of new drugs are at least two-dimensional, since they involve both magnitude of effect and duration, and to desist from observing trial subjects under controlled conditions because of early intimations of effect wastes an opportunity that will not come again and risks exposure of patients in future to agents with finite efficacy. To subject patients to comparative trials of ‘active’ drugs that are, in the long term, equally harmful or neutral in therapeutic effect is unethical, since the drugs will be interpreted as being equally ‘beneficial’.\textsuperscript{[19]}

Clinical trials have two goals—one is regulatory (a pharmaceutical company wants to put its drug on the market) and the other is clinical (physicians want to learn about the effects of the drug and the indications for its use). These goals may conflict; if early results suggest that there is a beneficial effect, there may be reasons proffered on marketing grounds to halt the trial and seek licensing. It is ethically undesirable to conduct a research trial that cannot provide an answer that is not generally applicable. Clinical experience would seem to suggest that 3 years is a minimum period for a trial to continue, and the attainment of significant benefit earlier than that is not a reason to discontinue the trial since prolongation might lead to a different conclusion. MS is a disease of long duration. Trials of immunomodulators have lasted for less than 3 years. Unless the therapy completely suppresses disease activity, all patients will ultimately deteriorate to a final state of severe incapacity. ‘If a trial is stopped after 3 years, it is difficult to know whether the curves are parallel, diverging or converging’.\textsuperscript{[19]} In order to be able to detect a small effect, long-term trials have to be large because of the inevitable loss to follow-up. Trials should not be terminated prematurely when an early positive effect is found. If a placebo-controlled study can be ethically justified, investigators
should not shorten the proposed study duration or reduce the study size in an attempt to minimize risk to participants who are foregoing available therapy.\[14\]

The results of extension trials done in selected patients are less valid but in the absence of any knowledge whatsoever about the long-term effects of the immunomodulators in use today, such monitoring is essential to prevent morbidity, to escape from drugs that have become ineffective, and to save money. Such supervision, with reporting of long-term effects to a central non-profit agency, should be mandated internationally. Since it is likely that ‘more and more clinical practice will take place in the setting of clinical trials,’\[4,5\] it is suggested here that it is time to regard all continuing treatment of patients with new drugs as extensions of the original clinical trials. While there will be less uniformity in the patient population, this will at least equate with the realities of the world and will not only improve the quality of long-term care but will also provide early warning about late unwanted effects and reassurance about the useful duration of effect of the therapy.

**Medical research involving human subjects should be conducted only if the importance of the objective outweighs the inherent risks and burdens to the subject**

In the context of MS, although there is a reduction in quality of life resulting from exacerbations, these reductions have not been shown to be associated with progression of the underlying axonal atrophy that must be the basis for clinical progression. Both the clinical and MRI evidence of exacerbations can be (and routinely are) treated with a short course of high-dose corticosteroids, and hospitalization is rarely required. Although relatively simple to measure, the number of relapses seems trivial as an endpoint in comparison with disease progression. Moreover, ideally a reduction in the progression of MS should be demonstrated in a group of patients selected because of their progression rather than their frequent relapses.\[13\]

**The physician may combine medical research with medical care** When obtaining informed consent, the physician must be cautious since the subject is in a dependent relationship with the physician or may consent under duress For a research subject who is legally incompetent, physically or mentally incapable of giving consent, or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative

The relevance of these statements is found in the demonstration of gray matter involvement in MS which it must be assumed is at least in part responsible for the occurrence of the cognitive impairment that is now known to be common in this disease. The close and prolonged relationship of physician and patient in the MS clinic could easily engender a paternalistic role for the physician, for which reason (despite the combination of clinical and research care allowed by the Helsinki Declaration) a neutral physician should be responsible for administering information and obtaining consent from the patient or designate.\[20\] It is recommended that the patient should decline in writing the use of recommended available medication before entering a clinical trial.\[14\]
The design of all studies should be publicly available. In publication of the results of research, investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available.

The prerogatives of the physician-researcher must not be denied by the dictates of an industrial sponsor, and clinical trials should not be undertaken by physicians who have a financial stake in the outcome. This includes inducements to enroll subjects. In this regard, it would be preferable for a flat rate compensation package to be paid to the physician’s clinical department independent of numbers of subjects enrolled but linked to the number of subjects screened. This would solve the ethical problems occasioned by the opportunity for a researcher’s clinical judgment to be influenced by self-interest.

That the results of the trial will be published in an appropriate manner should be guaranteed. As Foa pointed out, all trials are collaborations between participants, investigators and sponsors and no single party should have proprietary control over the information generated. A writing committee representing both the principal investigators and the sponsor should be provided with all the relevant information about the molecule tested and the trial results. The investigators will have to attest that this has been done if they want their papers published in any major peer-reviewed journal following the recent statement of the Council of Medical Journal Editors. It would have been appropriate for these editors to have committed themselves to publishing the negative as well as the positive results of research; journals are not newspapers and have a duty to report the facts, all the facts, and nothing but the facts. Unfortunately the opportunity was missed.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo or no treatment in studies where no proven therapeutic method exists.

The question of the use of placebo arises when a new drug is available and has a beneficial effect on the disease in question. In 1993, the American National Multiple Sclerosis Society stated, ‘In the absence of demonstrated treatments, placebo controls are essential in MS’; use of placebos could be reconsidered if efficacy data are available for a given agent for a specific phase of the disease, but the World Medical Association (WMA) statement above appears to bar not only placebo-controlled but actively and historically controlled trials as well. This opinion does not appear in the guidelines for the Council International Organizations of Medical Sciences (CIOMS) and the World Health Organization, the American Medical Association guidelines http://www.ama-assn.org/, or the Food and Drug Administration guidelines http://www.fda.gov/. The European Agency for the Evaluation of Medicinal Products guidelines, specifically related to MS www.eudra.org suggests that future clinical trials for MS should by preference be placebo-controlled and should continue for a duration adequate to demonstrate a convincing clinical endpoint. The International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use http://www.ifpma.org/ suggests that placebo-controlled trials are justified with full informed consent from participants if the only harm to subjects is ‘discomfort’,
which is not defined. An international task force concluded that placebo-controlled clinical trials in forms of MS for which partially effective therapies exist were ethical as long as the study subjects were fully apprised of the availability of such therapies and were encouraged to pursue them outside of a clinical trial.\[28\] Patients who decline to use available treatments, after proper education and counseling or who fail all therapies can be considered to have no treatment alternatives and thus may participate in a placebo-controlled trial.

The WMA was concerned that paragraph 29 of the revised Declaration of Helsinki\[2\] had led to diverse interpretations and possible confusion, and so it made an attempt to clarify the situation in October 2001, indicating that where, for compelling and scientifically sound methodological reasons, the use of a placebo is necessary to determine the efficacy of a therapeutic method or where a therapeutic method is being investigated for a minor condition and the patients who received placebo would not be subject to any additional risk or serious or irreversible harm, the use of placebo in research trials might be ethically acceptable.\[29\] As placebo-controlled trials are still the gold standard in MS,\[26\] this is something of a relief. However, the first part of the ‘clarification’ appears to reverse the Helsinki Declaration of 2000 since a placebo-controlled trial is now stated to be ethically acceptable, even if proven therapy is available for ‘compelling and scientifically sound methodological reasons’ and the interpretation of what such reasons might be is likely to be controversial. The WMA Statement of October 2000 and the published opinions of MS clinicians about the ethics of placebo-controlled clinical trials in MS are not congruent, and disorder will result until a final statement is prepared.

In the context of the original injunction against placebo use, the essential question is whether or not the interferons and glatiramer acetate can be considered to be truly effective drugs that must be used as comparators. If they are not considered as such, then there is no difficulty with placebo use; if they are, alternatives to placebo-controlled trials are required. The best evidence is that immunomodulators provide limited benefits in the relapsing-remitting stage of multiple sclerosis but cause a wide range of side effects. On-trial changes in disability tend to occur in that part of the disability scale that is most difficult to interpret. The criteria for ‘progression’ in some trials could have been fulfilled by bladder urgency, minor changes in visual acuity, or even asymptomatic examination findings.\[13\] We still do not know the long-term effect of interferons, but ‘evidence-based medicine’ decrees that it is invalid to extend the clinical use of medication beyond the indications established in phase III trials. The first interferon beta was licensed in 1993 on the basis of a reduction in the exacerbation rate and in secondary outcome measures such as time to subsequent exacerbations, their severity, and disease activity measured by MRI. No conclusive or important benefit has been shown on the crucial issue of sustained progression of functional impairment but only on MRI findings, and even now ‘no study of sufficient duration has shown that improvement in MRI parameters affects the MS disease course’.\[30\]

Is it ethical to exclude a patient from the opportunity of being involved in a research trial? Patients who end up in the placebo arm of a trial may not have been disadvantaged overall because of the psychological effects of trial entry. Better care, the placebo effect, and the probability of being offered the superior treatment when it becomes available are still significant benefits. The alternative is the best standard treatment, as long as it was
itself originally tested against a placebo. If treatment response can be measured accurately and cannot be affected by a person’s mental attitude, placebos may be unnecessary, but this is seldom the case. ‘In most therapeutic trials there is no major advantage or disadvantage at any one time for a patient in getting treatment A or treatment B. So there is no great issue about individual autonomy.’[5]

There are alternatives to the standard randomized placebo-controlled trial format.[30] Three arm studies distinguish between a drug that is not effective (the standard agent is superior to placebo but the new drug is not) and a study that fails to provide a credible answer (neither the standard drug nor the new drug is superior to placebo). Such a study can assess assay sensitivity and if this is confirmed, it can both measure the effect of the new drug and compare the effects of the two active treatments.[6]

Add-on trials dispense with placebos but do not allow determination of the value of the drug on trial as monotherapy.

Escape studies change assignment (e.g. back to the best current therapy) when a predetermined treatment failure point is reached, though the determination of this point may be difficult. They are appropriate for life-threatening diseases, but in other areas are seldom proposed by industry, probably because of the numbers and the time required.

Randomized withdrawal (enrichment) studies are a neglected option in MS research.[33] In this design, all subjects are given the investigational therapy in an open-label screening phase and those responding are later recruited into a double-blind crossover phase in which they are randomly assigned either to receive placebo or to continue with the active therapy. This design can show a persistent effect over periods for so long as to be unacceptable in placebo-controlled trials. The null hypothesis that the benefit in the first phase was only a placebo effect is tested,[34] and the method does allow comparison with a placebo but does not inform about the response that can be expected in a population.

Extension studies ‘provide an appealing mechanism to generate data for validating surrogate outcomes, capable of predicting long-term change in clinically relevant measures of disability’, [35,36] but they are often statistically under-powered and may involve patients in different demographic or clinical groups and in different proportions from the original study. Nevertheless, the quantity of data may in part compensate for lack of quality, and long-term follow-up does provide the ultimate in intention-to-treat data.

THE EVALUATION OF EQUIPOISE

Individual equipoise[37] exists when there is no evidence basis for a preference for either of the arms of a study, so that a rational informed person has no preferences between two or more available treatments and is in a state of genuine uncertainty as to whether one of the treatments is better than the other. If the investigator is not uncertain—even if he or she has the least margin of preference for one therapy—he or she should not enter patients into the clinical trial.[38] But even if theoretical equipoise were to be achieved, the fulcrum is shifted by the prospect of side effects from the treatment, so that the point of individual equipoise is no longer ‘no difference’ but ‘an effect sufficient to compensate for the treatment with the worst side effects’. This is unmeasurable.
The clinical researcher will also be aware that the experimental treatment has the promise of being better for his or her patient than the comparator is, but this cannot be determined until it has been tested; the researcher will also be aware that there may be global uncertainty within the expert medical community about the relative merits of the two agents, despite any personal preference for one of them. Such a situation is termed clinical (or collective) equipoise; it denotes collective uncertainty and is at present a predominant ethical principle in North America. However, belief is not knowledge; it should be possible for a physician with a preference for one therapy to acknowledge that such a preference is personal and possibly incorrect. If it is knowledge-based, the whole community will presumably accept it as well.

Clinical investigators often narrow excessively the conditions and hypotheses of a clinical trial in order to ensure the validity of its results, purchasing scientific manageability at the expense of an inability to generalize the results obtained to the rest of the clinical populations of patients falling outside the selection criteria for the trial. The theory of equipoise can be extended to suggest that overly fastidious trials fail to satisfy the ethical requirement of clinical research for generalizability, since the special conditions of the trial will render it unable to influence clinical decisions even if it is successfully completed. The results of a trial should resolve uncertainty; clinical equipoise requires a trial design that will compare two treatments under the conditions in which they will be applied in practice, answering the question, ‘Which of these two treatments should we prefer?’

Equipoise differs from ‘not knowing’ or being uncertain because it requires that there is no rational basis whatever for a preference. The resulting paradox is that, while a trial may be ethical because there is general uncertainty within the medical community on the merits of the agents to be compared, if that state results from evenly divided medical opinions (i.e. all physicians in the community have one of two possible opinions), there is collective equipoise but no physician will be ethically justified in entering any patients. For this reason, and given Sackett’s demonstration that the term ‘equipoise’ fails on utility, reality and consistency, it is reasonable to stay with ‘uncertainty’ and eschew ‘equipoise’.

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INTRODUCTION

The drug development process is both long and complex. The average time from discovery to approval has been estimated to be 10 years. Throughout this process regulatory authorities play a significant role. Charged with the responsibility of ensuring the safety and efficacy of drugs and biological products that are approved for use, these regulatory bodies define the rules and regulations that guide industry in the drug development process. Through the issuance of policy and guidance documents as well as specific regulations, the regulatory authorities affect drug development from preclinical testing through registration and commercialization. The complexity of the development process is confounded by the varying regulations that exist from one country or region to another. This chapter outlines the drug approval process in the USA, the European Union (EU), and Canada, contrasting the rules and regulations that govern approval in these regions.

DRUG REVIEW AND APPROVAL PROCESS IN THE USA

Structure of the Food and Drug Administration

The process of drug approval in the USA is regulated by the Food and Drug Administration (FDA). Applications for new drugs are reviewed and approved by the Center for Drug Evaluation and Research (CDER) and applications for new biologic products are reviewed and approved by the Center for Biologics Evaluation and Research (CBER).

The regulation of new drugs and biologics evolved from different legislation and regulatory agencies. The foundation of drug product regulation comes from the Food, Drug and Cosmetic Act, whereas biologic product regulation is based on the Public Health Services Act. Up until 1972, drug products were regulated by the FDA and biologic products were regulated by the Public Health Service. In 1972, the FDA assumed responsibility for regulating biologic products; as a consequence, biologics are now governed by both the Food, Drug and Cosmetic Act and the Public Health Services Act.
The investigational new drug or biologics application

Before starting any clinical trials with a new drug or biologic, the sponsoring company must first obtain the permission of the FDA to begin clinical testing. To do this a company must compile and submit preclinical information, manufacturing information, and clinical plans to the FDA in the form of an Investigational New Drug Application (IND). The IND is a request for an exemption from the federal statute prohibiting an unapproved drug or biologic from being shipped in interstate commerce. The FDA assesses the information to determine if the product is safe for testing in humans.

The sponsoring company agrees not to begin clinical investigations until 30 days after the receipt of the IND by the FDA unless the sponsor is notified that the investigations described in the IND can begin earlier or are subject to clinical hold under 21 CFR (Code of Federal Regulations) 312.42.

For gene transfer therapies, additional regulatory procedures are required that go beyond the requirements for most biologics. These additional procedures stem primarily from the uncertainties surrounding the use of gene therapy and the scientific complexities associated with the different vector types that are available. Before an IND is submitted to the FDA, gene transfer protocols must first be approved by the Recombinant Advisory Committee (RAC), which has been established under the auspices of the National Institutes of Health Office of Biotechnology Activities (OBA). The RAC application is reviewed primarily for the scientific merit of a proposed gene transfer study.

Throughout the process of drug development, there is continued interaction with the FDA. Sponsors are required to submit new protocols, changes to protocols, and changes to chemistry and manufacturing processes to the FDA as amendments to the IND. There are also opportunities to meet the FDA at each major stage of the drug development process. The FDA strongly encourages sponsors to request the following meetings at the appropriate times during the development process: a pre-IND meeting, an end-of-phase II meeting, a pre-phase III meeting, and a pre-BLA (Biologics License Application) or pre-NDA (New Drug Application) meeting.

The regulation of clinical testing by the FDA

The FDA regulates clinical testing by setting minimum standards for clinical trials, known as Good Clinical Practices (GCP). These standards are outlined in regulations and guidelines that cover the responsibilities of Institutional Review Boards (IRBs), the sponsor and the monitor, and obtaining informed consent for clinical subjects.
Institutional Review Boards

IRBs are used to ensure the rights and welfare of people participating in clinical trials both before and during their trial participation. IRBs at hospitals and research institutions throughout the country make sure that participants are fully informed and have given their written consent before studies ever begin. IRBs are monitored by the FDA to protect and ensure the safety of participants in medical research.[1]

For gene transfer clinical trials, there are additional GCP-related requirements, including safety reporting, patient follow-up, and Scientific Review Boards (SRBs), that go beyond what is required for most biologics. For instance, clinical trial safety data must be submitted to the RAC as well as the FDA. The RAC is then responsible for analysing these data across all gene transfer clinical trials in an effort to identify any safety-related trends. In addition, patients who have received a gene transfer product as part of a clinical trial must be followed for long-term survival, which could in some cases exceed 20 years. Lastly, many medical institutions have established SRBs that focus their review on the scientific aspects of gene transfer protocols. At most institutions, both the IRB and SRB must approve these protocols before the clinical trial can be initiated.

Protection of human subjects

Informed consent involves a written or oral notification to human subjects involved in clinical investigations that provides them with sufficient opportunity to consider whether or not to participate in the study. Informed consent is designed to ensure that patients voluntarily participate in a clinical trial and adequately understand the benefits and risks of participation in the trial. Regulations require that, except in special circumstances, no investigator may involve a person as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.[1]

License applications for new drugs or biologics

In order for a company to market a new drug or biologic, the FDA must approve an application to market the product.[2,3] The sponsor must file an NDA or BLA, which consists of non-clinical and clinical data, chemical and biological information, and product manufacturing and control information.

The FDA determines if the product is safe and effective for its indicated use, if the benefits of using the product outweigh the risks, and whether the methods used in manufacturing and quality control are adequate to preserve the product’s identity, strength, quality, potency, and purity. The FDA also determines if the proposed labeling is appropriate.

The FDA has set down very specific requirements for the content and format of labeling.[4] Regulations require that the package insert labeling be based on data derived from human experience with no implied claims. The labeling should constitute a summary of the essential scientific information needed for the safe and effective use of the
product. The labeling also sets out boundaries or limits as to how far the sponsoring company may go in advertising its product.

**Priority review**

In certain instances, the FDA has made provisions for marketing applications or supplements to applications to be granted priority review. In general, an application or supplement will receive priority review if the product, if approved, would be a significant improvement, compared with marketed products (including non-drug products and therapies) in the treatment, diagnosis, or prevention of a serious or life-threatening disease. The criteria of CBER and CDER for priority review differ slightly in that the CDER’s definition of priority review does not specify that the disease has to be serious or life-threatening. Priority applications and efficacy supplements have a target review time of 6 months in contrast to a standard application or supplement, which has a target review time of 10 months.

**Maintaining the marketing license**

After a product has been approved, there are a number of requirements to which the sponsor must adhere. These requirements include periodic reports, postmarketing commitments, and reporting changes to the product manufacturing process or labeling.

The FDA requires that certain periodic reports be submitted at varying intervals depending on how long the product has been on the market and whether it is classified as a drug or biologic. For example, Periodic Adverse Experience Reports are required to be submitted quarterly for the first 3 years after approval and then annually.

In most instances, the FDA outlines postmarketing commitments for new products, which the company is required to agree to perform before the product will be approved. These commitments could take the form of additional clinical studies or analytical studies. Additionally, the sponsor is responsible for reporting any changes to the chemistry, manufacturing, and control processes as well as any labeling changes to the FDA. Depending on the magnitude of these changes, the sponsor may or may not be required to submit a supplement for FDA approval before implementation of the change.

**Orphan Drug Act**

Congress enacted the Orphan Drug Act in 1983, which provides incentives for companies to develop treatments for rare diseases. A drug, biologic, or medical device is considered an orphan product if it is used to treat a rare disease. The term ‘rare’ disease or condition is defined as any disease or condition that affects fewer than 200,000 people in the USA or that affects more than 200,000 people in the USA but for which there is no reasonable expectation that the cost of developing and making available a drug for the disease or condition will be recovered from sales in the USA of such a drug. Some examples of rare diseases that have met the criteria under the Orphan Drug Act are multiple sclerosis, Gaucher’s disease, and AIDS-related Kaposi’s sarcoma. Responsibility for implementing the Act lies with the Office of Orphan Products Development, which is part of the FDA.
Orphan designation is the process by which a company can take advantage of incentives provided by the Act. These incentives include 7 years of marketing exclusivity upon approval of the product, a waiver from filing fees, a tax credit for a portion of the clinical research costs, and grants that may cover $200,000 per year of clinical research costs for up to 3 years. In order to receive orphan designation, a company is required to submit an application to the Office of Orphan Products Development. The application should include the treatment that the company seeks to develop, a description of the rare disease, the proposed indication, reasons why such therapy is needed, and documentation that the disease for which the drug is intended affects fewer than 200,000 people in the USA or that the cost of research and development of the drug cannot be recovered through sales of the drug in the USA. Upon approval of the application by the Office of Orphan Products Development, orphan status is granted to the product and the company is eligible for the incentives listed above.

During the 10 years preceding enactment of the Orphan Drug Act, only 10 products for rare diseases had reached the market. Since the Act was passed, there have been over 500 active orphan product designations and more than 200 products have been approved for treating rare diseases. Since the Orphan Drug Act has been such a success in the USA, similar initiatives have taken place in the EU, Australia, and Japan.

Recent initiatives to improve the review processes of the FDA

The Food and Drug Administration Modernization Act of 1997

The Food and Drug Administration Modernization Act (FDAMA) enacted by Congress in 1997 focused on reforming the regulation of food, medical products, and cosmetics. With the passage of the FDAMA, Congress enhanced the mission of the FDA in ways that recognized that it would be operating in a 21st century characterized by increasing technological, trade, and public health complexities. The law codifies many FDA initiatives undertaken during the Clinton administration’s ‘reinventing government’ program. The codified initiatives included measures to modernize the regulation of biologic products by bringing them into harmony with the regulations for drugs, eliminating the establishment license application, streamlining the approval process for manufacturing changes, and reducing requirements for environmental assessments as part of a product application. The act also codified the regulations and practice of the FDA to increase patient access to experimental drugs and medical devices and to accelerate review of important new medications, including the practice, in certain exceptional circumstances, of accepting a single clinical investigation as the basis for product approval.[5]

The FDAMA contained reauthorization for a further 5 years of the Prescription Drug User Fee Act of 1992 (PDUFA). The PDUFA provided the FDA with additional revenue to hire more reviewers and support staff and upgrade its information technology to speed up the application review process for pharmaceutical and biological products without compromising review quality. In its first 5 years, the PDUFA program enabled the FDA to halve the average time required for drug review, from 30 months to 15 months. Under the PDUFA, the FDA is required to meet review performance goals that are more stringent each year. By 2002, the goals for marketing applications, including NDAs,
BLAs, and efficacy supplements, are to act on 90% of priority review applications within 6 months of their initial submission, and 90% of standard review applications within 10 months.\[5,6\]

Reauthorization of the PDUFA, known as PDUFA II, added a new set of goals intended to improve the FDA’s responsiveness to and communication with industry sponsors during the early years of drug development. These goals specified time frames for activities such as scheduling meetings and responding to various other sponsor requests. The meetings addressed in the PDUFA are categorized as type A—a meeting critically necessary for a drug development program to proceed; type B—the milestone meetings (pre-IND meeting, end-of-phase II meeting, pre-phase III meeting and pre-NDA or pre-BLA meetings); and type C—all other meetings. The goals for scheduling meetings are within 30 days of receipt of request for type A, 60 days for type B, and 75 days for type C, with expected on-time performance increasing from 70% in 1999 to 90% in fiscal year (FY) 2001.\[6\]

PDUFA III is being enacted in 2002. PDUFA III covers a number of initiatives such as increasing user fees, allowing sponsors to include risk management plans in marketing applications, and allowing sponsors to request independent consultant review of clinical protocols for biotechnology products that represent a significant advance in treatment or have the potential to address an unmet medical need.

PDUFA III also proposes two pilot programs starting in 2004 which provide the opportunity for more communication between sponsors and FDA as well as allowing for the submission of continuous marketing applications for products designated as Fast Track which have demonstrated significant promise as a therapeutic advance in clinical trials. A drug or biologic that is designated as a Fast Track product is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs. The advantage of a continuous marketing application is that once a sponsor has completed a section (i.e. clinical, non-clinical, or CMC) of the marketing application, that section can be submitted to FDA for review. FDA will complete their review within 6 months and issue a letter for that section of the marketing application. This allows sponsors to receive FDA written feedback earlier in the process before all sections of the marketing application are complete.

Through FY2000, the FDA has met or exceeded nearly every PDUFA performance goal. The reduction in review time also increased the relative number of FDA-approved new molecular entities that were first introduced in the USA.\[7\] The enactment of PDUFA and FDAMA has clearly increased the efficiency of the regulatory review process for drug approval.

**Electronic submissions**

To support PDUFA II goals, numerous enhancements to the review process have been implemented. Among all of the ongoing efforts, one of the most crucial and far-reaching is in the area of information technology development.

The FDA has faced increasing pressures on resources due to PDUFA-defined timelines and the increasing number, size, and complexity of INDs, NDAs, and BLAs. This has made the need for computer-based solutions more urgent. The introduction of the 21 CFR Part 11 regulation created an electronic signature and record as official
record, and made it possible for the FDA to accept electronic originals in lieu of paper, although the FDA still requires signed paper forms and cover pages for reports. The FDA, specifically CDER and CBER, guided the industry to submit full electronic and standardized NDAs and BLAs. This, together with the creation of navigational support, made it possible for sponsoring companies to submit whole submissions contained on CD-ROMs, and tapes, instead of enormous truckloads of paper.

**DRUG REVIEW AND APPROVAL PROCESS IN THE EU**

**Structure of the EU and its regulatory bodies**

The European Economic Community, subsequently renamed the European Community and then the European Union (EU), was established in 1957. It has been enlarged on four occasions and now comprises 15 member states: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. Each member state has its own national regulatory agency responsible for the approval of clinical trial and marketing authorization applications in its territory.

A key principle of the EU is the free movement of goods, including medicinal products. Therefore, in order to remove any obstacles to the free movement of goods, and also to establish high levels of public health protection, a harmonized framework of legislation and guidance has been developed, including, for example, specific guidance on the clinical development of drugs for the treatment of multiple sclerosis. Therefore, although the national regulatory approval procedures are still diverse, significant progress has been made in harmonizing legislation and data requirements for marketing authorization applications. National legislation to obtain approvals to conduct clinical trials has not been harmonized, but the process for doing so is now under way.

The national regulatory authorities have a significant role in the approval of new drugs, and their activities are co-ordinated by bodies such as the European Agency for the Evaluation of Medicinal Products (EMEA). There are currently two procedures that can be used to obtain a Marketing Authorization: the Centralized Procedure and the Mutual Recognition Procedure.

**Clinical trial applications**

During the drug development process, the regulatory authorities in Europe oversee the process of review and approval of clinical trial applications. Clinical trial application procedures in the EU are complex because legislation is not harmonized and each member state has its own national procedures. Accordingly, timelines and requirements vary by country.

The study sponsor must obtain ethical approval via hospital Ethics Committees prior to study initiation. There are local committees for most of the European countries, but in France and Germany, the hospital Ethics Committee of the co-ordinating investigator plays the role of a central Committee, granting an opinion valid for the participating sites in the country. The study sponsor must also meet national administrative requirements,
which can include importation authorization procedures. Additional requirements are necessary for biotechnological and biological products in certain countries (e.g. viral safety committee submissions in France).

National requirements to enable clinical studies to be undertaken can generally be divided into notifications and authorizations. A notification is the procedure to inform a regulatory authority that a clinical trial is about to be undertaken in a country—no formal approval is required and the study can commence immediately. In contrast, some member states prohibit studies from starting until a formal authorization document has been issued. Notifications may occur in parallel to Ethics Committee submissions (e.g. in Denmark and the Netherlands) or after them (e.g. in France, Germany, Belgium, and Portugal). Similarly, authorizations can be obtained in parallel with Ethics Committee approvals (e.g. in Sweden, Ireland, and the UK) or afterwards (e.g. in Finland, Greece, and Spain). Approval times are generally between 1 and 4 months, but timelines can also vary by the study and medicinal product type. For example, in France, viral safety submissions must be made 1–2 months in advance and before Ethics Committee submissions. The UK is also exceptional in that most phase I studies in healthy volunteers do not require regulatory approval, although the Ethics Committee approval is still required.

European legislation is now being introduced to harmonize the national procedures for conducting and obtaining approvals to conduct clinical trials and to implement specific aspects of GCP. This legislation is scheduled to be implemented in each Member State by May 2004.

The Directive 2001/20/EC harmonizes the requirements to start a clinical trial. Both Ethics Committees and Regulatory Authorities will have to be consulted according to different procedures, depending on the investigational product.

One single Ethics Committee opinion will be required per member state before the start of the trial. Usually, this opinion should be granted within 60 days. Extensions of 30 days and then of 90 days will be permitted in the case of clinical trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products that contain genetically modified organisms. In the case of xenogenic cell therapy, there will be no time limit to the authorization period.

National regulatory authorities will be required to authorize clinical trials. Before commencing any clinical trial, the sponsor will be required to submit a valid request for authorization. The evaluation period may not exceed 60 days. This means that in the UK a regulatory approval will now be required for phase I studies.

Thus, a sponsor may not start a clinical trial until the Ethics Committee has issued a favorable opinion and the competent regulatory authority of the member state concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel.

The national implementation of this Directive may still lead to differences in the clinical trial process. Some regulatory authorities may not take the full duration permitted to grant approval and this may therefore offer the opportunity for faster regulatory approvals and earlier start times for clinical trials in those countries.

The marketing authorization application review and approval process
In 1995, two new procedures were implemented for obtaining marketing authorizations in the EU:\[8\]

1 Mutual Recognition Procedure, in which a marketing authorization is granted by the competent authority of a member state for its own territory (national authorization), which is subsequently recognized by other member states.

2 Centralized Procedure, in which a marketing authorization is granted by the European Commission for enforcement in the entire EU (a Community Authorization); this is under the control of the EMEA.

A marketing authorization is valid for 5 years and must then be renewed; this is done by filing applications at least 3 months before the expiry date.

**Mutual Recognition Procedure**

The Mutual Recognition Procedure relies on an assessment by one national authority (and not the EMEA). An application may be submitted to one or more member states. The application must be identical in each member state and all member states must be notified of the application. As soon as one member state decides to evaluate the application (at which point it becomes the ‘reference member state’), it notifies its decision to the other member states (‘concerned member states’), to whom applications have also been submitted. Concerned member states may then suspend their own evaluations and await the reference member state’s detailed assessment report on the product (in a time frame of 210 days). When the assessment report is completed, copies of this report are sent to all member states and they have 90 days to recognize the decision of the reference member state and the Summary of medicinal Product Characteristics (SmPC) as approved by it (by granting a marketing authorization with an identical SmPC).

If a concerned member state raises a serious objection (e.g. on public health grounds), it would be possible for the discrepancy to go to arbitration by the Committee for Proprietary Medicinal Products (CPMP). The CPMP would then evaluate the objection and give an opinion that leads to a binding decision for all affected member states. However, if the CPMP upholds the objection it is possible that the original marketing authorization could be rescinded and the product could be withdrawn from the market. Therefore, in practice, few companies go to arbitration since this is often seen as being too high-risk an approach.

The Mutual Recognition Procedure offers the possibility of a rapid review, the opportunity for the applicant to choose the reference member state, the ability to exclude any concerned member state in case of specific difficulties, and the option to withdraw applications when resolution cannot be reached. Marketing flexibility, with co-marketing agreements and the option of various trademarks in various countries, are also important advantages.

**Centralized Procedure**

The EMEA was created in 1995.\[10\] Its primary responsibility is to oversee the Centralized Procedure for authorizing medicinal products. EMEA staff use external assessors from the national regulatory agencies to provide scientific advice and assess
marketing authorization applications. In the Centralized Procedure, there is a single application, a single evaluation, one fee, and a resultant single authorization issued by the European Commission allowing direct access to the entire EU market.

The Centralized Procedure is compulsory for biotechnology products derived from recombinant DNA technology or from manipulation of genetic material, such as hybridoma and monoclonal antibody methods, the so-called ‘list A products’. For new active substances and other innovative medicinal products (‘list B products’), the choice of authorization procedure is the sponsor’s decision.

The Centralized Procedure offers significant advantages because the single authorization automatically confers the same rights and obligations in all member states as if each member state had granted a national marketing authorization. As with the Mutual Recognition Procedure, one SmPC and one package leaflet is approved for use in all countries. Disadvantages of the system include the need for a single EU trademark (which often causes considerable practical problems), a single packaging style, and—moreover—the possibility of a single rejection applicable to the whole EU, thus making it impossible to market the product anywhere in the EU without reapplying.

The procedure takes 240 days from validation of the application to CPMP opinion, not including the time needed for the sponsor to respond to questions. An accelerated evaluation by the Centralized Procedure might be initiated by the CPMP in exceptional cases when a product is intended to provide an answer to a major public health need.[9]

The opinion of the CPMP must be made legally binding by the European Commission and it is therefore the Commission that grants the Marketing Authorization. The positive opinion of the CPMP is forwarded to the Commission, and a timeline of 90 days is fixed for the issuing of an approval. Hence, from submission to approval, the Centralized Procedure predicts a 310-day process, excluding company response time.

Since the EMEA seeks to increase public awareness in the process of product approval, the European Public Assessment Report (EPAR) is released to the public within 3 months of the Commission decision. The EPAR is a summary of the assessment report for products approved through the Centralized Procedure. Reviewing EPARs of similar products already approved can facilitate the development of new products.

### Pricing and reimbursement

It is necessary to secure reimbursement following regulatory approval, by either Mutual Recognition or the Centralized Procedure. Reimbursement is under the control of national legislation. In certain countries, such as Germany and the UK, the sponsor is able to determine the price and to sell immediately as soon as the Marketing Authorization is obtained. In other member states, national procedures exist, varying in complexity and resulting in delays from approximately 2 weeks in Finland up to 15 months in Belgium.

France provides a good example of the potential negotiations. The French procedure has two steps: a technical dossier is first submitted to the Transparency Commission to justify that the drug adds therapeutic value, and then an economic file is submitted to the Economic Committee (Ministry of Social Security) to justify the proposed price and sales volume forecast. Despite legislation fixing the total procedure to 180 days, these negotiations can take up to 9–12 months.
Maintaining the Marketing Authorization License

Once a medicinal product has been approved through either the Centralized Procedure or the Mutual Recognition Procedure, the Marketing Authorization Holder (MAH) is responsible for a variety of post-approval activities, such as Periodic Safety Update Reports, Post-Approval Commitments, and reporting changes.

Periodic Safety Update Reports must be submitted by the MAH every 6 months after approval for 2 years, then annually for 3 years, and then at the time of product license renewal every 5 years.

Products that receive conditional approval through the Centralized Procedure are subject to annual assessment of the benefit to risk ratio. Post-Approval Commitments are fixed at the time of the approval according to a set timeline. Commitments include data to be submitted as part of clinical obligations, which are legally binding, and pharmaceutical follow-up measures, which are not legally binding but often require world-wide specification changes. The annual reassessment involves summarizing the status of these data and continues until the MAH has fulfilled these obligations.

The MAH may wish to alter or improve the product or to add additional safeguard measures for a variety of reasons. In order to do this, an MAH must submit a Variation, which contains information describing the change.

Orphan drugs

European directives have permitted medicinal products to be approved in circumstances where the indication was so rare that it was not possible to provide what is usually considered to be comprehensive data. Each member state therefore had its own national rules, regulations, and guidelines as to what constituted a rare disease and the possible incentives to encourage companies to develop treatments for them. Following the success of the orphan drug legislation in the USA, regulations were adopted to define a Community procedure for the designation of orphan medicinal products and to provide incentives for their research, development, and placement on the market. Furthermore, a Committee for Orphan Medicinal Products was established to examine applications for the designation of orphan drugs.

Accordingly, in the EU an orphan medicinal product is a medicinal product intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 per 10,000 persons in the EU. The incentives available to encourage companies to develop orphan medicinal products include: protocol assistance, access to the Centralized Procedure (if the drug would not usually qualify for the procedure), application fee waiver, market exclusivity for a period of 10 years, and research grants.

Orphan medicinal products do not automatically qualify for accelerated review, but they may qualify if they meet appropriate criteria.

A drug designated as an orphan drug in the USA does not necessarily confer orphan medicinal product designation in the EU, and vice versa.
DRUG REVIEW AND APPROVAL IN CANADA

Structure of Health Canada

The Food and Drugs Act and Regulations provide the regulatory framework for governing the drug development and approval process in Canada. The specific responsibility for overseeing this process rests with the Canadian Ministry of Health. The Health Products and Food Branch (HPFB) of Health Canada is responsible for maximizing the safety and efficacy of drugs and biologics in the Canadian marketplace. The Therapeutic Products Programme (TPP) is under the HPFB and is responsible for the regulation of drugs and biologics. The Biologic and Genetic Therapies Directorate (BGTD), a branch under the TPP, is responsible for regulation of biological and radiopharmaceutical drugs as well as blood and blood products, vaccines, gene therapy, and xenografts. The Therapeutic Products Directorate (TPD), another branch under the TPP, evaluates and monitors the safety, effectiveness, and quality of drugs, medical devices, and other therapeutic products. The HPFB Inspectorate is responsible for on-site evaluations, inspections, and enforcement activities related to the manufacture, packaging and labeling, importation, and distribution of regulated health products.

The clinical trial application

The Food and Drugs Act and Regulations authorize the HPFB to regulate drugs for the purpose of use in clinical trials. These regulations define the parameters for design, conduct, monitoring, and reporting requirements of clinical trials. Sponsors must file a Clinical Trial Application (CTA), formally referred to as an Investigational New Drug application, to conduct clinical trials. The CTA is a dossier that contains information about the drug to be used in the proposed clinical trial, including but not limited to a brief summary of the drug biologic current safety data, and a copy of the protocol, as well as chemistry and manufacturing information. A CTA is subject to a 30-day default period (i.e. unless told otherwise by the TPP, the study may begin after 30 days from the date of receipt).

New clinical trial regulations in Canada also require that specific information be included in the CTA regarding the clinical trial site. This information includes the proposed date each site will begin the study, the name of the qualified investigator at each site, and the name of the Research Ethics Board (REB) that approved the protocol and informed consent. REBs are charged with evaluating the ethical acceptability of a proposed clinical trial while balancing the risk-benefit ratio to the clinical trial subject. Before a subject can enter a clinical study, informed consent must be given. Informed consent is designed to ensure that subjects understand the purpose of the clinical study, do not enter the study against their will, and are given ample opportunity to ask the investigator questions about the study.

As part of maintaining the CTA, sponsors are required to submit changes in the manufacturing site, the manufacturing process, and changes to the protocol as
amendments to the CTA. CTA amendments must be approved prior to initiation of the change.

Before a CTA is submitted, sponsors are encouraged to request a pre-CTA meeting with the appropriate directorate. A meeting may be of particular use for sponsors of new active substances. The pre-CTA meeting provides an opportunity for the sponsor to present relevant data, discuss concerns, and resolve issues about drug development.

**The New Drug Submission**

The Federal drug regulations prohibit a company from offering a drug for sale in Canada, unless a New Drug Submission (NDS) has been submitted, reviewed, and approved by the appropriate directorate. Before they submit the NDS, sponsors are encouraged to request a pre-NDS meeting. One of the goals of the pre-NDS meeting is to introduce the dossier to the appropriate directorate. This can help to streamline the initial screening period. It is also an opportunity to address specific concerns reviewers may have as well as to give insight into questions that arise during the review process. The pre-NDS meeting typically includes presentations about the drug development process, chemistry and manufacturing information in addition to information regarding the clinical trials conducted during drug development.

Once the NDS has been received, the dossier will be subject to an administrative screening period of 45 days. If the dossier passes the initial screening, it is accepted for review and a letter is sent to the sponsor indicating the date of receipt, the file number, and the control number. These numbers should be referenced in all future communications regarding the NDS. The target review period for an NDS is 360 days. If review of the submission has not commenced during this time period, the sponsor will be notified and given the opportunity to update the dossier with any new information. If the sponsor elects to provide updated information, the directorate must be notified within 30 days. The sponsor then has 60 days to submit the updated information.

**Priority review of drug submissions**

The intent of priority review is to decrease the overall review times for applications. The scope of the Priority Review policy applies to NDSs as well as to Supplemental NDSs for a serious, life-threatening or severely debilitating illness or condition for which there is substantial clinical evidence that the drug provides either effective treatment, prevention, or diagnosis of a disease or condition for which no drug is presently marketed in Canada, or a significant increase in efficacy or a significant decrease in risk (or both) such that the overall risk-benefit profile is improved over existing therapies.

Sponsors should request a meeting with the appropriate directorate prior to the submission of a priority review request. A completed Clinical Assessment Package (CAP) must accompany the priority review request letter. A CAP includes but is not limited to a brief description of the disease, the indication for which priority review is being requested, a statement indicating that no other drug is available in Canada that provides the same therapeutic benefit, or a rationale for the improvement in the risk-benefit profile. Sponsors will be notified by the directorate of their decision within 30 calendar days of the receipt of the request. Sponsors must then submit the dossier within
60 days of receipt of the bureau’s positive decision or the priority review status will be forfeited. Submissions receiving a priority review status will be granted an accelerated review target of 180 days.

**Maintaining the marketing license**

Once a product is approved for marketing, the sponsor must then maintain the marketing license. This involves reporting changes to the chemistry and manufacturing sections, and any labeling changes. Health Canada does not require a sponsor to submit an Annual Safety Update Report unless one is specifically requested.

Changes to an approved biological product must be submitted to the BGTD and changes to a drug product must be submitted to the TPD. Changes are classified as to whether they are major or minor and this dictates whether a Supplement to the NDS or a Notification must be submitted. Supplements require approval before a change can be implemented and have a target review period of 180 days. Notifications have a 90-day default period after which the change can be implemented unless the sponsor is told otherwise.

**Cost recovery**

In Canada, cost recovery is a federal policy authorizing government departments to charge fees for services.[15] The TPP began implementing cost recovery in 1994. The TPP cost recovery program has five components: Authority to Sell Drug Fee (an annual fee for the maintenance of the right to market a drug in Canada), Drug Submission Evaluation Fee (a fee charged to evaluate a submission for the safety, efficacy, or quality of a drug), Drug Master File Fee (a submission containing proprietary information about specific components used in the manufacturing process), Drug Export Certificate Fee (a certificate provided by TPP to an exporter to facilitate the sale of a licensed Canadian drug in another country), and Drug Establishment Licensing Fee (a license that certifies the type of operations and products authorized to be handled by an establishment).

**CONCLUSION**

Historically, the differences around the world in the rules and regulations governing drug approval have added to the cost and time it takes for new products to reach the market. Over the past decade, there has been a major thrust to harmonize global regulations to address this issue. Both industry and regulatory authorities have contributed to these efforts.

Started in 1990, the International Conference on Harmonization (ICH) brings together the regulatory authorities of the EU, Japan, and the USA and technical experts from the pharmaceutical industry in these three regions. The goal has been, and continues to be, to produce a single set of technical requirements for the registration of new drugs and biologics, in order to allow a more economical use of human, animal, and material resources and to eliminate unnecessary delay in the global development and availability of new medicines. Other countries have a significant interest in the ICH, and the World
Health Organization, Canada, and the European Free Trade Association are official observers to the process.

Over 45 guidelines covering efficacy, quality (manufacturing), and safety (toxicology) topics have been developed through the ICH. Building on the harmonization of technical topics, the ICH developed the Common Technical Document (CTD) guidelines, which describe a common format for the scientific information included in an application for registration of a new drug or biologic. For each new drug, a vast amount of data are compiled and submitted to regulatory authorities. The presentation of the scientific information according to CTD guidelines will facilitate global registration of important new medicines, easing both the application preparation process and the review process. The ICH is also working on developing specifications that harmonize the exchange of the CTD in electronic format between a sponsor company and regulatory authorities in North America, Europe, and Japan. This standardization will help both the pharmaceutical industry and regulatory authorities streamline the approval procedure.

Overall, ICH has had a significant impact on streamlining the drug development process worldwide. These efforts will inevitably lead to decreases in costs and approval times.

ACKNOWLEDGEMENTS

We would like to acknowledge the following people for their contributions to the researching and writing of this chapter: Janet Casaubon, Emmanuelle Daclin, Aelie Fanchini, Gilles Fontan, Giovanni Garzella, Jennifer Jackson, Stacie Knight, Guillaume Mosnier, Elias Nyberg, Michael Sauter and Carey Smith.

REFERENCES


Sponsors, monitoring committees and investigators: the investigator’s perspective

Fred D Lublin and Stephen C Reingold

INTRODUCTION

The past 15 years have been a remarkably productive period for clinical trials in multiple sclerosis (MS). Five new therapeutic agents, representing three different classes of drugs, have been approved for use throughout most of the world, targeting relapsing forms of MS, secondary progressive disease and ‘worsening’ disease, depending on the country-specific regulatory approvals. At the time of this writing, pivotal studies on primary progressive disease and on new classes of agents are under way. Earlier-phase studies of promising new agents have been undertaken, some of which are destined to move to larger-scale, multicenter, pivotal studies. Some preliminary studies, as well as some larger, pivotal trials, have failed or have provided difficult-to-interpret results.

It remains the case that agents that have been shown to be relatively safe and effective have only modest treatment benefit, and there is a continued need for new products, new dosing regimens of available products, and increased formal study of combinations of agents. A major debate on the long-term efficacy of available agents is under way, with solid data to support or refute such benefits either lacking or being gathered in uncertain extension follow-up studies. Even harder to evaluate is the cost-benefit ratio for available agents (see chapter 12), but as these agents become more widely used, prescription drug reimbursement plans—private or governmental—are increasingly focused on these key, very difficult to obtain, data. All of this underscores the ongoing importance of, and increasing need for attention to, randomized controlled clinical trials for new therapeutic agents in MS and to the need for new ways to undertake and evaluate clinical trials.

PARTNERSHIP BETWEEN CLINICAL INVESTIGATORS AND INDUSTRIAL SPONSORS

The majority of MS clinical trials have been, and will continue to be, performed by clinical investigators in partnership with industrial sponsors. The ‘pipeline’ of innovative therapeutic modalities in pharmaceutical and biotechnological companies, coupled with the considerable expense of developing new agents from initial laboratory or animal testing through the pivotal trial phase, emphasizes the value and absolute necessity of such partnerships. Corporate sponsors may have the novel interventions and
the financial capability of supporting the very complex and expensive infrastructure needed to undertake multicenter studies. Clinical investigators offer expertise in MS clinical trial design and conduct, and can provide the desired independence and objectivity that is necessary in undertaking a trial and in interpreting results.

Clinical investigators and representatives of biotechnological and pharmaceutical firms all share an interest in finding safe and effective therapies for MS. However, the goals, needs, expectations, and priorities of clinical investigators, who may be academic physicians or private practitioners, may appear to differ at times from those of industrial sponsors. While both groups are focused on finding the best (efficacious and safe) possible therapies for MS, clinical investigators tend to be less concerned about such pragmatic issues as the corporate source of any given agent, patent rights, profit potential, marketability in an increasingly competitive marketplace, and internal corporate program prioritization. A commercial concern must, however, focus on such issues, since they relate to financial strength, corporate survival, and, often, the potential to continue pharmaceutical and biotechnological development in the future.

Although the joint interest of investigators and corporate sponsors in finding new MS treatments has led to successful synergies in recent times, it remains essential to recognize that these different perspectives can lead to difficulties in developing consensus during the planning stages of trials, difficulties in activities during the conduct of trials, and in difficulties interpreting and accessing data after trials.

The potential for such problems can be avoided, at least in part, by formally establishing, before the start of study, the elements of co-operation and interaction between corporate sponsors and clinical investigators. For large-scale, pivotal studies, these elements should include, among other details, the role of the investigators in the protocol design. An independent Advisory or Steering Committee should be created to work with the sponsor and any necessary consultants to design the study protocol, to advise the sponsor on any issues relating to the study before its initiation, during its conduct, or after its conclusion, and to serve during the study as a liaison between study investigators, other advisory groups and the sponsor. This Committee, as well as all other advisory groups and study investigators, should exclude anyone with significant financial interest in the agent’s development or any competing products. During the study, the advisory or steering committee should regularly review the progress of the trial and the impact of new developments in the field. The group should consider protocol amendments, if needed, and assist the sponsor in issues of protocol adherence, both in general and at specific centers.

An independent Data and Safety Monitoring Committee (DSMC) or an independent monitoring board should be established. Such a body will primarily serve to ensure the protection of human subjects in the study. Assessment of the protocol and its amendments and the evaluation of the ongoing study conduct may have an impact on the risk-benefit evaluation for the study. As such, review of a draft protocol for the scientific validity and conduct of the study is also part of the responsibilities of the DSMC. For most trials, the functions of ongoing monitoring of safety and efficacy data can be combined into a single monitoring group. Members of the DSMC should be independent of the study sponsor and of participating study sites and free from conflicts of interest. The DSMC should be composed of neurologists and others familiar with MS, people with expertise in monitoring adverse events, and biostatisticians experienced in clinical trials.
All members must be capable of understanding statistical, biological, and medical arguments related to the trial and all must be completely objective in their evaluations. Study investigators and employees of study sponsors should not participate in the discussions of the DSMC, except as a resource to clarify study conduct. A liaison between the DSMC, the Advisory or Steering Committee and the sponsor (who may be a sponsor employee or consultant) may be appointed to facilitate communication of information between the interested groups. The DSMC should remain blinded throughout the study (if this is part of the trial design) but it must have the option of requiring additional analyses and even unblinding (of the DSMC members only) in the event of significant safety or efficacy concerns. Unblinding of a study by the DSMC in the case of need should be able to be done expeditiously—essentially ‘on the spot’ at any DSMC meeting. On the basis of analyses of safety or efficacy data, or for ethical considerations, the DSMC may recommend early termination of the study to the Advisory or Steering Committee and to the sponsor. To perform their tasks, the DSMC must have complete and rapid access to study data. Before the study is initiated, the members of the DSMC must reach consensus among themselves, with the sponsor, and with any associated contract research organization about their own function and operation, including details relating to blinding, form of data presentation, frequency and format of meetings, and criteria for early stopping of the study. Those who are asked to participate in a DSMC function should be fully aware of the proposed protocol and its ramifications, fully able to justify and support the practical and ethical aspects of the protocol, and, in cases of difference of opinion, willing to debate issues or, in the end, willing and able to resign from that function with no consequences, if issues cannot be resolved.

A Publications Committee[2] should be created to determine the most expeditious way of reporting data analysis and of preparing manuscripts that describe the study and its outcomes. The Publications Committee must be committed to rapid reporting of results after the completion of a study. For this to take place, rapid data access and close communications between the Committee and corporate sponsors is essential. The Committee and sponsor, in association with the Advisory or Steering Committee, must formally agree, before initiation of the study, to any corporate data access or publication review procedures.

The role of investigators, advisory and monitoring committees, regulatory authorities, and the sponsor in evaluating need for any deviation in the original study plan or analysis should be determined. The maintenance of study design and integrity is of paramount importance. Because deviation in study plan can have consequences on interpretation of data, it is essential that any steps that might lead to changes while a study is in progress should involve key regulatory authorities.

The nature and independence of data analysis must be ascertained. ‘Ownership’ of trial data must be decided upon. This includes guaranteed access to all collected data by study investigators at the completion of the trial, including filing data in clinical trials data repositories, such as the newly established Sylvia Lawry Center for MS Research (Munich, Germany), so that they might contribute to future trial process revisions.

The role of the entire group of original study investigators in the interpretation and dissemination of data collected in ‘extension’ trials after the completion of the preplanned randomized trial must be decided upon.[3]
PATIENTS IN CLINICAL TRIALS

Patients who volunteer as study subjects do so, at least in part, out of a sense of duty to the greater good that may accrue to all with MS as a consequence of their participation. The interests of trial investigators and of study sponsors must, by necessity, be considered of secondary importance to the needs and interest of the patients involved in the study, and of patients more broadly. However, a trial that is undertaken without proper recognition of the necessary contributions of both trial investigators and corporate sponsors, and that does not involve planning in advance to ensure that the interests of all parties are well served, can diminish the contributions of the patient volunteers and compromise the ethics of all involved.

REFERENCES


INTRODUCTION AND RATIONALE

Randomized, controlled clinical trials (RCTs) are ideally designed with clear-cut prospective outcomes, on which trial design and statistical power are based. In some cases, patients may continue to be studied after the original RCT is complete. In such instances, extension studies are opportunistic, in that they aim to take advantage of data collected after the prescribed end of the trial for some or all patients originally enrolled. Extension studies thus provide a unique opportunity to collect efficacy and tolerability data and to help generate hypotheses to be tested in subsequent properly designed and implemented prospective RCTs. Extension studies also provide an appealing mechanism for generating data for validating surrogate outcomes capable of predicting long-term change in clinically relevant measures of disability.

However, by their very nature, extension studies may be underpowered statistically and may involve patients from different demographic or clinical groups, and in different proportions, from the original phase III RCTs. And yet, the tendency of the consumers—sponsors, clinicians, patients, and third party payers—is to view results from extension studies as being as powerful and meaningful as results from the original studies.

The proposed guidelines, developed as a result of recent experiences with extension studies that have followed phase III RCTs in multiple sclerosis (MS), are intended to promote standardized reporting of such studies. These guidelines may also be useful when reporting extension studies for other diseases and will help to ensure that issues that are relevant in reports of extension studies are adequately addressed. The authors believe that adherence to these standards will improve the design of such studies and the reader’s ability to interpret the results and validity of such reports.

*For the National Multiple Sclerosis Society Advisory Committee on Clinical Trials of New Agents in MS (Chair: F Lublin (Philadelphia, PA), M Clanet (Toulouse, France), D Cookfair (Buffalo, NY), G Ebers (London, Ontario), D Goodkin (San Francisco, CA), HP Hartung (Graz, Austria), R Lisak (Detroit, MI), WI McDonald (London), H McFarland (Bethesda, MD), J Noseworthy (Rochester, MN), H Panitch (Baltimore, MD), C Polman (Amsterdam), A Reder (Chicago, IL), P Rudge (London), W Sibley (Tucson, AZ), J Whitaker (Birmingham, AL), J Wolinsky (Houston, TX)
BACKGROUND

Based on the preplanned analyses of data from the phase III RCTs of interferon beta-1b, interferon beta-1a, and glatiramir acetate, MS is considered to be a treatable disease. Patients who were enrolled in these trials were randomly assigned to receive active therapy or placebo, resulting in treatment groups that were well matched for demographic and clinical variables. Enrollment in each of these 2–3-year studies was prolonged and staggered, thereby providing investigators with an opportunity to collect additional tolerability and efficacy data from patients who were willing to "extend" their participation in treatment or placebo arms of the studies after completing the original treatment protocols. Results from such extension studies have been reported formally but generally separately from and after the reports of the original RCT. The US Food and Drug Administration regulations currently allow a degree of advertising and promotion of results from such extension studies, even if product labeling does not include reference to such data.

Guidelines for reporting the results of RCTs have been published in the Consolidated Standards of Reporting Trials (CONSORT) statement. Although these guidelines are comprehensive and instructive, they do not adequately address issues that are relevant in reports of extension studies. These issues include the potential in such extension studies for:

• imbalance in relevant demographic and clinical variables between treatment groups at the beginning of an extension study resulting from informed censoring that occurred during the preceding phase III RCT;
• imbalance in relevant demographic and clinical variables between treatment groups at the beginning of an extension study that reflect a study subject’s choice not to participate in an extension study; and
• use and interpretation of exploratory subgroup analyses.

Since the validity and interpretation of findings reported from any clinical trial are dependent in part on how thoroughly and clearly the authors describe the study’s goal, design, subjects, methods, statistical methods, procedures, findings, and their analyses and interpretations, additional guidelines have been proposed to include the elements described below for reports of extension studies following phase III RCTs.

GUIDELINES FOR REPORTING RESULTS OF EXTENSION STUDIES

Title

The results of an extension study should be reported separately from its preceding RCT. The title or subtitle should identify the report as an extension study. The title should not contain a declarative sentence that is based on an exploratory subgroup analysis, whether favorable or unfavorable in comparison with the preplanned primary analyses of the preceding RCT.
Abstract

Unless otherwise specified by instructions for authors, an abstract with headings, structure, and content as specified by Haynes et al. is encouraged.[8] The content of the abstract should state any aspect of the objective, design, setting, patients, interventions, main outcome measures, main results, and conclusions that differs from the preceding phase III trial. There should be a summary of the extended results of preplanned primary and secondary outcome analyses adjusted for inequalities of demographic and clinical variables known to influence those outcomes. A key point is that equal emphasis must be given to positive and negative findings. Unless adequate justification is provided, exploratory subgroup analyses should not be reported in the abstract. Only conclusions directly supported by analyses of the preplanned primary and secondary outcomes should be stated. The clinical relevance of such analyses of extension data should be noted, as should any requirement for additional study before the information should be used in clinical settings.

Text

Introduction

The introduction should provide a summary of the preceding phase III RCT and its results, including primary and secondary outcomes. Hypotheses tested during the extension study should be stated.

Trial design and methods

A Design. The design of the phase III RCT should be recapitulated and any differences in design during the extension study should be noted.

B Setting. All study sites participating in the phase III RCT should be listed and any changes and reason for changes in the sites participating in the extension study should be noted.

C Patients. The inclusion and exclusion criteria for entry into the phase III RCT should be summarized and reasons for change in those criteria for patients entered in the extension study, if any, should be noted. The authors should indicate whether patients signed informed consent for the extension study and provide a comparison of patients who did and did not elect to participate after completing the phase III RCT.

D Interventions. The interventions administered during the phase III RCT should be reviewed and reasons for change in those interventions during the extension study should be noted.

E Outcome measures. Outcome measures for the extension study should be organized in the following order:

1 Outcome measures planned before initiating data collection during the phase III RCT and continued in the extension phase:

   a Primary endpoints.
   b Secondary endpoints.
c Exploratory endpoints.

2 Outcome measures added after initiating data collection but before analysis of the preplanned outcomes for the phase III RCT. The rationale for change in any outcome measure from those originally planned should be provided.

3 Exploratory outcome analyses performed after analysis of the preplanned outcomes. The rationale for each exploratory analysis should be provided.

F Statistical methods and data analysis. Statistical methods should be grouped under the same headings as those used for outcome measures. The principle of intention-to-treat should be applied to all analyses unless otherwise justified. Methods for selection of variables with a list of potential adjustment variables and their definitions should accompany the use of multivariate methods. Statistical adjustments for multiple comparisons should be explicitly stated. Procedures for monitoring and interim analyses should be described. The methods for comparing proportions of withdrawals from treatment arms and the methods to determine and adjust for imbalances of relevant demographic and clinical variables between treatment arms should be reported. The specific statistical methods for all analyses should be provided with references for non-standard methods.

**Results**

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS
An accounting of patients from onset of the phase III RCT to completion of the extension studies should be sufficiently detailed to enable the reader to determine the reason for any imbalance in relevant demographic and clinical variables between treatment groups at the beginning of and during the extension phase. Thus, relevant data by treatment group should be provided for patients who were randomized to treatment and who completed the phase III RCT and for those who were randomized and then lost to follow-up, for patients who completed the phase III RCT but refused to participate in the extension study, and for patients who initiated, were lost to follow-up, and completed the extension study. Any imbalance in those relevant variables across treatment groups should be noted with appropriate tests of statistical significance.

OUTCOME MEASURES
The results for all analyses of outcome data should be grouped under the headings noted above for groupings of outcome measures. Differences between the results of preplanned primary and secondary analyses, and the success of masking patients to treatment assignment during the phase III RCT and extension studies, should be noted.

ADVERSE EVENTS
A comparison of all clinically significant drug-related and non-drug-related adverse events during the phase III RCT and extension studies across treatment groups should be provided.

**Discussion**
The authors should recapitulate the main findings of the phase III RCT and discuss how the findings of the extension study differ from and extend earlier findings. The effect of differences in relevant demographic and clinical variables across treatment groups entering the phase III and extension studies and during the extension study on preplanned analyses should be discussed. The limitations of the extension study should be clarified and the rationale for all exploratory subgroup analyses and potential pitfalls of interpreting those analyses should be discussed. Unless adequately justified, a declaration of clinical efficacy should not be based on favorable results from exploratory subgroup analyses.

CONCLUSION

Extension studies are desirable when they provide a unique opportunity to collect long-term efficacy and tolerability data. These studies provide an appealing mechanism for generating data for validating surrogate outcomes capable of predicting long-term change in clinically relevant measures of impairment and disability. The proposed guidelines are intended to standardize the reports of data from extensions of phase III MS RCTs. However, these guidelines are applicable more broadly and will help to ensure that issues that are relevant in reports of extension studies are adequately addressed. Adherence to these standards will improve a reader’s ability to interpret the results and validity of scientific research.

REFERENCES


The failed clinical trial in multiple sclerosis
Lael A Stone, Richard A Rudick and Nancy D Richert

INTRODUCTION

Reading the clinical trial literature in multiple sclerosis (MS), one notices the paucity of published failed trials. Recently, several large MS clinical trials have produced negative or mixed results or have been terminated, owing to unacceptable toxicities. Detailed results from such studies should be published or made available through other means. Bias towards publication only of clinical trials with positive results presents a skewed view of MS therapeutics, and importantly may bury valuable lessons from failed trials. The purpose of this chapter is to discuss potential reasons for failed trials, to focus on one previously unpublished small negative trial of deoxyspergualin, and to emphasize the important lessons that can be learned from failed clinical trials and encourage their publication.

Since the publication of the previous edition of this book, leaders from academic medicine have noted that clinical investigators have a responsibility to ensure the integrity of clinical research reports. The International Committee of Medical Journal Editors (ICMJE) have revised their position on publication ethics. According to the revised requirements, prospective authors must sign a statement indicating that the author accepts full responsibility for the conduct of the trial, had access to all of the trial data, and had a major influence over publication decisions. These requirements imply an underlying concern about peer-reviewed publications of industry-sponsored clinical trials. The ICMJE guidelines remind academic physicians that their responsibility goes beyond simply checking the manuscript. The ICMJE guidelines also presumably apply to publication of negative or adverse results, as well as balanced presentation of positive results. Editors from all major neurology journals followed this publication with an endorsement of the ICMJE position, indicating their intention to enforce similar guidelines for neurology publications that report results of clinical research studies. According to the neurology journal editors, ‘Academic freedom includes the right of authors to have access to all of the data obtained in their study, to review it, to obtain statistical analyses independently, and to publish their data based on their own decisions and not those of the financial sponsor’.

Some in the clinical trials field have raised concerns that unpublished failed trials are forever invisible. To address this problem, there have been efforts to provide prospective registration of each clinical trial and to assign a unique number at each trial’s inception. It is hoped that complete clinical trial registries may be available to assist investigators and other interested parties who wish to access results from failed trials. The International
Standard Randomized Controlled Trial Number (ISRCTN) is a new system set up to assign a unique identification of randomized controlled trials worldwide. The ISRCTN would facilitate identification of trials and would track publications and reports resulting from each trial. Trials registered through the ISRCTN will be included in a metaregister of controlled trials (http://www.controlled-trials.com/, web site accessed March 2002). The metaregister is currently supported by a variety of organizations internationally. It is a searchable international database of ongoing randomized controlled clinical trials in all areas of health care.

It is hoped that more stringent standards for clinical investigators and increasingly complete prospective registration of clinical trials will minimize the tendency to publish only positive results. However, problems remain. There is a tendency to reject negative studies during peer review, even when the results are important and the data instructive, and investigators commonly lose interest in negative results. Journal editors, reviewers, and authors are urged to consider publications of studies containing negative results. The emphasis of these reports can be directed toward study design, disease behavior, or mechanistic studies included within the trial.

**WHAT ARE FAILED CLINICAL TRIALS?**

Negative clinical trials (failed clinical trials) can be defined in various ways (Table 17.1), with lessons to be learned from each. A ‘true negative’ clinical trial is defined as a trial that is adequately powered to demonstrate efficacy, is fully enrolled, utilizes sensitive and appropriate outcome measures, reaches completion, but finds no statistically significant difference between treatment and comparative groups. In a true negative trial, results are consistent across outcome measures. An example in this category is the intravenous immunoglobulin trial, which was a well-run and well-executed trial, utilizing sensitive and quantitative measures of motor strength; it showed no difference in motor power between treated and untreated groups. Theoretically, these data could result from a type II error.

**Table 17.1 Categories of ‘failed’ trials**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>True negative results</td>
<td>NIH-supported trial of intravenous immunoglobulin for fixed motor deficit[^3]</td>
</tr>
<tr>
<td>Mixed results</td>
<td></td>
</tr>
<tr>
<td>• Outcome measures with different results</td>
<td>Cladribine studies[^19]</td>
</tr>
<tr>
<td></td>
<td>IMPACT trial of interferon beta-1a for secondary progressive MS</td>
</tr>
<tr>
<td>• Subgroup analysis shows efficacy</td>
<td>SPECTRIMS trial of interferon beta-1a for MS[^20]</td>
</tr>
<tr>
<td>False-positive results</td>
<td>Oral myelin trial[^4]</td>
</tr>
<tr>
<td>Trial terminated early</td>
<td>Linomide trial, transforming growth factor-β trial (unpublished)</td>
</tr>
</tbody>
</table>

NIH, National Institutes of Health.
(a false-negative result), or they could be due to a true negative result (no difference between the treatments). To the extent a trial is well-planned, well-executed, and large enough, the latter is the more likely.

A ‘mixed-result’ clinical trial results in both negative and positive results. Mixed results may indicate an effect of the therapy on one of the outcome measures but not on another or on one subgroup of patients but not another. In several trials of cladribine, magnetic resonance imaging (MRI) data indicated a strong beneficial effect, but there were few significant benefits on clinical measures. These results raised important questions about the relationship between MRI parameters and clinical outcomes. Specifically, the cladribine trials suggested the possibility that beneficial effects on MRI parameters may translate into clinical benefits at a future point in time. An alternative explanation is that the MRI parameters that responded to treatment have no clinical relevance. Distinguishing between these two very different possibilities remains central to the use of MRI in MS trials, and to concepts of MS pathogenesis generally. Recently completed clinical trials of interferon beta in secondary progressive MS may be considered mixed-results studies, both from the standpoint of variability in results depending on outcome measures and from the standpoint of subgroup analyses (see chapter 21).

Another category of failed trials is the false-positive study, commonly referred to as a type I error. This can result from technical problems such as unblinding of subjects or examiners or inappropriate control groups. In some trials, explanations for a false-positive result are not evident, and a trial in this category may only be classified after a more definitive trial shows negative results. An example in this category is the initial oral myelin trial that showed improvement in a small subset of patients. A subsequent multicenter trial showed no difference between treatment and control groups.

Smaller trials (e.g. with fewer than 250 patients), which abound in the MS literature, are particularly prone to false-negative and false-positive results. The difficulty is to know, at trial completion, whether the trial outcome is a false-positive or a false-negative result. Failure to replicate a finding is a painful but informative method of establishing prior small trials as false-positive or false-negative. There are no perfect examples of this type of trial in MS. An example might be the initial trial of glatiramer acetate in progressive MS patients, where the drug was beneficial in one center and not in the other, although this is more clearly a mixed-result trial, whereas the larger multicenter trial led to approval of the compound in the US by the Food and Drug Administration (FDA).

Another type of failed clinical trial is one that is terminated before its anticipated end. Trials are most commonly terminated after an interim analysis by a data monitoring and safety board. A failed trial of this type could be stopped early owing to unanticipated and unacceptable toxicity unrelated to MS (e.g. termination of the linomide trial because of cardiac toxicity, termination of the transforming growth factor-beta trial because of nephrotoxicity, termination of one of the altered peptide ligand trials because of hypersensitivity reactions). Although toxicity data may be available in animals or other patient groups it is not always known whether the same type of problem will occur with human use or in MS patients. For example, azathioprine causes a much higher rate of adverse effects, including cancer, when it is used in transplant patients who are on many other potentially toxic agents than when it is used in rheumatological patients who are on many fewer concomitant medications. Trials can also be terminated early owing to...
interim analyses that reveal no potential for reaching a statistically significant difference between the groups by continuing the trial to its intended endpoint, such as the National Institutes of Health (NIH) deoxyspergualin trial, or the University of California at Los Angeles thalidomide trial.

It is not possible to estimate accurately the number of failed clinical trials, since many of these trials are never reported. Table 17.2 provides a list of selected failed trials. Dissemination of information is slower and less complete for these trials. Hohlfeld and Wiendl published an editorial listing a few of the published negative trials in MS grouped by mechanism of action, which is most helpful. However, failed clinical trials are often not published at all, and the only way we learn about the results is through the professional grapevine at meetings and by other informal modes of communication. Therefore, those who are most heavily involved in MS research are most informed on negative trials, while professionals outside the inner circle rely exclusively on the results of published trials, putting them at a disadvantage in designing their own trials or in generating hypotheses regarding disease pathophysiology.

Some medical specialties may be more or less inclined to publish failed trials. A study of publication practices in the AIDS field revealed that positive results were published an average of 4.7 years after enrollment began, while failed trials required 6.5 years. Trials that are not published or have substantially delayed publication cannot be included in meta-analyses, affect clinical practice, or contribute widely to our understanding of the disease process, and cannot contribute to the design of future clinical trials.

Table 17.2 Contemporary clinical trials in MS with negative or mixed results

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Linomide[^9]</td>
<td>4-Aminopyridine</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Initial glatiramer acetate[^5]</td>
<td>Ibuprofen</td>
<td>Azathiaprine</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>Cyclosporine</td>
<td>Interleukin-10</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>Transforming growth factor-β</td>
<td>Interferon-α</td>
</tr>
<tr>
<td>Anti-CD4</td>
<td>Acyclovir</td>
<td>Oral copaxone</td>
</tr>
<tr>
<td>Altered peptide ligand (CBP77116)[^13–14]</td>
<td></td>
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</tr>
</tbody>
</table>

[^4]: Reference for Oral myelin
[^19]: Reference for Cladribine
[^9]: Reference for Linomide
[^14]: Reference for Deoxyspergualin
[^11]: Reference for Anti-tumor necrosis factor-α
[^5]: Reference for Initial glatiramer acetate
[^13]: Reference for Altered peptide ligand (CBP77116)
Trials may fail for many reasons (Table 17.3). Many of these reasons have to do with the therapeutic agent being tested. The pharmacokinetics of the agent may not have been fully appreciated before the trial was started such that too high or too low a dose may be selected (e.g. the deoxyspergualin and oral myelin trials). The oral myelin trial may have been negative because of the use of the wrong dose or the use of myelin from a non-human source or because of the use of whole myelin versus the most pertinent peptides. In addition, the route or frequency of administration may turn out to be wrong for the disease to be studied, or remain controversial even after FDA approval of the medications (e.g. the beta interferons). The agent may turn out to have unanticipated toxicities, such as cladribine, which causes long-term bone marrow suppression in some patients. The duration of treatment or length of follow-up may have been too short. We still do not know the optimum length for follow-up of a trial. Clinicians, patients, and pharmaceutical companies would like to utilize trial designs that are as short as possible. However, many of these designs utilize measures, such as relapse rate or gadolinium-enhancing lesions on MRI, that may or may not predict disability progression.

There may be unanticipated design problems, or problems with patient selection, particularly in

Table 17.3 Reasons for failed clinical trials

<table>
<thead>
<tr>
<th>Reason for Failure</th>
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<tbody>
<tr>
<td>Therapeutic agent not effective in MS or in the type of MS tested</td>
</tr>
<tr>
<td>Therapeutic agent not administered in correct dose, frequency or route to affect disease process</td>
</tr>
<tr>
<td>Unanticipated toxicities of agent</td>
</tr>
<tr>
<td>Too short a time period to detect efficacy of therapeutic agent</td>
</tr>
<tr>
<td>Inappropriate outcome measure to detect effect</td>
</tr>
<tr>
<td>Technical problems, including unblinding of examiners or patients</td>
</tr>
<tr>
<td>Type 1 error</td>
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<tr>
<td>Type 2 error</td>
</tr>
</tbody>
</table>

a disease as heterogeneous as MS. Although the linomide trial was terminated early because of unanticipated toxicity of the agent, it appears that MRI characteristics for the patients differed by center. Enrollments may also be slowed, skewed or influenced by release of FDA-approved agents during the course of the trial, such as occurred with the release of interferon beta-1b during the enrollment phase of the NIH deoxyspergualin trial.
Unanticipated results or problems may arise with outcome measures. For example, MRI methodology is changing so rapidly that MRI parameters may be significantly different during the course of a clinical trial. Scanners change, techniques change, and postprocessing image analysis methods may change. The phase III study of interferon beta-1a for relapsing-remitting MS included a preplanned analysis of brain atrophy using ventricular diameter as an indirect measure of brain tissue loss. Following the study, a fully automated technique for normalized whole brain atrophy was developed and applied in a blinded fashion to the image sets from the original phase III study (see chapter 9). The multicenter 4-aminopyridine trial showed no significant change in the primary outcome measure, the expanded disability status score (EDSS). However, a significant therapeutic effect could be shown with another outcome measure, timed ambulation. Our expertise grows in the choice of the most clinically relevant outcome measure and in the use of composite measures such as the Multiple Sclerosis Functional Composite (MSFC). The correlation between MRI and clinical outcome measures is also under continual re-evaluation, particularly in light of the delayed effect that some agents may have on MRI parameters such as brain atrophy.

LESSONS TO BE LEARNED FROM NEGATIVE TRIALS

Table 17.4 lists lessons to be learned from clinical trials, with examples of each type. Performing a clinical trial may change our assumptions about the compound to be tested or our hypotheses about the disease process. The example of interferon gamma was already cited, but another example is tumor necrosis factor (TNF)-α. Two patients with rapidly progressive MS were treated with intravenous infusion of a humanized mouse monoclonal anti-TNF-α antibody. No clinically significant neurologic changes were noted in the patients, but the number of gadolinium-enhancing lesions and the cells and immunoglobulin in the cerebrospinal fluid of both patients increased. The researchers suggested that this treatment caused immune activation and increased disease activity. Over the past several years, release and use of etanercept has supported this hypothesis. Etanercept is a fusion protein consisting of the extracellular portion of the human TNF receptor linked to the Fc portion of the human immunoglobulin G. This drug is very effective in the treatment of refractory juvenile arthritis. While there is only one case report of a patient who developed MS after treatment with this compound in the neurology literature, a warning was issued in October 2000 about the increased incidence of central nervous system demyelinating events with this agent. This case report quotes a company source as stating that close to 25 cases had been reported to the company by November 2001.

Another interesting example in this category is the altered peptide ligand, CGP77116, which was designed as specific immunotherapy for MS based on the myelin basic protein peptide (amino acid 83–99). A small MRI-based clinical trial of
Table 17.4 Lessons to be learned from clinical trials

<table>
<thead>
<tr>
<th>Lesson</th>
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<tbody>
<tr>
<td>Changes in our assumptions about the mechanism of action of the</td>
</tr>
<tr>
<td>proposed agent (e.g. oral myelin)</td>
</tr>
<tr>
<td>Changes in our assumptions about the mechanism of pathophysiology of</td>
</tr>
<tr>
<td>MS (e.g. interferon gamma)</td>
</tr>
<tr>
<td>Demonstrates heterogeneity of the disease MS (e.g. oral methotrexate,</td>
</tr>
<tr>
<td>interferon beta)</td>
</tr>
<tr>
<td>Work through logistical problems (e.g. linomide MRI)</td>
</tr>
<tr>
<td>Test new outcome measures (e.g. IMPACT—interferon beta-1a a in</td>
</tr>
<tr>
<td>chronic progressive MS)</td>
</tr>
<tr>
<td>Test new trial designs (e.g. NIH deoxyspergualin trial)</td>
</tr>
<tr>
<td>Examine placebo effects (e.g. NIH deoxyspergualin trial)</td>
</tr>
</tbody>
</table>

NIH, National Institutes of Health.

CGP77116 demonstrated that it was poorly tolerated at the dose tested, and the trial was stopped. Three patients developed relapses, and in two they were linked to CGP77116 treatment by immunological studies that demonstrated the markedly increased T-cell responses to the encephalitogenic myelin basic protein peptide (amino acid 83–89) with treatment.[13] This small trial is another interesting example of subgroup analysis, on the molecular level, and may shed very interesting light on the heterogeneity of MS, as discussed in an editorial accompanying the paper. Another larger multicenter trial with the same altered peptide ligand was terminated early because of hypersensitivity reactions, but it produced mixed results—improvement on MRI but no measurable effect clinically.[14]

Compounds may have unanticipated toxicities that are not related to the disease process, such as occurred with the cardiac toxicity seen with linomide. The linomide experience underscored the need for large phase III trials for safety, but also the difficulty of predicting toxicity from preclinical data. While beagle dogs exhibited vasculitic changes, and cancer patients had pericarditis, these complications were not anticipated in the MS population. However, when larger numbers of patients were treated, the trial was terminated early because of unanticipated cardiac events.

Several trials have illustrated the heterogeneity and the unpredictability of the disease process in MS. For example, the low-dose oral methotrexate trial showed beneficial effect of the agent in patients with secondary progressive MS but not in patients with primary progressive MS.[15] Several studies have illustrated the placebo effect in MS patients, which makes it difficult to demonstrate a significant beneficial effect of the agent to be tested. This happened with the large-scale oral myelin study. Both the treatment group and the control group did well in this unpublished negative trial.

Logistical problems can also be worked through in a trial that produces negative results, and the lessons learned from setting up the trial can be applied to other similarly designed trials. For example, the linomide trial involved frequent MRI scanning with a proprietary MRI sequence that was sent out and run on many scanners throughout the USA. Technical improvements, such as training examining physicians and technicians, and the use of new outcome measures can also add value to a clinical trial regardless of the efficacy of the therapeutic agent to be tested (e.g. the IMPACT trial) (see chapter 21).
THE NIH DEOXYSPERGUALIN TRIAL

The NIH deoxyspergualin trial is presented here as a way of illustrating many of the points made in this chapter. The rationale for the deoxyspergualin trial grew out of the author’s work at the NIH in the early 1990s on the natural history of contrast-enhancing lesions on MRI in early relapsing-remitting MS patients.[16,17] While we do not fully understand the significance of contrast-enhancing lesions, they were, and remain, the only generally available non-invasive method to look at breakdown of the blood-brain barrier caused by inflammation. The inflammatory component of the disease process is felt to be particularly important in early relapsing-remitting MS. In the NIH natural history study, the authors performed MRI scans on a group of relapsing-remitting patients on a monthly basis for 4 years. The statistician, Paul Albert, performed repeated sampling (‘bootstrap analysis’) of these monthly data in order to design trials using MRI contrast-enhancing lesions as a primary outcome measure.

The major advantage of using MRI contrast-enhancing lesions as a surrogate marker for disease activity and thus for trial design was that very small numbers of patients were required to do phase II trials to screen compounds for efficacy in MS. For a baseline versus treatment trial design, as few as 12 patients could be enrolled if the baseline was 6 months before a 6-month treatment period. The trial design is shown in Figure 17.1. In order to use contrast-enhancing lesions as the outcome measure, the patients had to have a certain number of contrast-enhancing lesions on MRIs during the baseline period. For this trial, the entry criterion was set at 0.5 lesions per month over a 3-month enrollment period. Patients were thus followed on a monthly basis with contrast-enhanced MRI scans and clinical examinations to determine EDSS scores. During the treatment phase, patients were to receive 4 mg/kg of deoxyspergualin by infusion on a monthly basis for 6 months. The primary outcome measure was comparison of the frequency of monthly contrast-enhancing lesions between the baseline and treatment periods.

![Fig. 17.1 Trial design of NIH deoxyspergualin trial.](image)

Ten patients with relapsing progressive MS were enrolled in the trial, with an enrollment goal of 14 patients. There was an unanticipated enrollment difficulty because of the FDA approval and commercial release of interferon beta-1b immediately before the enrollment period, although interferon beta-1b was not widely available initially and was at that time used with very narrow clinical indications. In this type of trial design, each patient effectively serves as his or her own control, and thus all personnel are unblinded to the treatment phase. An interim analysis was performed after 10 patients were enrolled, eight of whom completed treatment. Results are shown in Table 17.5. There were no
differences between the baseline and treatment phases in any of the patients. Unlike many trials in MS, no placebo effect was seen in clinical or MRI parameters. The trial was thus terminated before full enrollment, as it was determined that even if the remaining two patients were enrolled and turned out to show significant positive effects, the trial overall would still have a negative result. There were no toxicities or adverse effects of the treatment noted.

LESSONS FROM THE NIH DEOXYSPERGUALIN TRIAL

Although this small NIH deoxyspergualin trial showed no clinical or MRI effect, as was confirmed by the larger trial on deoxyspergualin carried out by Kappos et al.,[18] several lessons can be taken away from the trial. The first is one of trial design. When this trial was performed, few if any trials had been undertaken with MRI parameters as the primary outcome measures. Owing to the minimum level of contrast-enhancing lesions required for entry, a significant amount of time and energy was needed to screen enough patients to meet the MRI criteria. Second, the authors did not think that MRI parameters would show a placebo effect without clinical improvement, and indeed, there was no improvement in either clinical or MRI measures with the agent administered at this dose in this way. It is not known whether patients in control or placebo groups who show improvement clinically would have improved MRI parameters as well. A third lesson was the unanticipated, unprecedented release of an FDA-approved com-

Table 17.5 Results from NIH deoxyspergualin trial

<table>
<thead>
<tr>
<th>EDSS Ambulation index</th>
<th>Count of gadolinium-enhancing lesions</th>
<th>Area of gadolinium enhancement (in pixels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 4.2</td>
<td>2.9 (2.2–3.7)</td>
<td>7.9 (1.8–13.9)</td>
</tr>
<tr>
<td>(3.3–5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment 4.2</td>
<td>2.7 (1.6–3.9)</td>
<td>8.0 (0.9–15.1)</td>
</tr>
<tr>
<td>(3.0–5.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NIH, National Institutes of Health; EDSS, expanded disability status score.

pound for the treatment of MS. The approval of interferon beta-1b meant that the entry criteria needed to be rewritten to exclude patients who were eligible for what was suddenly standard therapy in MS, even though they might have been the best candidates for deoxyspergualin. The fourth and fifth lessons are frequent in MS: results from animal studies in animal models may not correlate with future success in MS patients, and positive results from a few MS patients may not translate into positive results in an actual trial setting.

The NIH group and others have gone on to use the same treatment design in several other trials, including the safety and efficacy of recombinant insulin-like growth factor-1
with a 24-week treatment baseline and 24-week treatment period. No significant
difference between the baseline and treatment periods for any MRI or clinical measure of
disease activity was found, but the trial did demonstrate the continued usefulness of this
trial design for screening compounds in MS.

CONCLUSIONS AND RECOMMENDATIONS

A few of the most important conclusions from this discussion are:

1. There is a bias to publishing positive over failed trials, since many of the trials
discussed here have not been, and will probably never be, published.
2. We must consciously design trials in such a way that we add to our knowledge base, regardless of the outcome of the trial.
3. Trial results should be published, whether positive, negative, or mixed.
4. Leaders of academic medicine and journal editors should insist on full, objective reporting of clinical trials, whether negative, positive, or mixed.
5. Efforts by international organizations, such as the Cochrane Collaboration, to spearhead objective evaluations and comprehensive reporting of clinical trials should be supported.

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The challenge of long-term studies in multiple sclerosis: use of pooled data, historical controls, and observational studies to determine efficacy

John H Noseworthy

RANDOMIZED TRIALS: SHORT-AND MEDIUM-TERM EFFICACY

There have been considerable advances in our understanding of the impact of a number of new approaches to the treatment of multiple sclerosis (MS) in the past decade. We owe much of this progress to the use of modern clinical trial methodology, especially the classic randomized controlled clinical trial design. The final quarter of the last century witnessed the transition to this more rigorous approach from what had been applied earlier, including personal observations, small case-controlled studies and retrospective series, and studies using historical controls. With the ascendancy of randomized trials we have seen increasingly careful scrutiny of the details of trial design and conduct. This has been critical to the efforts to identify promising trends and ultimately progress to better therapies for MS patients.

At the time of writing, there is evidence from several randomized trials that it is possible to alter the short-term course of relapsing-remitting MS favorably with the beta-interferons (interferon beta-1a and interferon beta-1b) and glatiramer acetate. There are also data to support the hypothesis that interferon beta-1a, administered early in the course of what is likely to ultimately develop into MS (clinically isolated syndromes with positive magnetic resonance imaging (MRI)), may prolong the time until there is clinical evidence of recurrent disease activity. Although a number of studies have now shown that interferon therapy continues to reduce relapse rates, new MRI lesion formation, and increases in T2 lesion load during the secondary progressive phase of the disease, there has been only a partial and inconsistent benefit shown on measures of disability progression and brain atrophy. The short duration of follow-up in relapsing-remitting MS trials together with the observation that clinical measures of disability generally worsen during treatment despite continued evidence of anti-inflammatory activity in secondary progressive MS, raises questions about the certainty that these drugs should be used indefinitely.

For each of these important short- and medium-term observations, randomized trial methodology has been used to good advantage. As is discussed extensively in this chapter, there is little resistance to the notion that randomized trials are the preferred method for demonstrating efficacy in trials of short and medium duration (less than 3...
years). What is less certain is how best to demonstrate benefit from treatment over periods of extended use. This is an area of great interest and importance. To date, little has been written on the preferred approach to this next step in MS therapeutics, although one excellent recent review addresses the use of databases in MS research.[25]

**CHALLENGES IN ADDRESSING LONG-TERM BENEFITS IN MS**

What is the most reliable method to determine whether we have influenced the long-term course of the disease? On the one hand, it is possible that treatment approaches that are ineffective in the short term may have late benefit. Examples might include treatment strategies that are ‘neuroprotective’ (e.g. treatments that prolong axonal survival or promote axonal regeneration and remyelination).[26,27] Current research strategies may fail to detect this benefit (a type 2 error). Perhaps of equal importance, however, is recognition that there are currently no mechanisms in place to identify the magnitude and duration of any extended benefit from the use of the currently identified, partially effective agents. This is a problem of enormous economic proportions related to costs of the treatments and the financial consequences of chronic illness.

There are significant difficulties in addressing this issue. MS is a serious, chronic disease. Most patients ultimately develop significant and progressive disability, although a minority of patients do well for decades and some escape long-term disability.[28–30] Disability can begin early in the disease course or, more typically, may be delayed for a decade or more. To date there is no treatment that will reverse established neurological impairment.[31,32] As such, there is consensus that a concerted effort must be directed to preventing disability. There is hope that early treatment may alter the long-term course of MS, yet there is little evidence that currently available therapies, even if applied early, will do this. This hope, coupled with the knowledge that disability from MS is serious and largely irreversible, encourages early and now widespread use of the expensive, partially effective, injectable therapies as soon as it appears that patients have active relapsing MS. To date (now 7 years after the first drug—interferon beta-1b—was approved for use in relapsing-remitting MS), we are no closer to knowing whether early or prolonged administration has merit.

How to proceed? There are a number of options, none of them perfect. These options include long-term randomized trials, extension trials, phase IV studies, and non-randomized, observational studies.

**LONG-TERM RANDOMIZED TRIALS**

Randomized trials bring many important methodological advantages. The process of randomization ensures, or at least enhances, the likelihood that important but as-yet unidentified demographic variables that influence the course of the disease and the response to treatment will be balanced between treatment groups. With this step, allocation bias is reduced. This key principle is revisited in the discussion of extension
trials, below. Randomization permits tests of statistical significance to be used to analyse the findings of such studies.

The disease course in MS is extremely variable in the short term; the illness becomes more predictable with longer periods of observation. There is consensus that historical controls introduce an unacceptable risk of a type 1 error (false-positive result) for clinical trials of limited duration. As such, it is hazardous to assume that any apparent stabilization or improvement demonstrated over a period of a few weeks or months compared with the predicted natural history of the disease can be attributed to the treatment given. The use of an appropriate, concurrent control group is necessary to demonstrate superiority with the putative treatment approach. The choice of the most appropriate control group is of paramount importance. Until recently, there was consensus that suitably designed placebos (e.g. placebos that are indistinguishable from the active agent) should be used in all randomized trials, since there was no effective treatment for MS. Placebo-controlled pivotal trials helped to show, and with repeat observations, often confirmed, that several agents favorably influence disease course for at least a limited period of time (up to 3 years). This methodology has also helped to identify treatment programs that were unlikely to be beneficial.

The future of placebos as acceptable or required control therapies is receiving considerable attention now that partially effective therapies exist for MS. Recent revisions have been made to the Helsinki Accord in order to protect experimental subjects from being denied potentially effective control therapies. These changes jeopardize the use of placebos in future trials. Conversely, the Food and Drug Administration (FDA) in the USA does not accept ‘equivalency trials’ as sufficient evidence of benefit to lead to approval for licensing purposes. This stance discourages the use of active agents as controls in that the sample size needed to demonstrate superiority to a partially-effective therapy becomes prohibitively large, especially for uncommon diseases.

Blinding of treatment assignment enhances the utility of the control group. In our ‘modern’ era of MS trials, we need to recognize that few recent trials have been adequately blinded, however. The majority of treatments tested (the beta-interferons, glatiramer acetate, mitoxantrone, and others) have common and easily identifiable adverse effects that limit patient blinding. We know that ‘evaluator blinding’ is key to the integrity of a trial. We can assume that patient blinding may be equally important, especially when subjective variables are used as the primary outcome measure (e.g. relapse variables such as relapse rate, time to first relapse, and proportion of patients who are relapse-free). There is no published research on the consequences of incomplete patient blinding in MS, regretfully. From what has been learned of the bias introduced by evaluator unblinding, however, one may assume a similar threat to the integrity of the findings if patients’ subjective responses are used in the primary analysis. It is important to note that the theoretical superiority of randomized trials over observational studies lessens considerably when randomized trials are not blinded.

Currently we have only a limited understanding of pathogenesis and disease course. Although recent efforts have clarified our application of descriptive terminology (relapsing-remitting, secondary progressive, primary progressive and progressive relapsing MS), these descriptors do not define groups of patients according to pathogenesis. We are admittedly naïve as to how best to select patients for specific
experimental treatment protocols. As such, we look for ‘responders’ from large groups of patients who presumably have considerable pathogenic heterogeneity; this dilutes trial outcomes and may lead to type 2 errors. One might anticipate that it should be possible to increase the chance that a putative therapy would benefit a group of patients if selection criteria could be developed to identify the subgroup of patients most likely to respond to the treatment being studied.

Along this theme, preliminary work suggests that there may be a limited number of patterns of tissue injury in MS. It appears that MS patients may follow one of perhaps four disease patterns throughout the course of their illness. Based on their considerable preliminary pathological data, Lucchinetti and colleagues\cite{40,41} have hypothesized that there may be a limited degree of pathological heterogeneity in the MS lesion. They postulate that there may be essentially four different patterns of tissue injury in MS. Patterns I and II involve T-cell and macrophage inflammation without (pattern I) or with (pattern II) immunoglobulin and complement C9neo deposition. Pattern III involves subacute oligodendrocyte dystrophy, which is possibly virally induced. Pattern IV involves extensive loss of oligodendrocytes (nuclear fragmentation) without remyelination. Lucchinetti’s studies suggest that patients could be classified accordingly, with one pathological pattern predominating throughout the patient’s lifetime of MS. This finding, if confirmed, is of enormous potential interest and may have important implications for the treatment of the disease. Essentially, if one could correctly anticipate the pattern of tissue injury, treatments could be tailored appropriately, presumably with improved outcomes and smaller trial sample sizes than are currently needed with the large ‘mixed’ groups of study patients. If this work is confirmed, it may ultimately be possible to identify, early in a patient’s illness, the presumed primary underlying mechanism of injury and then select groups of patients with like patterns for study with experimental protocols designed for their type of disease course.

Randomized trials are not without limitations, however. These shortcomings apply to the MS story, as well.\cite{42} The primary goal of those designing and conducting treatment studies is to identify treatment approaches that provide meaningful benefits to patients. Type 1 (false-positive) errors and type 2 (false-negative) errors plague trial research and merit close scrutiny. Type 1 errors may be identified by failure to confirm preliminary positive results with repeated studies. Type 1 errors may be suspected when clinical experience in the post-trial era suggests that meaningful benefits are not commonly realized in patients sharing the clinical characteristics of those studied in published trials. Not uncommonly, when promising treatment strategies are applied more generally to patients ineligible for the pivotal trials, there is less apparent benefit (generalizability). Type 2 errors may escape recognition unless enthusiasts repeat or extend studies of the putative treatment approach after publication of a negative trial. Statistical significance may not indicate clinical significance. We may be left to ponder the clinical relevance of an apparently minor change in an unvalidated but apparently sensitive clinical or laboratory-based surrogate endpoint measure.

Most would agree that long-term randomized trials would be the ideal methodology for studying extended benefits from experimental therapies. Parenthetically, MS trials are considered ‘long-term’ by FDA standards in that trials of antidepressants and analgesics are conducted over a period of not more than a few months. As discussed earlier, the randomized design enhances the ability to determine that there is a consistent therapeutic
benefit that is distinguishable from the ‘noise’ introduced by the variability of the disease course.

It is probably unrealistic to expect that randomized trials can be continued for much longer than 3 years in MS, however. There are several reasons for this. There is no consensus about what would be the ideal comparison trial for a study spanning the better part of a decade. Each of the partially effective agents have their proponents, yet few investigators believe that patients could be restricted to receive only one form of therapy for such a long trial. A subgroup of patients may be excluded from enrollment into such prolonged trials (‘consent bias’) and this limits the generalizability of the results. It is recognized from experience in the clinical setting that many patients eventually ‘fail’ treatment with the currently approved drugs. At that point many wish to try something else. Patients tire of the rigors of controlled trials unless they are clearly benefiting from treatment. Although it is possible to encourage many loyal patients to continue for many months even in the face of apparent disease progression if there are no obvious options (e.g. in the case of primary progressive MS presently), when treatment options exist, many will drop out, eroding statistical power. The costs of prolonged trials involving experimental therapies are enormous. As mentioned, patient blinding may be impossible. Randomized trials by definition permit only a limited number of hypotheses to be tested. Indeed, it has been said by proponents of the randomized trial design that when randomized studies are not feasible, other options should be explored.\[43\]

**EXTENSION TRIALS**

Extension trials are theoretically simple. Patients consent to continue to participate in the research setting following completion of a randomized trial. The specifics of such studies vary depending on the question being asked. Typically, extension studies are initiated when there is reason to believe that the putative treatment strategy is showing promise (interim analysis) or has demonstrated partial benefit (final analysis). In an effort to define the magnitude of benefit or to determine the duration of change in the natural history, a decision is reached to extend the period of study. Most commonly, patients initially randomized to the control group are switched to active drug,\[44\] or are randomized to one of multiple doses of the active drug under investigation.\[45\] The patients who were originally randomized to receive the active drug are continued on their original treatment. To reduce costs, the frequency of follow-up visits may be reduced and expensive surrogate studies, such as MRI, may be done less often. Extension studies are feasible, reasonably cost-efficient, and provide some evidence of continued benefit during the protracted period of follow-up.

One concern with extension trials is the fact that the study population that participates in the extension phase usually differs significantly from the original cohort. Many patients elect not to continue. Commonly, patients doing poorly have either already been censored as ‘failures’ or drop out to seek other treatments. As a result, there may be an important selection bias favoring ‘responders’ in the active treatment limb. The extension cohort is no longer protected from bias by the original randomization step. Changes from the original study design may reduce the sensitivity of recognizing late treatment failures (e.g. fewer clinical visits or MRI studies may obscure recognition of clinical relapses or...
imaging evidence of subclinical disease activity). In one recently published example, the investigators inappropriately compared the findings of their extension study of patients with relapsing-remitting MS to a historical control group that included both relapsing and progressive patients.\textsuperscript{[44]}

PHASE IV STUDIES

Postapproval phase IV studies are currently used to monitor for unanticipated safety concerns. Generally these studies are not conducted with sufficient rigor to measure prolonged benefit. Phase IV studies could be designed prospectively with great care, with the primary objective of demonstrating continued long-term efficacy. Continued approval of drugs that are intended for use in chronic diseases and that were initially licensed on the basis of data from studies of limited duration could theoretically be tied to the demonstration of convincing long-term efficacy using this design. This approach would require sponsors to form partnerships with clinical investigators for periods of 5–10 years. This approach would probably be more acceptable to investigators than to sponsors.

One potential compromise that may be acceptable to all parties, including patients, would be to provide preliminary and rapid drug approval if a single phase III study demonstrated convincing evidence of efficacy, provided that the benefit was continued during the postmarketing period. This approach has considerable hazards, however, including both the possibility of introducing type 1 errors and the difficulties inherent in the conduct and analysis of long-term trials. The approach of using phase IV trials to maintain drug licensure has not been embraced by licensing authorities.

NON-RANDOMIZED (OBSERVATIONAL) STUDIES

As mentioned above, most experts feel that, when feasible, randomized methods are the preferred approach to address questions of short- and medium-duration efficacy. When a randomized trial is deemed not feasible or unethical (e.g. very large and prolonged trials may be needed to measure small treatment effects,\textsuperscript{[46]} and this may raise concerns about costs, ethics, or other problems), properly designed observational studies may be a suitable alternative.

There is currently considerable interest in defining the merits of observational studies. A review of the literature demonstrates a division of opinion on the sensitivity and reliability of observational studies.\textsuperscript{[47]} Carefully designed and monitored observational studies that address a specific hypothesis clearly have more merit than non-systematic retrospective analyses of existing databases. Problems arise when non-randomized studies are performed on existing datasets created for other purposes (e.g. hospital discharge abstracts).\textsuperscript{[48]} For the purposes of this discussion, particularly in view of the many complexities of evaluating outcomes in MS, only the most carefully designed, prospective observational studies would be likely to provide a valid result. Proponents argue that prospective observational studies may be the preferred method of determining
the true effect in practice (effectiveness). The Cochrane Collaboration regularly considers the merits of including non-randomized studies in their systematic reviews.

Historical controls fell into disfavor in the 1980s when it became clear that their use increased the likelihood of false-positive outcomes in treatment trials. There is now renewed interest in exploiting the very extensive datasets developed prospectively from large MS clinical centers. Arguably there is more natural history data available for MS than for any other chronic disease. The population-based London, Ontario MS Clinic database has been used to create models of disease progression. This resource now has more than 25 years of prospectively collected outcomes on an essentially treatment-naïve population. In addition, through the recent efforts of the Sylvia Lawry Center for MS Research in Munich, models are being developed to define expected short- and medium-term outcomes using the growing number of control group datasets donated for this purpose from completed phase II and III trials.

There are a number of obvious strengths in the use of a non-randomized observational design. These studies are feasible in that treating physicians are free to use whatever treatment approach is currently in favor (‘equipoise’). Observational studies more closely reflect what is done in practice (‘effectiveness’) and are therefore largely sustainable over prolonged periods of observation provided that there is funding for the necessary infrastructure to continue this effort. With proper planning at the start of such a study, investigators have the opportunity to establish high-quality clinical databases (HQDBs). HQDBs eliminate many of the problems inherent in using existing databases such as clinical registries and institutional databases that were created for other purposes.

Non-randomized studies in MS could be constructed to compare outcomes prospectively against ‘expected’ behavior modeled from robust natural history datasets. In MS, several such databases exist, including the population-based data set from London, Ontario and those from France and Sweden. Published work from these centers has identified demographic variables of moderate predictive value. There is reasonable consensus on the ‘expected’ long-term clinical course of MS (e.g. clinical status at 5, 10, and 15 years’ duration of MS using ‘hard outcomes’ such as ‘time to Disability Status Scale scores of 3, 6 and 8’ and the ‘time to progressive MS’). This resource puts the MS field in a very favorable position to test the premise that non-randomized methods could be used to measure long-term outcomes in chronic illnesses.

In 2001, the Sylvia Lawry Center for MS Research was established at the Technical University of Munich with funds obtained from the private sector and international MS societies under the direction of the MS International Federation. This center was initiated with the purpose of advancing the study of clinical trial design and surrogate outcome measures in MS using existing datasets from natural history and completed clinical trials. Work is currently under way to create mathematical models of expected clinical and laboratory measures of disease activity from these data sets. A group of internationally recognized experts in MS trial design and MRI analysis are working in collaboration with mathematicians at the center to explore optimal methods of study. This work will be extended to determine whether it may be possible to create virtual placebo groups for the purpose of evaluating new therapies. Conceivably, additional strategies, including artificial intelligence methodology, may be of merit. Proposals from independent investigators will be reviewed to extend this work. It is expected that this center will be a
catalyst for moving the field forward with prospective long-term studies of effectiveness. This concept is clearly in its infancy and is not validated. Nevertheless, this work represents a novel approach to the complex problems facing the contemporary MS clinical trial field.

Retrospective analyses of existing large databases may have merit in generating hypotheses, including inferences of future therapeutic studies. This approach, however, lacks scientific rigor and may lead to erroneous conclusions. Problems of treatment allocation bias, lack of evaluator blinding, variability in defining outcomes, multiple interventions, and missing data seriously undermine any inference that might result from this approach. Recognizing these limitations, investigators have developed strategies to enhance the quality of prospectively designed observational studies following the lessons learned from the randomized design approach. These methodological strategies include carefully designed enrollment criteria, including both restricted and expanded cohorts, to evaluate the reproducibility of the original trial and to address the generalizability of published findings to patients ineligible for the randomized trial. Other steps include adjustment for known prognostic demographic variables and adopting a predetermined primary outcome analysis plan, thereby minimizing multiple comparisons.

Observational studies can be designed to evaluate both the generalizability of previous findings to groups of patients not previously studied (‘external validity’) and to evaluate long-term outcomes in groups of patients previously identified to be ‘responders’ in trials of short duration. This approach allows predetermined surrogate measures to be validated over long periods of follow-up, a much needed step in current MS trials. This design would require a renewable resource (e.g. multiple study sites with modest infrastructure and data co-ordinators, study nurses and clinical investigators), which could well be seen as an investment of value for adjunctive studies. Observational studies are not burdened by the need to fund the costs of expensive study drugs. The costs of potentially expensive surrogate marker studies such as MRI are minimized in that less frequent evaluations may be required than are usually needed in a study of short duration. This design permits flexibility for studying new, unanticipated ‘breakthrough’ treatment strategies (e.g. by enrolling more patients as an incidence cohort at the time of drug discovery) and allows multiple questions to be asked of the HQDBs. Prospective pharmacogenomic and pharmacoeconomic questions are readily studied in this manner. As mentioned above, the differences in observational and randomized trials lessen when the nature of the agent being studied prevents effective patient blinding.

This approach has at least one major weakness, however—data analysis is enormously complex. How can one measure outcomes in studies that have considerable confounding from multiple changes of treatment program (bias) and variable duration of follow-up? In addition, there is currently considerable uncertainty as to whether natural history datasets are sufficiently reliable to forgo the use of a concurrent control group.

There are a number of methods to overcome the potential biases introduced by the lack of randomization. These include risk adjustment techniques, instrumental variables approaches, cohort selection, cluster analysis, hierarchical linear modeling, propensity analysis, and retrospective case-control matching. Despite the use of these corrective steps, however, it is impossible to be certain that one has fully accounted for bias from unidentified prognostic variables and immeasurable patient and physician behavior introduced by the lack of randomization. Consequently, there remains considerable
controversy in the literature as to whether such observational studies can be more than ‘hypothesis-testing’. Are the results of non-randomized studies significantly more likely to be ‘positive’ than those of randomized trials? Again, the literature is mixed on this question. Proponents argue that observational studies may confirm a large effect that was previously demonstrated by randomized trial and may help to determine generalizability of a positive effect to a larger at risk cohort yet admit to less sensitivity to identify small treatment benefits than a randomized trial would. Some argue that non-randomized studies can confirm what has been demonstrated in randomized trials and thereby help to support practice guidelines.

With respect to MS, it appears possible that observational studies could be designed with sufficient rigor to test a hypothesis (e.g. ‘Does prolonged treatment delay disability when measured at 5 (10) years of follow-up?’). A variety of models of expected medium- and long-term outcomes derived from natural history datasets, especially population-based data, and models of short-term expected outcomes derived from control group data from randomized trials (from the Sylvia Lawry Center for MS Research) could be used to anticipate ‘expected’ outcomes for untreated patients. With these models as comparison groups (‘virtual placebo groups’), prospective observational studies could be designed with care to approach the standards set for randomized MS trials. As outlined above, observational trials may confirm or extend the expected findings from published randomized trials, especially when the effect is ‘large’. Arguably, the beneficial effects from the currently approved MS therapies are only modest, however. As such, a study design that is less sensitive than a standard randomized trial may overlook a small effect. Some argue that observational studies are more likely to incur a type 1 error. Either way, it seems highly unlikely that randomized trial methodology will be applied to measure long-term outcomes in MS. Currently these expensive agents are being widely used in the hope of delaying late decline in function without a mechanism to validate this practice. It is likely that this approach of using randomized methodologies to measure short-term strategies will continue to be used to determine efficacy, and ultimately licensure, for new, and presumably comparably priced, therapies. Consequently, additional expensive treatment options will be added to our armamentarium for short-term use in this disease. Currently the annual costs of the interferons and glatiramer acetate exceeds $US 1 billion in the USA alone.

From this author’s perspective, a properly designed and conducted observational study that suggested considerable and protracted benefit at 5 years and 10 years using observational methods would lend considerable support to their continued aggressive use in early MS. The risk of an error with this approach may be considerable (the risk of a type 2 error may be greater than the risk of a type 1 error in this setting) but is probably acceptable while the search for additional insights into pathogenesis, identification of ‘responder’ profiles, and more effective agents continues. I think this risk is preferable to the pragmatic concern that a decade from now we still will not know whether we have altered the natural history of this illness with the use of existing treatment programs.

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Emerging concepts of pathogenesis: relationship to therapies for multiple sclerosis

Jorge R Oksenberg, Sergio E Baranzini and Stephen L Hauser

INTRODUCTION

The pathogenesis of multiple sclerosis (MS) is complex and multifactorial. A complex disorder is defined by a genetic component that is not strictly mendelian (dominant, recessive, or sex-linked), and involves the interaction, either programmed or stochastic, of two or more genes (Table 19.1). Beyond the impact of genes that are inherited and act in their germline configuration, disease risk in complex disorders may be influenced by a number of post-genomic DNA changes. In MS, these include genes that rearrange to encode a vast variety of T-cell recep-

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<td><strong>Susceptibility genes (polygenic disorders)</strong></td>
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<td>Genes with common or rare alleles with weak but cumulative effects and penetrance (i.e. polymorphisms)</td>
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tors and immunoglobulins, somatic mutations, post-transcriptional regulatory mechanisms, and incorporation of retroviral sequences. Finally, it is also likely that interactions with infectious, nutritional, climatic, and other environmental influences affect susceptibility considerably (Fig. 19.1).

This complex array of factors results in a dysregulation of the immune response, loss of immune homeostasis and self-tolerance, and the development of abnormal (i.e. autoimmune) inflammatory pathogenic responses against structural components of the central nervous system (CNS). Myelin loss, gliosis, and varying degrees of axonal pathology culminate in progressive neurological dysfunction (e.g. sensory loss, weakness, visual loss, vertigo, inco-ordination, sphincter disturbances, altered cognition).

The autoimmune model of MS pathogenesis has set the tone for immunotherapy in this disease, first by global immunosuppression using anti-inflammatory drugs and, more recently, by selective targeting of specific components of the immune response. The past few years have seen progress in defining additional aspects of the molecular basis of MS,
preparing the stage for new therapeutic approaches based on correction of specific underlying disease mechanisms.

**Fig. 19.1 The multifactorial etiology of MS.** The incomplete penetrance of MS susceptibility alleles probably reflects interactions with other genes, post-transcriptional regulatory mechanisms, and significant environmental influences.

### THE MS LESION

The pathological hallmark of MS is the plaque, a well-demarcated gray or pink lesion, characterized histologically by inflammation, demyelination, proliferation of astrocytes with ensuing gliosis, and variable axonal degeneration (Fig. 19.2). MS plaques are typically multiple, asymmetric, and clustered in deep white matter near the lateral ventricles, corpus callosum, floor of the fourth ventricle, deep periaqueductal region, optic nerves and tracts, corticomedullary junction, and the cervical spinal cord. Plaques vary in size from 1–2mm to several centimeters in diameter. Although the prevalence of cortical lesions is unknown, some observers suggest that they are greatly under-reported.[1] Motor and sensory cortex lesions may contribute to ambulatory decline and cognitive dysfunction. It is also important to note that diffuse pathological characteristics are also evident in the normal-appearing white matter of MS brains when they are analysed by imaging or molecular techniques.[2,3]

Perivascular and parenchymal infiltration by mononuclear cells, both T cells and macrophages, is characteristic of the acute MS lesion but is rarely found at autopsy. Parenchymal and perivascular T cells consist of variable numbers of CD4+ and CD8+ cells.[4,5] Although the vast majority bear the common form of the antigen receptor (i.e. the α-β heterodimer), T cells carrying the other form, the γ-δ heterodimer, have been also identified.[6–8] The selective accumulation of activated T cells during certain stages of the
plaque cycle indicates a specific pattern in the trafficking of T cells to the lesion, and suggests that an immune response to discrete antigenic molecules is present.\textsuperscript{[9–15]} Although fewer in number, B cells and plasma cells also contribute to the inflammatory response.\textsuperscript{[3,16]} The role of this inflammatory response in MS pathogenesis is discussed later in this chapter.

At sites of inflammation, the blood-brain barrier is disrupted but the vessel wall itself is preserved, distinguishing the MS lesion from vasculitis. In some inflammatory lesions, there is dissolution of the multilamellated compact myelin sheaths that surround axons. Myelin-specific autoantibodies have been detected bound to the vesiculated myelin fragments, at least in some patients; these autoantibodies are thought to promote demyelination.\textsuperscript{[17]} As lesions evolve, axons traversing the plaque show marked beading, proliferation of astrocytes occurs, and lipid-laden macrophages that contain myelin debris are prominent. Progressive fibrillary gliosis ensues and mononuclear cells gradually disappear. In some MS lesions, but not all, proliferation of oligodendrocytes appears to be present initially, but these cells are apparently destroyed as the gliosis progresses. In chronic MS lesions, complete or nearly complete demyelination, dense gliosis (more severe than in most other neuropathological conditions), and loss of oligodendroglia are found. In some chronic active MS lesions, gradations in the histological findings from the center to the lesion edge suggest that lesions expand by concentric outward growth.

Up-regulation of major histocompatibility complex (MHC) molecules has been proposed as a marker of plaque activity.\textsuperscript{[18,19]} Class I MHC molecules have been identified in plaque tissue on endothelial cells, infiltrating lymphocytes, and astroglia, while class II determinants are reported in various studies to be expressed on endothelial cells, macrophages, microglia, and astroglia. On the other hand, a study by Bo et al. provided compelling evidence that the only cells in the active lesions expressing class II antigens are macrophages and microglia.\textsuperscript{[20]} The high level of expression of MHC class II molecules in MS brains suggests that the local microenvironment may be enriched in MHC-activating factors such as interferon (IFN)-\(\gamma\), and that antigen is possibly presented to T cells.\textsuperscript{[21]} Because the level of cell surface expression of MHC class II molecules directly affects the nature and magnitude of the immune response, the study of the mechanisms involved in the regulation of class II expression in the MS plaque is essential for understanding the inflammatory response in the affected brain. The class II transcriptional transactivator (CIITA) is a key intermediate responsible for constitutive and IFN-\(\gamma\)-inducible MHC class II expression.\textsuperscript{[22]} CIITA also directs expression of the invariant chain (Ii) and HLA human leukocyte antigen (DM), two molecules involved in class II biosynthesis and antigen processing.\textsuperscript{[23]} Soos and colleagues reported that murine astrocytes express CIITA, Ii, DM, and the co-stimulatory molecule B7–1, suggesting that
**Fig. 19.2** Histopathology of the MS lesion. (a) Coronal section of an MS brain displaying an acute periventricular area of demyelination and edema in the left temporal white matter and a smaller, linear plaque in a mirror position. The older plaque is less edematous and therefore better demarcated. (b) Low-power horizontal section through the medulla at the level of the inferior olives illustrating multiple asymmetrical, sharply outlined areas of myelin loss, which appear clear (luxol fast blue stain). (c) Microscopic section of a recent lesion,
in which lymphocytes and macrophages appear as black, rounded nuclei surrounding a blood vessel. Some inflammatory cells have migrated further into the brain parenchyma. (d) Electron micrograph of MS myelin pathology from a biopsy of subcortical white matter. Disintegrating myelin membranes around the axon (center) have been transformed into a vesicular network. Fibrous astroglial processes, naked axons, and a reactive ameboid microglial cell (lower left corner) can also be identified.

non-professional CNS antigen-presenting cells participate in the processing and presentation of autoantigens as well as T cell activation.\cite{24,25} Hence, regulation of CIITA expression or function may offer an important therapeutic opportunity for MS. The regulatory cytokines transforming growth factor (TGF)-β and IFN-β suppress class II expression by interfering with IFN-γ-inducible CIITA transcription and activity.\cite{26,27} It is important to note, however, that in many silent plaques devoid of T-cell infiltrates, class II MHC may be expressed at high levels on reactive microglia. In addition, upregulation of MHC class II antigens is not unique to MS tissue—it has also been detected in neurodegenerative diseases and after trauma. One school of thought proposes that glial MHC class II expression is necessary, but not sufficient, for effective antigen presentation to encephalitogenic CD4⁺ T cells.\cite{28} In vitro studies suggest that, under some conditions, class II-expressing microglia may actually protect the CNS from autoreactive T cells by inducing their apoptosis. Although the co-stimulatory molecules ICAM-I and B7 have also been identified on microglia from humans and rodents; the case for effective antigen presentation in the brain remains incomplete. Other molecules up-regulated in the MS lesion include a variety of cytokines, adhesion molecules, fibronectin, urokinase plasmin activator receptor, and stress proteins.\cite{29–35} Of interest are the observations that a number of growth factors are secreted by various cell types in the MS lesion, since they are, in other neurological disorders, associated with tissue injury and repair. In a recent pilot trial in non-human pri-mates, nerve growth factor (NGF) was administered intracerebroventricularly 7 days after immunization with recombinant myelin oligodendrocyte glycoprotein (MOG). An unexpected anti-inflammatory NGF-mediated effect was observed, probably mediated by induction of interleukin (IL)-10 on astrocytes, resulting in substantial reduction of clinical and histological signs of experimental allergic encephalomyelitis (EAE).\cite{36}

Recent technological advances have facilitated the accumulation of gene expression data in the MS brain. The construction of gene expression databases will permit temporal and topographic transcriptional patterns to be identified, essentially providing a
molecular fingerprint of the demyelinating process defined by the complete array of MS disease genes. The high-through-put sequencing of diseased brain-expressed transcripts was recently reported; cDNA non-normalized brain libraries generated from MS lesions and control brain were used. Using this protocol, mRNA populations present in the brain specimens are accurately represented, enabling the quantitative estimation of transcripts. More than 11000 clones were sequenced, and analysis focused on genes present in MS libraries, but absent in the control library. This yielded 423 genes, including 26 novel genes with no match at GeneBank at the time of analysis. Transcripts for α-B-crystallin, an inducible heat shock protein localized in the myelin sheath and targeted by T cells in MS, were the most abundant transcripts unique to MS plaques. The five next most abundant transcripts included those for prostaglandin D synthase, prostatic binding protein, ribosomal protein L17, and osteopontin (OPN). OPN, also called early T-cell activation gene-1, has pleiotropic functions, including roles in tissue remodeling, cell survival and cellular immunity. OPN co-stimulates T-cell proliferation and is classified as a T helper cell type 1 (Th1) cytokine, owing to its ability to up-regulate IFN-γ and IL-12 production and to down-regulate IL-10. OPN is also a chemoattractant for various cells, including macrophages, T cells, and astrocytes, in conditions such as stroke, myocardial necrosis, and sarcoidosis. OPN was also found in lesions of EAE, expressed broadly in microglia near perivascular inflammatory lesions during both relapses and remission from disease. In addition, OPN expression in neurons was detectable during acute disease and relapse but not during remission. In the acute monophasic form of EAE induced in Lewis rats, OPN expression was predominant in microglia and neurons close to acute lesions. OPN-deficient mice were resistant to progressive EAE and had frequent remissions. Finally, myelin-reactive T cells from OPN−/− mice produced more IL-10 and less IFN-γ and IL-12 than those from wild-type +/+ mice. OPN may regulate Th1 responses involved in CNS autoimmunity, and it may be an attractive target for new therapies designed to block the development of progressive MS.

Transcripts detected in both MS and control brain libraries include myelin basic protein (MBP), heat shock protein 70 (HSP-70), glial fibrillary acidic protein (GFAP), and synaptobrevin. The high levels of MBP expression in the MS and control libraries suggest a very high turnover rate for this protein. Expression of HSP70–1, which is involved in myelin folding, was significantly elevated in the MS library. Myelin repair is known to occur in MS lesions and in EAE, and it is responsible for the formation of ‘shadow plaques’ in MS. Remyelination seems to occur through the differentiation of precursor oligodendrocytes that recolonize the fresh lesion. The extent of remyelination is known to vary between individual cases and lesions, perhaps depending on the degree of preservation of the progenitor pool and on the metabolic activity of the adult oligodendrocytes. Although not differentially expressed, GFAP was among the three most abundant species in all the libraries, consistent with a prominent glial (or astrocytic) response in MS brain. Synaptobrevin transcripts were more abundant in the control brain. The decreased transcription of synaptobrevin in MS might relate to axonal loss, since this molecule belongs to a family of small integral membrane proteins specific for synaptic vesicles in neurons.

The two quantitatively major myelin proteins, MBP and proteolipid protein (PLP), make up about 30% and 50% of myelin proteins by weight, respectively (Fig. 19.3). It has been suggested that exposure to ion channels as a result of demyelination affects
**Fig. 19.3** Schematic representation of the molecular architecture of the central myelin sheath and the myelin surface-associated zone. Myelin is formed by membrane extension of oligodendrocytes, which wraps around the axon. Central myelin consists of about 75–80% lipids and 20–25% proteins. PLP accounts for about 50% of total myelin protein and myelin basic protein for another 30%. Myelin-associated glycoprotein (MAG) and MOG each constitute about 3% of whole myelin protein. PLP is integrated in the myelin membrane. Myelin basic protein is a cytosolic protein. MAG is located in the periaxonal space of the myelin sheath. MOG is located at the surface, so it is the myelin protein most exposed to humoral and cellular immune responses. PLP, myelin basic protein, and MOG are encephalitogenic in
sensitive animals. Figure courtesy of Dr CA Bernard, La Trobe University, Melbourne, Australia. Adapted from Crang and Rumsby.[211]

propagation of action potentials across the demyelinated region of the axon. Preliminary clinical studies demonstrated some therapeutic benefit of 4-aminopyridine (4-AP), a blocker of rapidly activating voltage-gated (potassium) channels in MS and spinal cord injury.[49] Whereas the traditional neuropathological view of MS highlights myelin loss as the prominent event occurring in the plaque, the early literature on MS already described substantial axonal damage in actively demyelination lesions.[50] It is not known whether this process is independent of or a consequence of demyelination, but renewed interest in this aspect of MS pathology has focused attention considerably into the neurodegenerative aspects of this disease.[51,52] Recent studies confirm that partial or total axonal transection begins early in the disease process[53] and suggest that the cumulative axonal loss may ultimately determine neurological disability.[54] Histopathological studies reveal abundant transected and dystrophic axons in sites of active inflammation and demyelination. Axonal loss is perhaps the principal contributor to atrophy in MS, although demyelination may also decrease tissue volume. Axonal loss and cavitation are particularly prominent in the subtype of MS known as neuromyelitis optica (or Devic’s syndrome). Axonal injury, as identified by amyloid precursor protein (APP) accumulation and reduced axonal density, was also observed in inactive and remyelinated lesions, cortical tissue, and the normal-appearing white matter.[55] N-acetyl aspartate (NAA), a chemical component of CNS axons involved in energy storage, provides a relatively specific pathological marker of axonal degeneration. Reduced NAA in acute lesions is partly reversible, indicating that early axonal damage due to inflammatory demyelination can be reversible, an observation compatible with the observed clinical recovery accompanying remissions.

It is important to emphasize that MS plaques are heterogeneous in their structural and immunopathological patterns. Lucchinetti et al. reported that although most lesions contain an inflammatory reaction, diverse patterns of myelin destruction can be observed.[56] In their series, the majority of active MS lesions were characterized by the deposition of immunoglobulins and complement at sites of myelin breakdown, similar to what has been observed in the MOG-induced model of EAE. Other cases are more suggestive of oligodendrocyte dystrophy, as reflected by loss of myelin-associated glycoprotein and oligodendrocyte apoptosis. These lesions were more reminiscent of viral-, ischemic-, or toxin-induced demyelination. These different types of lesions appeared to be consistent in individual cases (i.e. all lesions from the same case are of the same type). The therapeutic implications of such pathological heterogeneity are considerable because they may reflect fundamentally distinct immunopathogenic mechanisms.

A MODEL FOR MS PATHOGENESIS

An important conceptual development in the understanding of MS pathogenesis has been the compartmentalization of the mechanistic process into two distinct but overlapping
and connected phases—inflammatory and neurodegenerative.[57] During the initial stage of the inflammatory phase, lymphocytes with encephalitogenic potential are activated in the periphery and home to the CNS, become attached to receptors on endothelial cells, and then proceed to pass across the blood-brain barrier, through the endothelium and the subendothelial basal lamina directly into the interstitial matrix (Fig. 19.4). Remarkably, the presence of immunocompetent cells with autoimmune potential appears to be an embedded characteristic of the (healthy) immune system in vertebrates. [58–60] These cells may provide important inflammatory signals necessary for wound healing, angiogenesis, neuroprotection, and other maintenance functions. [61–63]
The transition from physiological to pathological autoimmunity involves at least two factors:\[64,65\]

- the loss of immune homeostasis, normally maintained through inhibitory signaling pathways, induction of anergy or apoptosis, and anti-idiotypic networks; and
- the engagement and activation of lymphocytes by adjuvant signals including, conceivably, recurrent exposures to endogenous pathogens.

This could occur via non-specific polyclonal activation of T and B cells by bacterial or viral antigens, or, alternatively, as a consequence of structural homology between a self-protein and a protein in the pathogen, a process commonly referred to as molecular mimicry. It is notable, for example, that components of the myelin sheath share amino acid homologies with pro-teins of measles virus, influenza viruses, herpes viruses, papillomavirus, adenovirus, and other viruses. Homology may be necessary at only a few amino acids for efficient T-cell recognition to occur.\[66–68\] For example, the stretch between residues 88 and 99 of MBP—PWHFFKNTVTP, a region known to be commonly recognized by human MBP-reactive T cells and antibodies—shares identical contigs of between four and six amino acids with Epstein-Barr virus, papillomavirus variants, adenovirus type 12, and influenza virus type A. These pathogens acquired sufficient homology to permit HLA binding and interactions with MBP-specific T cells, with the potential for a misguided response. In addition, amino acid identity may not even be required for cross-reactivity to occur between the autoantigen and the mimic, as long as they share chemical properties at critical residues that allow anchoring to HLA and interaction with the T-cell receptor (TCR).\[69,70\]

Various microbes have been implicated in MS pathogenesis.\[71\] Eighty years ago, spirochetes were claimed to be the cause of MS. This was a reasonable assumption given that syphilis can cause a relapsing-remitting CNS inflammatory disease with synthesis of oligoclonal immunoglobulins in the cerebrospinal fluid. Since then, more than 20 infectious agents, ranging from retroviruses to mycobacteria have been associated with MS onset or relapses.\[72–75\]

The extensive deconstruction of the antigenic properties of MBP resulted in the development of an attractive therapeutic strategy using autoantigenic peptides with modifications in TCR contact positions (i.e. altered peptide ligands (APLs)). APLs can mediate anergy, TCR antagonism, or, most interestingly, bystander suppression. This last-mentioned mechanism refers to the induction of an APL-specific T helper cell type 2 (Th2)-like cell population that cross-reacts with the native autoantigen and thus dampens immune responsiveness whenever autoantigen is released.\[76\]

Recently, an APL of the immunodominant MBP peptide (amino acids 83–99) was tested in clinical trials, and several interesting observations emerged. There was no increase in disease exacerbations and no worsening of disability in this 144-patient, placebo-controlled, double-blind trial.\[77\] A decrease in the size of new lesions in white matter on magnetic resonance imaging (MRI) scans was also observed. Patients who had active scans before treatment showed reduced volume of enhancement on MRI scans after 4 months of treatment in 17 of 21 cases. Local allergy was seen in 9% of patients, similar to what is seen in patients treated with glatiramer acetate, and consistent with a shift to a Th2 immune response.\[77\]
Bielekova and colleagues studied eight patients treated with the same APL. They reported exacerbations in three of these patients. There was an increase in MBP-reactive T cells in one patient with MS who had an exacerbation, as well as another patient with both demyelinating CNS and peripheral nervous system disease who had a relapse. In another patient who worsened during this study, there was initial improvement in chronic symptoms and improvement on MRI scans. After 5 months there was a relapse, but MBP-reactive T cells had disappeared after treatment with the altered peptide.

Although these studies show that our basic concepts about disease induction by specific autoantigens are probably correct, they also highlight that the correct dose of APL and its route of administration need further investigation. At a high dose, some patients showed disease exacerbations that were mediated by APL-specific Th1 cells with cross-reactivity with the native MBP peptide. In contrast, a lower dose showed a trend towards clinical benefit, probably via a Th2 shift. Optimization of dosage and timing of administration might allow further trials of this promising approach involved in shifting the balance of cytokines from autoaggressive to suppressive. Pedotti et al. have recently shown that myelin antigens can induce classic anaphylactic responses, although these responses can be easily contained with antihistamines. Induction of Th2 shifts may be initially beneficial for T-cell mediated autoimmunity, but may also induce elevated titers of pathogenic antibodies.

An alternative hypothesis proposes that activation of autoimmune cells occurs as a consequence of viral infection of CNS cells; such infections may be asymptomatic but cause cytopathic effects to target cells in the course of an antiviral response. The prolonged release of neural antigens may induce autoimmune responses that eventually become self-perpetuating and pathological. For example, anti-MBP responses are detected during measles encephalitis and human T-cell leukemia virus (HTLV)-1 infections. This process may even start during the embryonic period or shortly after birth. Zinkernagel suggests that deficiencies in the degree of protection conferred by the mother’s neutralizing antibodies in plasma or milk may influence the likelihood that viral infections will propagate from the gastrointestinal tract to other anatomical sites and initiate insidious bystander autoimmunity.

Once activated, T cells express surface molecules called integrins, which mediate binding to the specialized capillary endothelial cells of the blood-brain barrier (see Fig. 19.4). One such integrin, VLA-4, binds the vascular cell adhesion molecule (VCAM) expressed in the capillary endothelial cells following induction by TNF-α and IFN-γ during an inflammatory response. In EAE, blockade of VLA-4 reverses clinical paralysis and prevents further relapses. Clinical trials with an antibody to VLA-4 are now in phase III, following promising phase II trial results in which the incidence of relapses in treated patients was reduced. As the activated T cells migrate across the blood-brain barrier to reach the CNS parenchyma, they express gelatinases (matrix metalloproteinases (MMP)) responsible for lysis of the dense subendothelial basal lamina. The clinical relevance of metalloproteinases is underlined by the observation that some members of this family of molecules are present in the cerebrospinal fluid of patients with MS but not of normal controls. It is also noteworthy that the sequence in the putative cleavage of the TNF-α precursor reveals homologies with peptide sequences known to be cleaved by metalloproteinase-like enzymes. Thus metalloproteinases may act not only as mediators of cell traffic across the blood-brain barrier, but may also increase the...
inflammatory and homing reactions through TNF processing. Furthermore, a direct neurotoxic effect for metalloproteinases has also been proposed; microinjection of activated MMPs into the cortical white matter of experimental animals results in axonal injury, even in the absence of local inflammation.\[90\] Inhibition of gelatinases by enzyme inhibitors results in suppression of cell migration across endothelium in vitro and produces amelioration of clinical symptoms in EAE.\[91\] Application of rationally designed metalloproteinase inhibitors to human disease was handicapped by the high incidence of side effects. Interferon beta, on the other hand, is a potent inhibitor of gelatinase transcription and expression and has an acceptable side effect profile.\[92–95\]

A different group of molecules involved in leukocyte homing and extravasation comprises soluble chemoattractants (chemokines) and their receptors. Chemokines are members of an expanding family of small serum proteins of between 7 and 16 kDa in size, primarily involved in selective trafficking and homing of leukocytes to sites of infection and inflammation, leukocyte maturation in the bone marrow, tissue repair and vascularization, and hematopoiesis and renewal of circulating leukocytes.\[96\] The spatial and temporal expression of chemokines correlates with disease activity in EAE and MS.\[97,98\] In addition, chemokine receptors have been shown to mediate entry of microorganisms into target cells\[99,100\] and also to participate in the viral-mediated induction of Th-1 cytokines\[101\]—both potential mediators of the encephalitogenic response. Even though the chemokine network is remarkably redundant and promiscuous, some investigators have proposed that individual chemokines and receptors might be rationale targets for therapeutic intervention in MS.\[102\]

After traversing the blood-brain barrier, pathogenic T cells are believed to be reactivated by fragments of myelin antigens\[103\] presented in the framework of MHC class II molecules on the surface of antigen-presenting cells (macrophages, microglia, and perhaps astrocytes) (Table 19.2). Reactivation induces release of proinflammatory cytokines that further open the blood-brain barrier and stimulate chemotaxis, resulting in additional waves of inflammatory cell recruitment and leakage of antibody and other plasma proteins into the nervous system. Pathogenic T cells may not be capable of producing or inducing tissue injury in the absence of the secondary leukocyte recruitment. For example, in EAE mediated by adoptive transfer of MBP-reactive encephalitogenic T cells, these inflammatory cells are among the first to infiltrate the CNS but constitute only a minor component of the total infiltrate in the full-blown lesion.

**Table 19.2 MS potential autoantigens**

<table>
<thead>
<tr>
<th>Autoantigen</th>
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<tbody>
<tr>
<td>Myelin basic protein (MBP)</td>
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<tr>
<td>Proteolipid protein (PLP)</td>
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<tr>
<td>Myelin oligodendrocyte glycoprotein (MOG)</td>
</tr>
<tr>
<td>Myelin-associated glycoprotein (MAG)</td>
</tr>
<tr>
<td>Myelin oligodendrocyte basic protein (MOBP)</td>
</tr>
<tr>
<td>Astrocyte-derived calcium-binding-protein (S1000(\beta))</td>
</tr>
<tr>
<td>Heat shock proteins ((\alpha)-B crystallin)</td>
</tr>
<tr>
<td>Galactocerebroside</td>
</tr>
<tr>
<td>(\beta)-arrestin and arrestin</td>
</tr>
<tr>
<td>Glial fibrillary acidic protein (GFAP)</td>
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<td>Transaldolase</td>
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</table>
The neuroinflammatory process was recapitulated in a humanized mouse model of MS expressing the disease-associated HLA-DR heterodimer (DRA*0101/DRB*1501), a T-cell receptor from an MS-patient-derived T-cell clone specific for the DR2-bound immunodominant MBP 84–102 peptide, and the human CD4 co-receptor. Following immunization with the MBP peptide together with adjuvant and pertussis toxin, mice developed focal CNS inflammation, demyelination and paralytic relapsing disease. Spontaneous disease was observed in 4% of the transgenic mice. When the animals were backcrossed into a Rag2-deficient background, the incidence of spontaneous disease increased, suggesting that the DR2:MBP peptide trimolecular complex is necessary and sufficient for the development of autoimmune demyelination. The basis for the high incidence of spontaneous disease in the DR2/TCR Rag2$^{-/-}$ transgenics is most likely due to the inability of the animals to generate regulatory T cells.

Since a low level of autoreactivity is apparently physiological, some authors have speculated that the differential response to self and non-self depends to some degree on the specificity of the cytokine microenvironment associated with the response. Immunohistochemical and molecular analyses of CNS samples, particularly dissected MS plaques from autopsy tissue and cerebrospinal fluid cells, provide support for a model of lesion development driven by a Th1-type inflammatory response. Although patterns of local proinflammatory cytokine production correlate fairly well with disease in experimental models of MS, the dogmatic application of the Th1-Th2 paradigm to human demyelination is considered somehow simplistic. Kinetic reverse transcriptase polymerase chain reaction (RT-PCR) was used to analyse in detail the quantitative expression profile of 56 genes in brain samples from eight MS patients with active demyelinating lesions. The analysis showed a predominant expression pattern of Th1 cytokines, mainly represented by the MIP-1$\alpha$-RANTES-CCR5 and caspase-1-IL-1$\beta$-IL-18 axes. Surprisingly, key inflammatory-type molecules such IL-2, IFN-$\gamma$ and TNF-$\alpha$ did not display consistent and reproducible elevated expression patterns. On the other hand, concurrently with elevated expression of IL-5 and IL-6 and IL-6R, prototypic Th2-type molecules such as IL-4, IL-10, IL-13, and CCR8 were undetected.

Altogether, the transcriptional pattern of cytokine expression suggests a complex, not fully polarized regulation of the local immune response in human autoimmune demyelination. Transgenic over-expression of cytokines as well as knock-out experiments were expected to provide valuable insights into the role of cytokines in CNS inflammation. However, drawbacks inherent to the technology, such as the constitutive on-or-off expression during development, and difficulties in controlling the copy number and site of integration, prevent a straightforward interpretation of the phenotypes. An improved generation of inducible promoters will allow better replication of the physiological consequences resulting from unbalanced cytokine responses.

A large body of experimental data has firmly established that myelin-specific T cells in MS patients are present in greater numbers than in healthy controls, have lower thresholds of activation, and have different effector profiles. However, whereas the role of CD4$^+$ and CD8$^+$ T cells as initiators and regulators of the CNS
inflammatory response is well established, their role as direct effectors of myelin injury remains uncertain. Potential T-cell-mediated mechanisms of myelin damage have been established in vitro; TNF-α kills myelinating cells in culture,[126,127] anti-MBP CD4+ cells can display cytolytic functions,[128] and CD8+ cells induce cytoskeleton breaks in neurites.[129] Interestingly, axonal injury correlates better with the presence of CD8+ T cells and macrophages than CD4+ T cells.[51] It is clear, however, that the MS lesion is not exclusively T-cell-mediated; rather a synergistic cellular and humoral response is required to produce demyelination and axonal damage (Table 19.3). The most convincing mechanisms of tissue injury involve antibody binding and complement activation[130] and macrophage-microglia activation followed by myelin phagocytosis and release of toxic factors (see Table 19.3).

B-cell activation and antibody responses are necessary for the full development of demyelination, both in human and experimental disease.[131,132] In most MS patients, an elevated level of intrathecally synthesized immunoglobulins can be detected in the cerebrospinal fluid.

Table 19.3 Cellular components in MS pathogenesis

<table>
<thead>
<tr>
<th><strong>MS as a T-cell-mediated disease</strong></th>
</tr>
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<tbody>
<tr>
<td>T cells express gelatinases necessary for blood-brain barrier extravasation</td>
</tr>
<tr>
<td>Significant T cell infiltration in the acute lesion</td>
</tr>
<tr>
<td>Peripheral myelin-specific T cells display an activated state in vivo</td>
</tr>
<tr>
<td>T-cell-derived cytokines (either pathogenic or protective) are expressed in the lesion</td>
</tr>
<tr>
<td>TCR rearrangements from MS brain lesions encode CDR3 regions identical to those found in T cells recognizing MBP</td>
</tr>
<tr>
<td>T cell receptor genes influence disease susceptibility in MS and EAE (controversial)</td>
</tr>
<tr>
<td>MHC class I restricted CD8+ T cells can lyse oligodendrocytes and axons in vitro</td>
</tr>
<tr>
<td>EAE can be transferred by myelin sensitized T cells in rodents and non-human primates</td>
</tr>
<tr>
<td>T-cell inactivation prevents and cures EAE</td>
</tr>
<tr>
<td>Apoptosis of T cells may correlate with EAE resolution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MS as a B-cell-mediated disease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated level of restricted intrathecally synthesized immunoglobulins</td>
</tr>
<tr>
<td>Plasma immunoglobulins from MS patients induce in vitro myelinolysis</td>
</tr>
<tr>
<td>CNS immunoglobulins from MS patients induce in vitro myelinolysis</td>
</tr>
<tr>
<td>Clonally expanded B cells detected in the CNS</td>
</tr>
<tr>
<td>Anti-MBP antibodies in the brain and cerebrospinal fluid</td>
</tr>
<tr>
<td>Anti-MOG antibodies bound to the disintegrating myelin in EAE and MS</td>
</tr>
<tr>
<td>Anti-MOG antibodies induce in vitro myelinolysis</td>
</tr>
<tr>
<td>Requirement for anti-MOG antibodies to induce demyelination in EAE</td>
</tr>
<tr>
<td>Complement deposition at the edge of lesions</td>
</tr>
<tr>
<td>Immunoglobulin deposition on macrophages contacting myelin</td>
</tr>
<tr>
<td>Immunoglobulin RFLPs associated with disease susceptibility</td>
</tr>
</tbody>
</table>
Although the specificity of these antibodies is mostly unknown, anti-MBP specificities have been detected.\textsuperscript{[133]} Warren et al. reported that 111 of 116 patients with progressive MS had anti-MBP antibodies in the cerebrospinal fluid.\textsuperscript{[134]} The epitope for this antibody response to human MBP fits precisely the minimal T cell epitope PWHFFKNTVTP for HLA-DRB1*1501 restricted T cells. Warren et al. postulated that this antibody response may be directed to a processed fragment of MBP presented on MBP-specific B cells and thus be able to trigger T cells reactive to the same epitope.\textsuperscript{[135]} In this way, the antibody need not be directed to MBP in its native conformation in the myelin sheath, but it may be directed to a processed epitope of MBP or to a microbe sharing homology with the epitope (i.e. molecular mimicry). Myelin-specific infiltrating B cells have been detected in the MS brain,\textsuperscript{[136]} and there is an elevated frequency of clonally expanded B cells with properties of post-germinal center memory or antibody-forming lymphocytes in the cerebrospinal fluid and brain of affected patients.\textsuperscript{[3,137–140]} The pathogenic potential of antibodies is exemplified in EAE and in vitro experimental paradigms. Little or no demyelination is usually observed when EAE is induced in Lewis rats by injection of purified MBP or by passive transfer of MBP-reactive lymphocytes, but extensive demyelination is observed following intravenous injection of anti-MOG monoclonal antibodies once the blood-brain barrier has been breached.\textsuperscript{[141]} Genain et al. used immunogold-labeled peptides of myelin antigens and high-resolution microscopy to detect MOG-specific autoantibodies bound in situ to the disintegrating myelin in lesions of non-human primate EAE and in human MS.\textsuperscript{[17]} Antibodies may participate in myelin destruction through different mechanisms, such as opsonization which facilitates phagocytosis by macrophages or complement fixation (or both).\textsuperscript{[130,142]} CNS immunoglobulins may also induce myelinolysis via activation of a calcium-dependent myelin-associated protease acting on MBP.\textsuperscript{[143]} Interestingly, in the Theiler’s virus model of demyelination, a natural antibody with specificity for a unique CNS component promotes remyelination.\textsuperscript{[144]} Hence, similar to what has been previously suggested for T cells, a pathogenic as well as reparative role for the humoral immune response could be postulated. Recent results showing the ability of MBP and MOG-specific T cell lines, as well as B cells and monocytes to produce brain-derived neurotrophic factor (BDNF), provide additional support for the hypothesis that the inflammatory infiltrate in the MS brain may, in certain circumstances, have a neuroprotective effect.\textsuperscript{[145]} A third class of cells, the resident microglia, lying within the parenchyma, also becomes activated as a result of locally released cytokines.\textsuperscript{[146]} Microglia act as scavengers that remove debris and as antigen-presenting cells that present processed antigens to T cells, contributing to their local clonal expansion. Mutual interactions...
between T cells and macrophages induce proliferation of both cell types through mediation of such molecules as IL-2 and colony stimulating factors. Furthermore, endothelia and T cells provide colony-stimulating factors that maintain macrophage activation and prevent apoptosis and cell death. Microglia are also likely to induce myelin damage and killing of oligodendroglial cells directly through the release of mediators such as free radicals (nitric oxide and superoxide anion), vasoactive amines, complement, proteases, cytokines (e.g. IL-1, TNF-α), and eicosanoids (Fig. 19.5).[147–149] Excess of glutamate released by microglia and macrophages during inflammation, accompanied by a decrease in glutamate intake and metabolism, activates α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA), which is toxic to oligodendroglial cells and

![Fig. 19.5](image_url)

**Fig. 19.5** Macrophages and demyelination. The macrophage is a key participant in the inflammatory response in MS. Courtesy of Dr E Waubant, University of California at San Francisco.

neurons.[150,151] Blockade of AMPA-responsive glutamate receptors with AMPA antagonists ameliorates neurological sequelae in EAE, increases oligodendrocyte
survival, and reduces dephosphorylation of neurofilament H, an indicator of axonal damage.\cite{152,153} A role for microglia in the protection of oligodendrocyte survival and remyelination has been considered as well.\cite{145} As the disease progresses, irreversible CNS damage accumulates, a phase that some authors consider to be neurodegenerative; there is evidence of axon loss and atrophy of the brain and spinal cord, and its extent correlates with permanent functional deficits. This model of MS immunopathogenesis provides a useful conceptual framework for understanding the mechanisms of action of existing therapies for this disorder, as well as for the failed therapies and the rationale behind drugs currently under development. Beta interferons most likely have pleiotropic effects, including antagonism of IFN-γ-mediated MHC up-regulation on antigen-presenting cells, altering the profile of cytokine expression to a Th2 pattern, and blocking migration across endothelia (Table 19.4). Glatiramer acetate also affects the cytokine expression pattern and may induce active T-cell suppression against MBP and saturate MHC molecules on antigen-presenting cells, preventing presentation of autoantigens. Corticosteroids are potent inhibitors of the antigen-presenting cell function. The chemotherapeutic drug cyclophosphamide is lympholytic and stimulates production of Th2 cytokines. Most experimental therapies focus on interference with antigen presentation to encephalitogenic T cells (e.g. altered peptide ligand, intravenous antigen), induction of a Th2 response (e.g. oral tolerance), T-cell depletion (e.g. anti-CD52, anti-Vβ5), blockade of adhesion molecules (e.g. anti-VLA4 antibody), administration of anti-inflammatory cytokines (e.g. IL-10, TGF-β2), or neutralization of proinflammatory cytokines (e.g. type IV phosphodiesterase inhibitors, nerve growth factor, TNFR p55 Ig fusion protein, anti-TNF-α immunoglobulin G1). Interestingly, a case report recently suggested an association between onset of MS and anti-TNF therapy for juvenile rheumatoid arthritis. The use of inert anti-MOG antibody mimics has also been proposed. Antibody fragments have been shown to protect animals against experimental myasthenia gravis.\cite{155}

Other approaches, such as the use of statins, which inhibit LFA-1 and block the development of EAE,\cite{156} and antihistamines, which engage histamine (H)1-receptors

### Table 19.4 Proposed biological effects of IFN-β on MS

<table>
<thead>
<tr>
<th>Effect</th>
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<tr>
<td>Antiproliferative effect</td>
</tr>
<tr>
<td>Antiapoptotic effect</td>
</tr>
<tr>
<td>Reduction in the expression of lymphocytic matrix metalloproteinases</td>
</tr>
<tr>
<td>Reduction in the expression of activation markers</td>
</tr>
<tr>
<td>Regulation of MHC expression and antigen presentation</td>
</tr>
<tr>
<td>Regulation of natural killer cell activity</td>
</tr>
<tr>
<td>Suppression of IL-12 production</td>
</tr>
<tr>
<td>Suppression of RANTES production</td>
</tr>
<tr>
<td>Stimulation of IL-10 production</td>
</tr>
<tr>
<td>Reinstatement of deficient suppressor cell function</td>
</tr>
<tr>
<td>Antiviral effect</td>
</tr>
<tr>
<td>Reduction in induced nitric oxide production</td>
</tr>
<tr>
<td>Limit astrocyte proliferation</td>
</tr>
</tbody>
</table>

Emerging concepts of pathogenesis 337
found in MS brain and when given orally can block EAE,[81] may provide new approaches for previously approved drugs. The use of agents that block subtypes of glutamate receptors is a new direction in the development of therapies for stroke and neurodegenerative conditions, and this approach may also prove useful for treatment of the chronic degenerative phase of MS. Neuroprotection against glutamate insult was observed by immunizing mice with glatiramer acetate, perhaps as a result of the activation of regulatory T cells.[157] Finally, it is now possible to reverse ongoing paralysis in the EAE model, with vectors encoding regulatory cytokines or inflammatory cytokine inhibitors[158–160] or by inducing tolerance in the immune system by injecting DNA that encodes myelin antigens along with DNA that encodes the Th2 cytokine IL-4.[161] DNA vaccination has been taken into the clinic for infectious disease and cancer, and trials are now being organized to apply this approach to autoimmune diseases, including MS. The partial, negligible, or deleterious effects that some of these approaches have demonstrated in the laboratory and in the clinic reflect the complex molecular interactions operating in autoimmunity and the limitations of the proposed model as a true reflection of MS pathogenesis.

**MS AS A GENETIC DISEASE**

Compelling data indicate that susceptibility to MS is inherited (Table 19.5). Familial aggregation, recognized by Charcot in the late nineteenth century, is well documented with an increased relative risk of 20–40 to siblings of MS patients compared with the general population. Concordant sibs tend to share age of symptom onset rather than year of onset, and second-and third-degree relatives of MS patients are also at an increased risk of MS, suggesting that inherited factors distinct from a common environmental exposure influence susceptibility. Concordance within multiply affected families has recently been reported for a pattern of optic nerve or spinal cord manifestations in the first and second attacks[162] and for disability and handicap scores.[163] Studies of half-siblings[164] and adoptees[165] support the concept that genetic factors, and not environmental factors, are primarily responsible

<table>
<thead>
<tr>
<th>Familial aggregation of MS cases</th>
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<tr>
<td>Increased relative risk to sibs ($\lambda_s=20–40$)</td>
</tr>
<tr>
<td>MS sibling pairs tend to cluster by age of onset, rather than year of onset</td>
</tr>
<tr>
<td>No detectable effect of shared environment on MS susceptibility in first-degree non-biological relatives (spouses, adoptees)</td>
</tr>
<tr>
<td>High disease concordance in monozygotic twins (25–30%) compared with dizygotic twins and non-twin siblings (3–5%)</td>
</tr>
<tr>
<td>Racial clustering of MS cases, with resistant ethnic groups residing in high risk regions</td>
</tr>
<tr>
<td>Suggestive correlations between certain polymorphic loci and disease susceptibility</td>
</tr>
</tbody>
</table>
for familial aggregation. Furthermore, twin studies from different populations consistently indicate that a monozygotic twin of an MS patient is at higher risk (25–30% concordance) of MS than a dizygotic twin (2–5%),\textsuperscript{[166,167]} providing additional evidence for a significant, but complex, genetic etiology (Table 19.6). A simple mendelian model of inheritance for all MS is unlikely because it cannot account for the non-linear decrease in disease risk in families with increasing genetic distance from the proband. Estimates of recurrence risk in families combined with twin data predict that the MS-prone genotype results from multiple independent or interacting polymorphic genes, each exerting a small or at most a moderate effect to the overall risk. Hence, although a mendelian-like genetic etiology can not be ruled out for a small subset of pedigrees, overall the data support the long-held view that MS is a polygenic disorder. It is also likely that primary genetic heterogeneity exists in MS, meaning that different genes can cause identical or similar forms of the disease (Table 19.7).

Table 19.6 MS as a complex genetic disease

<table>
<thead>
<tr>
<th>Etiological heterogeneity</th>
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<tbody>
<tr>
<td>Identical genes, different phenotypes</td>
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<tr>
<td>Genetic heterogeneity</td>
</tr>
<tr>
<td>Different genes, identical phenotypes</td>
</tr>
<tr>
<td>Unknown genetic parameters</td>
</tr>
<tr>
<td>Single versus multiple genes</td>
</tr>
<tr>
<td>Dominant versus recessive mode of inheritance</td>
</tr>
<tr>
<td>Incomplete penetrance</td>
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<tr>
<td>Gene-gene interactions</td>
</tr>
<tr>
<td>Post-genomic mechanisms</td>
</tr>
<tr>
<td>Unidentified non-heritable (environmental) factors</td>
</tr>
</tbody>
</table>

Table 19.7 Model of genetic contributions to MS

| Multiple genes with common allelic variants of small or moderate and cumulative effect |
| No major MS gene or locus with the exception of the MHC |
| Susceptibility versus disease-modifier genes |
| Complex gene-gene and gene-environment interactions |
| Genetic heterogeneity may result in clinical isoforms |

Gene discovery in the post-genomic era

Although genetic components in MS are clearly present, the lack of an obvious and homogeneous mode of transmission has prevented the application of classical genetic epidemiological techniques. Statistical techniques to identify disease loci have been available since the 1950s, however, only recently have newer techniques been applied to the problem of detecting susceptibility loci (Fig. 19.6). A reasonable approach for gene discovery in complex disorders involves first determining the chromosomal region of the genomic effect by linkage analysis. The establishment of genetic linkage requires the collection of pedigrees with more than one affected member to track the inheritance of
discrete chromosomal segments that deviate from independent segregation and co-segregate with the disease. Once these regions have been identified and confirmed,

**Fig. 19.6 Methods of genetic analysis.**

a narrow and well-defined list of candidate genes can be compiled for analysis, even in the absence of a unifying model of pathogenesis. The early success of this approach with complex traits such as the discovery of the role of \( APOE \) in late-onset Alzheimer’s disease\(^{[168]} \) and the availability of detailed maps of highly polymorphic markers (i.e. microsatellites) for all chromosomes, powered the rationale for the wide application of this method in non-mendelian disorders. The potential of genetic mapping for gene identification in complex diseases was highlighted in a study of type 2 diabetes.\(^{[169]} \) The investigators followed original linkage data that implicated the distal long arm of chromosome 2 and identified a disease-associated intronic polymorphism in calpain-10, a ubiquitously expressed member of the calpain-like cysteine protease family. The identification in 1996 of a locus linked to Crohn’s disease on chromosome 16 resulted in the recent identification of a frameshift mutation in \( NOD2 \), a member of the Apaf-1/Ced-4 super-family of apoptosis regulators, associated with disease susceptibility.\(^{[170,171]} \)

Genetic studies in MS in the 1990s were influenced by three large multi-stage whole genome screens performed in multiply affected families ascertained in the USA, UK, and Canada.\(^{[172–174]} \) A fourth study concentrated on a genetically isolated region of Finland but was based on a small number of families.\(^{[175]} \) Follow-up screenings in confirmatory and additional data sets have been completed as well.\(^{[176–179]} \) The studies taken together identified about 60 genomic regions with potential involvement in MS, but total or even
predominant replication between the different screens was absent. This was in part due to
the strategy of reporting all ‘hits’ suggestive of linkage, recognizing that false-positive
results will be generated along with the true-positive results. It is also possible that the
study design in each case underestimated the confounding influence of disease
heterogeneity and the limitations of parametric methods of statistical analysis. It should
be noted, however, that because each study used a somewhat overlapping but different set
of genetic markers and different clinical inclusion criteria, direct comparison of results is
not straightforward.

Nevertheless, a detailed analysis of the composite published data identified 13
common regions of interest among the four original genomic scans (Table 19.8). In
addition, a formal meta-analysis of the published data singled out discrete overlapping
MS-susceptibility regions on chromosomes 5, 6, 17, and 19. Recently, raw
genotyping data from the genome screens was pooled to conduct a global
metaanalysis. A total of eight regions had cumulative positive (but modest) scores,
including the 17q11 and 6p21 segments. A second type of meta-analysis attempted to
cluster autoimmune-susceptibility loci from a comparison of the linkage results from 23
human and experimental immune-mediated diseases, including MS and EAE. Overlapping of susceptibility loci was detected, suggesting that, in some cases, part of the
pathophysiology of clinically distinct autoimmune disorders may be controlled by a
common set of genes.

Although further work is necessary to define better the complete roster of MS loci,
these studies represent real progress in mapping the full set of MS-associated genes. The
next step is to explore systematically the degree of variability, primarily in coding but
also in regulatory and intronic regions, in genes mapped to the candidate regions for
direct association with disease (see Fig. 19.6). Single-nucleotide polymorphisms (SNPs)
are the most frequently found DNA

Table 19.8 Regions of overlap between whole
genome scans in MS

<table>
<thead>
<tr>
<th>US*</th>
<th>UK†</th>
<th>Canada‡</th>
<th>Finland§</th>
</tr>
</thead>
<tbody>
<tr>
<td>3q22–q24</td>
<td>3q22–q24</td>
<td>3q22–q24</td>
<td></td>
</tr>
<tr>
<td>4q31–qter</td>
<td>4q31–qter</td>
<td>5p14–p12</td>
<td>5p14–p22</td>
</tr>
<tr>
<td>5q13–q23</td>
<td>5q12–q13</td>
<td>5q12–q13</td>
<td></td>
</tr>
<tr>
<td>6p21</td>
<td>6p21</td>
<td>6p21 (LD)</td>
<td>6p21</td>
</tr>
<tr>
<td>6q27</td>
<td>6q22–q27</td>
<td>7q21–q22</td>
<td></td>
</tr>
<tr>
<td>7q11–q22</td>
<td>17q22</td>
<td>17q22–q24</td>
<td></td>
</tr>
<tr>
<td>18p11</td>
<td>18p11</td>
<td>19q13</td>
<td></td>
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<tr>
<td>19q13</td>
<td>19q12–q13</td>
<td>19q13</td>
<td></td>
</tr>
</tbody>
</table>

*52 families, 81 affected sib-pairs, 58 affected relative pairs
†129 families, 143 affected sib-pairs, 0 affected relative pairs
‡61 families, 100 affected sib-pairs, 0 affected relative pairs
sequence variation events in the human genome (on average 1 per 1000 or 2000 bases). SNPs are thought to represent old and stable mutations evenly distributed throughout the entire genome. These characteristics make them good markers for genetic studies.\cite{183} In addition, although most SNPs are most likely neutral, some may contribute to disease susceptibility or resistance and may directly mark the ‘causative’ sequence difference. Studies will require large collections of multiplex or nuclear families, or well-matched cases and control groups. Key to the success of the proposed studies will be the availability of rapid, reliable, non-labor-intensive methods for high-throughput polymorphism screening. In all likelihood, the use of phenotypic (clinical and paraclinical), epidemiological, and demographic variables will assume increasing importance as stratifying elements in order to address the fundamental question of genotype-phenotype correlation in autoimmune demyelination. These studies will be necessarily linked to the development of novel mathematical formulations designed to identify modest genetic effects, as well as interactions between multiple genes and interactions between genetic, clinical, and environmental factors.

**MS1, the major histocompatibility complex**

The HLA-DR2 haplotype (DRB1*1501 DQB1*0602) within the MHC on the short arm of chromosome 6 is the strongest genetic effect identified in MS, and has consistently demonstrated both linkage and association in family and case-control studies.\cite{177,184} MHC class I and class II molecules are polymorphic cell-surface glycoproteins whose primary role in an immune response is to display and present short antigenic peptide fragments to peptide or MHC-specific CD4\(^+\) and CD8\(^+\) T cells, which can then become activated by a second stimulatory signal and initiate an immune response. In addition, MHC molecules on stromal cells in the thymus during development help to determine the specificity of the mature T cell repertoire. The human MHC (the HLA system) consists of linked gene clusters located at 6p21.3, spanning almost 4 million base pairs (Fig. 19.7). Many of the HLA genes are highly polymorphic, resulting in the generation of enormously diverse numbers of different genotypic combinations or haplotypes. The polymorphic residues that define an HLA allele are clustered in the antigen-peptide-binding groove of the molecule. Hence, the ability to respond to an antigen, whether foreign or self, and the nature of that response, is to a large extent, determined by the unique amino acid sequences of HLA alleles, an observation that provided the rationale for focusing on associations between HLA genotypes and susceptibility to autoimmune disease.\cite{185}

The mechanism(s) underlying the genetic association of HLA-DRB1*1501-DQA1*0102-DQB1*0602 with MS are not yet fully understood. One possibility is that these MHC molecules fail to negatively select (i.e. to delete) autoreactive T cells within the embryonic thymic microenvironment. Alternatively, HLA-DRA1*0101-DRB1*1501 or DQA1*0102-DQB1*0602 genes may encode class II recognition molecules with a propensity to bind peptide antigens of myelin and to stimulate encephalitogenic T cells. The HLA-DR\(\alpha\)0101-DR\(\beta\)1501 heterodimer binds with high affinity to the myelin basic protein (MBP) 89–98 peptide. X-ray crystallography of the DR-MBP peptide complex
reveals a DRβ1501 structure different from other DRβ molecules in that aromatic residues are preferred in the P4 pocket of the peptide binding domain (Fig. 19.7).\textsuperscript{[186,187]} In addition, it was found that two peptide side chains of the p85–99 MBP immunodominant peptide—Val89 and Phe92—are the primary anchors and account for the high-affinity binding of the MBP peptide to HLA-Drα0101/DRβ1501. The structural analysis also revealed that only two primary T-cell receptor contact residues of MBP p85–99 had to be conserved to stimulate antigen-specific clones properly.\textsuperscript{[188]} The data increase the likelihood that microbial peptides with only limited sequence identity with a self-peptide could well activate autoreactive T cells. Using family data, Haines and collaborators estimated the proportion of the total λs explained by the HLA-DR locus. At the upper end, under a multiplicative genetic model and assuming a λs of 15, the HLA-DR association can explain as much as 60% of the genetic etiology of MS. At the lower end, under an additive model and assuming a λs of 40, it could explain as little as 17%.\textsuperscript{[177]} Overall, the available data indicate that although the MHC region plays the most important role in MS susceptibility, much of the genetic effect in MS remains to be explained.

**MS2, chromosome 19q13**

Chromosome 19q13 has been of consistent interest since the first description of positive linkage results in 1993.\textsuperscript{[189]} Genomic screens have shown some support for linkage to this region (Table 19.8), and a meta-analysis of all four genomic screens identified 19q13 as the second most significant region after the MHC.\textsuperscript{[180]} Additional evidence for this region came from allelic association studies\textsuperscript{[190,191]} and, more recently, from follow-up analyses by the authors’ group.\textsuperscript{[192]} On the basis of this study, the effect of the 19q13 locus is likely to be small, with an estimated locus-specific λs of 1.5, thus accounting for 4–6% of the overall genetic component in MS. As with most complex diseases, the data are not entirely consistent; not all studies have shown
Fig. 19.7 The 6p21–23 region and MS. The full sequence of the MHC region has been completed and reported by the MHC sequencing consortium in 1999. From 224 identified loci, 128 are predicted to be expressed and about 40% to have immune-response functions. The diagram shows the relative positions of class I and II loci involved in antigen presentation. Other genes mapped in the MHC region include complement proteins, genes for the 21-hydroxylase, tumor necrosis factor and heat-shock proteins,
collectively known as class III. Given the extended linkage disequilibrium in this region, the detected association with the HLA-DR2 allele could also represent disequilibrium with a susceptibility allele at another locus in the extended 6p21 segment. The graphic representation of the crystal structure is a top view of HLA-DRA*0101, DRB*1501 in complex with a putative MS auto-antigen, the myelin basic protein peptide 86–99.

evidence of linkage, and association results were based on polymorphisms in different markers.

This region contains many attractive candidate genes. The well-documented involvement of APOE in neurological disease, for example, makes this gene an interesting candidate for MS studies. The apoE protein has long been associated with regeneration of axons and myelin after lesions of central and peripheral nervous tissue, and its isoforms have been shown to have differential effects on neuronal growth. Additional suggestive candidate genes include TGF-β1, immunoglobulin-like transcripts, killer cell inhibitory receptors, the leukocyte-associated inhibitory receptors, the Fc receptor, IL-11, the heavy chain of the MHC class I-like Fc receptor, and APOC4.

**Locus heterogeneity**

Locus heterogeneity, meaning that different genes can cause identical or similar forms of the disease, is a key element for the understanding of MS pathogenesis. In a recent analysis of 184 rigorously ascertained families in the USA with more than one affected member, linkage and association to the HLA-DR locus, and a strong association with the specific DR2 haplotype were observed (Table 19.9). Remarkably, all of the linkage information and evidence for association

<table>
<thead>
<tr>
<th>Max Lod Score (linkage)</th>
<th>PDT (association)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>All families</td>
<td>3.80</td>
</tr>
<tr>
<td>DR2-positive families</td>
<td>4.62</td>
</tr>
<tr>
<td>DR2-negative families</td>
<td>−0.03</td>
</tr>
</tbody>
</table>
is derived from families in which DR2 was present in at least one nuclear member. No genetic effect of the HLA-DR locus could be discerned in the DR2-negative family set. In fact, the results exclude linkage for at least 20 cM around HLA-DR in the DR2-negative families for both autosomal-dominant and -recessive models. These data provide strong evidence that heterogeneity at the HLA locus exists in MS and suggest a fundamentally different disease mechanism in the DR2-negative families without discernible genetic influence of other DR alleles or HLA genes. On the other hand, a recent report describes evidence of positive linkage in DR2 negative MS families. [196]

Another example of heterogeneity in MS is provided by studies in Japanese patients. In this group, one form of MS is apparently characterized by disseminated CNS involvement and is associated with the HLA-DR2 haplotype, whereas more restricted forms of disease in which optic nerve and or spinal cord involvement predominate are not associated with DR2; lesions in the non-DR2-associated condition are frequently more severe and necrotizing than in the disseminated form. [197] The strength of the association between primary progressive MS and DR2 is also uncertain. A number of small studies failed to show any association between primary progressive MS and DR2, although a more recent larger study from Northern Ireland appeared to show the association. [198] The implications of heterogeneity are considerable because they may reflect fundamentally distinct immunopathogenic mechanisms. The pharmacogenomic consequences of HLA locus heterogeneity in MS are also important and could potentially explain individual differences in treatment response to glatiramer acetate, a molecular mimic of a region of myelin basic protein that is immunodominant in HLA-DR2 positive patients. [199] Whether the genotype dictates different forms of MS in response to a common causative agent or trigger, or whether the genotype reflects different diseases with different environmental causes is not known. Clearly, however, clinical and demographic variables will assume critical importance as stratifying elements for genetic studies in MS.

**Susceptibility genes versus modifiers**

Clinical symptoms in MS are extremely variable. The course may be relapsing-remitting or progressive, or severe or mild, and it may involve the neuraxis in a widespread fashion or predominantly affect the spinal cord and optic nerve. Very little is known about the underlying cause of disease variability in MS. For example, the MHC locus has consistently demonstrated both association and linkage with MS in case-control and family studies; however, the role of a gene within this region in determining clinical features or subtypes of MS remains unclear. The HLA-DRB1*1501–DQA1*0102–DQB1*0602 haplotype has been variously reported to be associated with lower age at onset, the patient’s sex, severe disease, relapsing-remitting courses, and mild disease, or to have no influence. [200,201] In EAE it appears that MHC genes primarily influence susceptibility and penetrance, whereas other loci modulate specific phenotypes such as location in brain or spinal cord, demyelination, and severity of inflammation. [202] By analogy, it will be of interest to identify which loci are involved in the initial pathogenic events or influence the development and progression of the disease.

Several studies have reported an association between the APOE-4 allele and more severe disease. [203–206] Another study reported some evidence for a protective effect of the APOE-2 allele, observing that the time to reach secondary progression for patients whose
initial disease type was relapsing-remitting was significantly longer for APOE-2/3 genotypes than for APOE-3/3 and APOE-3/4 genotypes. Some biological support for the APOE-4 association with disease progression was suggested by an MRI investigation, which revealed more extensive tissue destruction or less efficient repair in APOE-4 carriers with MS. In the authors’ data set, it was observed that the proportion of APOE-4 carriers was significantly higher in the severe disease group than in the non-severe group (Fig. 19.8). On the other hand, the proportion of APOE-2 carriers was significantly higher in the mild disease group than the non-mild group. Several studies examining the influence of other non-HLA genes (IL-1R, TNF, TGFB, CTLA4, and CCR5 among others) on disease course and severity in MS have been reported and await confirmation. Their characterization will help to define the basic etiology of the disease, improve risk assessment, and influence therapeutics.

**Fig. 19.8** Comparison of APOE genotypes for severe and non-severe MS. p-values from PROC GENMOD, using logistic regression with correction for familial correlations and adjustment for age of onset, sex, and DR2 status. Odds ratio of severe MS for APOE-4 carriers: 2.67 (95% CI 1.12–6.36, p=0.03); reference group APOE-3/3 genotype.
The promise of pharmacogenomics

The benefit of available MS treatments is partial, and a substantial number of patients are non-responders. Side effects have been also experienced by many patients, inconvenience is significant, and the cost of the drugs is substantial. Hence, in the absence of predictive clinical, neuroradiological, or immunological markers of treatment response, and given that 10–15% of patients have relatively benign forms of the disease, neurologists are often uncertain when to initiate or terminate treatment. The field of ‘pharmacogenomics’ focuses on genetic polymorphisms and how this translates into inherited differences in response to drug treatment. Several genomic variants in drug receptors, metabolizing enzymes, transporters, and targets have been linked to inter-individual differences in efficacy and toxicity of many medications. Genetic factors operating at the level of the disease pathway may also have an important role in the differential response of patients to therapeutic modalities. For example, pharmacogenetic studies have established that ApoE-4 not only correlates with an elevated risk of developing Alzheimer’s disease, but also predicts poor response to cholinesterase inhibitor treatment. In MS, the pharmacogenomic literature is relatively sparse, but a substantial effort is currently under way in different laboratories to address directly the question of genetic heterogeneity and the response to immunotherapy by analysis of the correlation between different genotypes and clinical response to therapeutic modalities.

ACKNOWLEDGMENTS

The authors are supported by the National Multiple Sclerosis Society, the National Institutes of Health, and the Nancy Davis and Sandler Foundations. SEB is a National Multiple Sclerosis Society post-doctoral fellow.

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III
Clinical trials of disease-modifying therapy
Interferons in relapsing-remitting and secondary progressive multiple sclerosis

Ludwig Kappos

BACKGROUND

It was 35 years after the first description of interferons as antiviral agents by Isaacs and Lindenmann in 1957[1] and 12 years after the first successful therapeutic trial of interferon for multiple sclerosis (MS)[2-4] that the first interferon (interferon beta-1b) was approved for treatment of MS in 1993.[5,6] Since that time, three different interferon beta products have been introduced in the market for treatment of relapsing-remitting MS and to some extent also secondary progressive MS in nearly all countries of the world. Interferon beta now has a key role in the management of MS patients. The available evidence on the mode of action of interferons in MS, their efficacy on clinical and laboratory measures, and current knowledge about their emerging differential indication are reviewed in this chapter.

MODE OF ACTION

Interferons are pleiotropic molecules with a wide range of pro- and anti-proliferative, pro- and anti-apoptotic, antiviral and complex immunoregulatory activities. While first attempts to use interferons as therapeutic agents in MS were based on their antiviral effect,[2] attention has subsequently focused on their immunomodulatory and to some extent their anti-proliferative effects.[7-10] After a first trial with interferon gamma demonstrated a sharp increase of exacerbations[11] (most probably related to up-regulation of major histocompatibility complex (MHC) molecule expression, which facilitates antigen presentation and thereby augments and accelerates immune responses), type II interferons were abandoned as MS therapeutics. Type I interferons (interferon alpha and interferon beta) share components of the same receptor. They are produced by almost all mammalian cells upon stimulation. They trigger the synthesis of many host cell proteins that contribute to the inhibition of viral replication, and they are believed to mediate most of the biological effects of interferons. Like interferon gamma, type I interferons increase expression of MHC class I and thereby enhance the ability of virus-infected cells to present viral peptides to CD8+ T cells. In contrast to interferon gamma, type I interferons do not induce but rather suppress the synthesis of MHC class II proteins. Apart from the inhibition of MHC class II expression interferon beta has been shown to up-regulate expression of interleukin (IL)-10. This has also been shown in myelin basic protein
(MBP)-specific CD4+ T-cell lines, where in addition both proliferation and production of lymphotoxin is suppressed. Another important aspect of interferon activity is inhibition of T-cell migration across basement membranes in vitro, owing to decrease of secretion of matrix-degrading enzymes (metalloproteases).\[^{12}\] This is believed to be pertinent for the fast suppression of inflammation as depicted by reduced numbers of enhancing on magnetic resonance imaging lesions (MRI) or cell counts in the cerebrospinal fluid after interferon treatment. Additional mechanisms include increase in soluble vascular cell adhesion molecule (VCAM-1) and down-regulation of its corresponding partner adhesion molecule, very late activation antigen (VLA-4).\[^{13}\] Numerous other effects, especially of interferon beta, have been described (Table 20.1).\[^{9,12,14–34}\] Inhibition of T-cell proliferation, different immunomodulatory effects on microglia, reduction of circulating CD8+ T cells and B cells, stimulation of nerve growth factor (NGF) production by astrocytes, inhibition of human glial inducible nitric oxide synthase, inhibition of mitogeninduced astrocyte proliferation, and many more. Because interferon alpha and beta bind to the same receptor, similar effects would be expected in MS. However, they bind at different sites of the receptor and induction of signalling by interferon alpha requires the simultaneous binding to both the interferon receptor α and β chains. These differences could translate into different clinical effects and side effects. Small studies have suggested similar effects of interferon alpha and interferon beta on relapse rates.\[^{35–37}\] Experience in other diseases such as hepatitis or in oncology suggests a higher incidence of encephalopathic side effects as well as moderate to severe reversible hair loss with interferon alpha.

In summary, the beneficial effects of interferon beta in MS are believed to be mainly related to its anti-inflammatory effect, based on reduced MHC class II expression, shift of cytokine production from T helper cell type 1 (Th1) profile to T helper cell type 2 (Th2) profile, and direct effects preserving the integrity of the blood-brain barrier.

**CLINICAL EVIDENCE OF EFFICACY**

The rationale, design and key results of phase I, II and the pivotal phase III studies with interferon beta in relapsing-remitting MS have been comprehensively reviewed in the first edition of this book\[^{38}\] and are summarized in Chapter 34. In the meantime, additional evidence has accumulated concerning efficacy of interferon beta in secondary progressive MS, longer-term observations of patients included in the pivotal trials, and attempts to compare different products directly in prospective controlled or observational studies. Some evidence of efficacy has been presented,\[^{14}\] but the results of two phase II studies with interferon beta in primary progressive MS (ref. 39, Montalban, personal communication 2002) await peer reviewed publication. In addition, two placebo-controlled studies have addressed the efficacy of interferon beta once weekly after the first clinical event suggestive of MS (see ‘Treatment of clinically isolated syndromes’). With the extended observations in controlled trials, but also with widespread open-label use of interferon beta, more evidence has accumulated about the side-effect profile and especially the frequency and possible impact of neutralizing antibodies to interferon. This chapter addresses many of these newer findings related to interferon beta in MS. The trials are summarized in Tables 20.2–20.4.\[^{5,6,40–64}\]
Table 20.1 Effects of interferon beta on the immune system

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reported effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC class I expression</td>
<td>Increased</td>
</tr>
<tr>
<td>MHC class II expression</td>
<td>Increased/decreased/no change</td>
</tr>
<tr>
<td>B7–1 expression (B cells)</td>
<td>Decreased$^{[14]}$</td>
</tr>
<tr>
<td>B7–2 expression (macrophages)</td>
<td>Increased$^{[14]}$</td>
</tr>
<tr>
<td>CD40 expression (T cells, B cells; monocytes)</td>
<td>Decreased; increased$^{[14]}$</td>
</tr>
<tr>
<td>CD40 ligand expression (T cells)</td>
<td>Decreased$^{[15]}$</td>
</tr>
<tr>
<td>FcR expression, phagocytosis, antibody-dependent cellular cytotoxicity</td>
<td>Increased</td>
</tr>
<tr>
<td>(macrophages)</td>
<td></td>
</tr>
<tr>
<td>Antigen presentation</td>
<td>Increased/decreased</td>
</tr>
<tr>
<td>(macrophages/microglia)</td>
<td></td>
</tr>
<tr>
<td>Proliferation (T cells)</td>
<td>Decreased/increased</td>
</tr>
<tr>
<td>Apoptosis (T cells)</td>
<td>Decreased/increased$^{[16-21]}$</td>
</tr>
<tr>
<td>Fas expression (T cells)</td>
<td>Increased$^{[22]}$</td>
</tr>
<tr>
<td>Cytotoxic T-cell function</td>
<td>Increased</td>
</tr>
<tr>
<td>Production of complement-fixing antibody isotypes (B cells)</td>
<td>Increased</td>
</tr>
<tr>
<td>Dendritic cell maturation</td>
<td>Increased</td>
</tr>
<tr>
<td>Natural killer cell numbers</td>
<td>Decreased$^{[23]}$</td>
</tr>
<tr>
<td>Complement activation</td>
<td>Increased initially</td>
</tr>
<tr>
<td>Adhesion molecule expression (T cells, endothelial cells)</td>
<td>Decreased$^{[24]}$</td>
</tr>
<tr>
<td>Matrix metalloproteinase-9 activity (T cells)</td>
<td>Decreased$^{[12]}$</td>
</tr>
<tr>
<td>Tissue inhibitor of matrix metalloproteinase expression (T cells)</td>
<td>Increased$^{[25]}$</td>
</tr>
<tr>
<td>Interleukin-2 production (T cells)</td>
<td>Increased</td>
</tr>
<tr>
<td>Interleukin-2 receptor expression (T cells)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Interferon-γ production (T cells, natural killer cells)</td>
<td>Increased/decreased$^{[26,27]}$</td>
</tr>
<tr>
<td>Interleukin-4 production (PBMCs, T cells)</td>
<td>Increased</td>
</tr>
<tr>
<td>Lymphotoxin production (T cells)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Interleukin-1 production (macrophages)</td>
<td>Increased</td>
</tr>
<tr>
<td>Interleukin-1 receptor antagonist production (macrophages)</td>
<td>Increased$^{[28]}$</td>
</tr>
<tr>
<td>Transforming growth factor-β production (PBMCs)</td>
<td>Increased</td>
</tr>
<tr>
<td>Tumour necrosis factor-α production (macrophages/microglia)</td>
<td>I Increased/decreased</td>
</tr>
<tr>
<td>RANTES, macrophage inflammatory protein-1α expression (T cells)</td>
<td>Decreased$^{[29,30]}$</td>
</tr>
<tr>
<td>CCR5 expression (T cells)</td>
<td>Decreased$^{[29]}$</td>
</tr>
</tbody>
</table>
Prostaglandin E2 production (macrophages) | Decreased
Nitric oxide secretion (macrophages, microglia) | Increased/decreased\[31\]
Interleukin-10 production (T cells) | Increased\[32–34\]
Interleukin-12 production (monocytes/macrophages, DCs) | Decreased\[34\]

Adapted from Karp CL et al.\[9\]

PBMC, peripheral blood mononuclear cell; RANTES, regulated upon activity, normal T-cell expressed and secreted (chemokine); DCs, dendritic cells

**IMPACT OF DOSING, FREQUENCY, AND ROUTE OF ADMINISTRATION**

The pivotal trials with interferon beta-1b and interferon beta-1a all recruited patients with established relapsing-remitting MS after a mean duration of disease between 4 and 8 years, who had no or mild disability at entry and relatively high relapse rates (Table 20.2). In these patients the effect on the relapse rate was consistent across studies, with approximately 30% reduction, although some controversy exists about lower rate of relapse reduction in the pivotal interferon beta-1a trial, depending on whether calculations were based on all patients recruited (−18%) or on patients having had the chance to continue treatment for 2 years (−32%).\[38\]

The PRISMS trial, which compared interferon beta-1a 22 µg versus 44 µg three times a week versus placebo over 2 years, while demonstrating clear-cut effects of both doses compared with placebo, failed to show significant dose response on relapse rate and disability progression, although significant dose-related differences between doses were shown for MRI activity and MRI burden of disease.\[30,40–42\] Together with a tendency for better efficacy of the higher dose in most clinical parameters, this raised the possibility that important clinical differences could have been delayed beyond the 2-year follow-up. PRISMS 4 addressed this question.\[43\] Patients completing the 2-year placebo-controlled study were offered entry into another 2-year study. Placebo patients who agreed to participate were randomized to either 22 µg or 44 µg three times a week, while interferon beta-1a-treated patients were assigned the same dose they had in the first 2 years. Ninety percent of the patients originally randomized in PRISMS entered PRISMS 4, and approximately 80% completed the 4-year follow-up. Patients switching from placebo to active treatment had a significant reduction in relapse count, MRI activity and lesion burden accumulation compared with their placebo period. In the high- and low-dose groups the dose effect regarding relapse rates for 4 years approached significance (p=0.069; risk ratio 0.88), favouring the higher dose. Time to sustained disability progression was significantly prolonged over 4 years for the 44 µg group compared with the cross-over group (p=0.047). In an intention-to-treat analysis time to first confirmed expanded disability status scale (EDSS) progression was significantly prolonged (42.1 months) in the 44 µg group compared with 24.2 months for the cross-over group (40th percentile; p=0.047). Time to first confirmed progression did not differ significantly between the 22 µg group (35.9 months) and the cross-over group (p=0.289) or between the 44 µg group and the 22 µg groups (p=0.33). A dose response between 44 µg and 22
µg was observed for time to first progression only in years 3 and 4 (with month 24 reset as baseline).

In summary, results from the 4-year PRISMS study support superiority of early treatment with interferon beta versus delayed treatment and also provided some support for superiority of the higher dose, although relapse rate over 4 years and time to disability progression over 4 years did not reach statistical significance. Differences observed in several secondary clinical and MRI-based measures, all favouring the higher dose, led to the recommendation of 44 µg three times a week as the standard dose for patients treated with this interferon beta-1a product. In spite of higher pricing (approximately 30% more than 22 µg three times a week or other competitors), this standard dose recommendation has been endorsed by most funding agencies.

### Table 20.2 Evidence from pivotal trials with interferon beta in relapsing-remitting MS

<table>
<thead>
<tr>
<th>Populations studied</th>
<th>Interferon beta-1b[^5,^6]</th>
<th>Interferon beta-1a[^40]</th>
<th>Interferon beta-1a[^53,^54]</th>
<th>Interferon beta-1a[^44]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose comparison</td>
<td>8 MIU on alternate days, Placebo</td>
<td>22 µg three times a week, Placebo</td>
<td>44 µg three times a week, Placebo</td>
<td>30 µg once weekly, Placebo</td>
</tr>
<tr>
<td>Duration of disease (mean) years</td>
<td>4.7</td>
<td>3.9</td>
<td>7.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Prior 2-year relapse rate (per year)</td>
<td>1.7</td>
<td>1.8</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>EDSS at entry (mean)</td>
<td>3.0</td>
<td>2.8</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>EDSS range</td>
<td>0–5.5</td>
<td>0–5.0</td>
<td>1–3.5</td>
<td>2–5.5</td>
</tr>
</tbody>
</table>

**Duration of follow-up: numbers of patients continuing in active treatment arm**

<table>
<thead>
<tr>
<th>Interferon beta-1b[^52]</th>
<th>Interferon beta-1a[^43]</th>
<th>Interferon beta-1a[^54]</th>
<th>Interferon beta-1a[^46]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 MIU on alternate days, 22 µg three times a week, 44 µg three times a week</td>
<td>30 µg once weekly, 30 µg once weekly, 60 µg once weekly</td>
<td>30 µg once weekly, 60 µg once weekly</td>
<td></td>
</tr>
</tbody>
</table>
The European interferon beta-1a Dose Comparison Study\textsuperscript{[44,46]} was planned and conducted to determine whether 60 µg intramuscularly once weekly could improve upon the efficacy of 30 µg interferon beta-1a intramuscularly in reducing the rate of sustained disability progression in patients with relapsing MS (Table 20.4). As compared with the pivotal trials with interferon, patients included in this study had a higher EDSS at entry (mean 3.6), 40% were in the EDSS range of 4.0–5.5, and 15% in each group were within 6 months of switching into secondary progressive disease. After 3 years, 81% of the 402 patients randomized to 30 µg and 82% of those randomized to 60 µg were still on the study. No significant dose response was detected for the primary endpoint (time to disability progression, confirmed after 6 months). In both groups the proportion of subjects with progression of disability by 36 months, estimated from Kaplan-Meier curves, was 37%. No dose effects were observed on any of the secondary clinical endpoints, including relapses, number of corticosteroid treatments, change in nine-hole peg test, and others. Only one MRI measure at one time point, number of new or enlarging T2 lesions at 36 months compared with 24 months, showed a difference favouring the 60 µg dose. Both doses were well tolerated, although slightly higher incidence of flu-like symptoms and muscle weakness was observed in the 60 µg group. The incidence of neutralizing antibodies was 2.3% in the 30 µg and 5.8% in the 60 µg group. Four-year follow-up is now available for more than 60% of the patients initially recruited (not all centres participating during year 4) and supports the findings at year 3.\textsuperscript{[46]}

The comparative trial of interferon beta-1a (Rebif\textsuperscript{®} 44 µg subcutaneously three times a week versus interferon beta-1a (Avonex\textsuperscript{®} 30 µg once weekly intramuscularly (EVIDENCE study) was designed to show superiority of the higher and more frequent dose over once-weekly intramuscular interferon beta-1a over a period of 24 weeks with an extension for a total of 48 weeks.\textsuperscript{[47,48]} A total of 339 patients with relapsing-remitting MS were randomized to the subcutaneous treatment and 338 to the intramuscular treatment. Owing to the different routes and frequency of administration, treatment was not blinded for patients and their treating physicians. A second physician, not involved in the care of the patients, was responsible for assessment of relapses and neurological impairment and disability. After 24 weeks a significant difference favouring the
A separate study (INCOMIN), initiated by Italian investigators with the support of the Italian MS Society compared interferon beta-1b 8 MIU subcutaneously on alternate days with interferon beta-1a 30 µg intramuscularly once weekly over a period of 2 years. Patients with relapsing-remitting disease were randomized to one of the two treatment arms and followed prospectively by clinical evaluations every 3 months and by MRI assessment every year for 24 months. No effort was made to blind patients and treating or evaluating physicians, but the MRI scans were analysed in the study’s lead and coordinating centre without knowledge of treatment assignment. A total of 94 of 96 subjects assigned to the subcutaneous treatment and 88 of 92 of those assigned to the intramuscular treatment had a complete clinical 2-year follow-up. The annualized relapse-rate in the subcutaneous group was 0.5, corresponding to a 76% reduction versus baseline, while it was 0.7 in the intramuscular group, representing a 37% reduction versus baseline. Forty-nine percent of patients in the subcutaneous group and 64% of patients in the intramuscular group had at least one relapse, 14% and 30%, respectively, had progression by one or more steps in the EDSS for more than 3 months and confirmed at 24 months. Forty-nine percent of the subcutaneous group and 75% of the intramuscular group had active scans (scans with new or enlarging T2 or gadolinium-enhancing lesions). Interestingly, in this study differences favouring interferon beta-1b on relapse rate and disability progression increased with the duration of the trial. This finding of increasing superiority over time contrasted with findings in the EVIDENCE trial. Taking into account that the study was not blinded, part of this effect might also be due to increasing bias, since the results of the first year analysis had been presented while the study was still ongoing.

An observational open-label study comparing patients assigned to treatment with interferon beta-1b 8 MIU subcutaneously on alternate days, interferon beta-1a 30 µg intramuscularly once weekly, glatiramer acetate 20 µg daily or no treatment was published by Khan et al. No blinding was attempted, and the criteria for treatment allocation to different groups were not clearly defined. Eighteen months of follow-up was available for approximately 80% of the patients in each group. Significant reductions of annualized relapse rates versus baseline were reported for the interferon beta-1b group (−54%) and the glatiramer acetate group (−60%), while the reduction (−29%) in the interferon beta-1a group did not reach significance. Patients without treatment had no
change in relapse rates. Owing to the relatively low number of subjects and the non-
randomized, open-label design, the results are difficult to interpret.

A population based study from Denmark was recently presented—all Danish patients
with relapsing-remitting MS applying for interferon beta treatment between June 1996
and November 1997 were asked to participate in a randomized, open-label observational
study (KochHenriksen, personal communication). If they agreed, they were randomly
assigned to interferon beta-1a 22 µg subcutaneously once weekly (n=143) or to interferon
beta-1b 8 MIU subcutaneously on alternate days (n=160). Those who were unwilling to
be randomized were treated with interferon beta-1b 8 MIU subcutaneously on alternate
days (n=125). Totals of 76%, 72% and 63% of the patients in these treatment groups,
respectively, completed a 24-month follow-up. The annualized relapse rate in the three
groups was 0.70, 0.71 and 0.84, respectively, representing a 55%, 53% and 39%
reduction versus baseline, respectively. Reasons for drop-out were more commonly side
effects in the 8 MIU groups and lack of efficacy in the 22 µg once-weekly group. Annual
MRI scans were also performed, but these results and full publication of the study are not
yet available. The open-label design and limited information on methodological details
make study interpretation difficult.

Several other observational studies have been reported at scientific meetings, but not
fully published. Trojano and co-workers in Southern Italy followed patients treated with
interferon beta-1b or interferon beta-1a in the approved dosage in their centres for up to 2
years (personal communication). A total of 209 of 234 patients in the interferon beta-1b
group and 169 of 217 in the interferon beta-1a group were available for 2-year follow-up.
Fifty-one percent of the interferon beta-1b patients and 67% of the interferon beta-1a
patients had one or more relapses during this 2-year treatment period; the respective
reduction of the annualized relapse rate was 52% and 39% in the first year, and 54% and
46% over 2 years.

In conclusion, available data on direct head-to-head comparisons of the three
interferon products show that doubling the dose of once-weekly interferon beta-1a does
not add to the efficacy of the drug. Through observation periods of 4 years, higher doses
of frequently applied subcutaneous interferon beta have advantages of more rapid onset
and more pronounced suppression of disease activity. However, results indicate a ceiling
effect related to dose response. It remains to be seen whether the shape of the dose-
response curve is different in different patients with MS, in different disease courses, or
in different phases of disease evolution. Regarding direct comparison of frequent versus
weekly interferon dosing, available data from both the re-analysis of the pivotal trials and
the head-to-head studies support a more rapid onset and most probably more pronounced
effect of frequent subcutaneous dosing over once-weekly intramuscular dosing. This
advantage is not consistent across studies, and the true magnitude and clinical importance
is still matter of debate.

STUDIES IN SECONDARY PROGRESSIVE MS

As discussed above, the pivotal trials of interferons included patients with relapsing-
remitting disease and relatively mild impairment or disability (Table 20.2). Four large
controlled trials have studied the effects of interferon beta in more disabled patients in the
secondary progressive phase of the disease. Key data on baseline variables, study conduct, and main study results are summarized in Tables 20.3 and 20.5.

The first reported study, the European Secondary Progressive MS (EUSPMS) trial, comparing 8 MIU interferon beta-1b subcutaneously on alternate days with placebo, found a highly significant effect on the primary endpoint, time to disability progression by ≥1 step in the EDSS, confirmed after 3 months. In the active treatment group, progression was delayed by 9–12 months. The effect was equally apparent across disability grades (EDSS 2.5–6.5), and in patients with or without superimposed relapses. Positive results were found for the time to become wheelchair-bound, relapse rate and relapse severity, number of corticosteroid treatments and hospital admissions, as well as on measures of quality of life and neuropsychological deficits. Statistically significant but modest clinical effects were accompanied by pronounced benefits on MRI measures of inflammation. MRI markers of tissue destruction (atrophy of brain and spinal cord and magnetization transfer histograms) were studied in smaller subgroups and did not show statistically significant treatment effects. The only exception was T1-weighted scan hypointensities (‘black holes’), where a significant treatment effect was shown. Recently published data of the final analysis of the European Secondary Progressive MS study confirmed the original results.

A second trial with interferon beta-1b, conducted in North America (NASPMS) and including a third arm with body surface-adapted doses (5 MIU/m² on alternate days), another study with interferon beta-1a comparing subcutaneous doses of 22 µg and 44 µg three times weekly with placebo (SPECTRIMS), and another study comparing interferon beta-1a 60 µg once weekly intramuscularly with placebo (IMPACT) failed to demonstrate effects on disability progression measured using the EDSS. In the IMPACT study, EDSS was not the primary endpoint; the primary endpoint for MS-related disability was the Multiple Sclerosis Functional Composite (MSFC) (see chapter 2). Active treatment resulted in significantly lower change in the MSFC compared with placebo (see chapter 21). Looking at the results for the three components of the MSFC, no significant effect was found regarding timed 25-foot walk, and only a tendency in favour of active treatment for the PASAT (Paced Auditory Stimulus Attention Test), a measure of neuropsychological function. The treatment difference was mainly due to results from the nine-hole-peg-test, a measure of arm function. Because the MSFC is new, neurologists have less familiarity with the measure, and the clinical implications of the observed benefits are currently a matter of discussion.

Across all four studies in secondary progressive MS, significant beneficial effects were observed for relapses and markers of inflammatory activity in MRI. Although the studies had very similar inclusion criteria, baseline variables across studies were not identical (see Table 20.5). The European Secondary Progressive MS study recruited younger patients and more patients with relapses superimposed on a progressive course. Only about 30% of this study’s patients were exacerbation-free during the 2 years preceding randomization, compared with 50% for SPECTRIMS, 55% for NASPMS, and about 50% in the IMPACT study. Interestingly, the percentage who were relapse-free during the study was nearly identical in the European and the SPECTRIMS placebo groups (36% versus 37%) but increasingly higher in the NASPMS and IMPACT placebo groups (62% versus 63%) (see Table 20.5). It is unclear whether these remarkable
differences are due to differences in the populations or to differences in the method for defining relapses.

Subgroup analyses from the secondary progressive MS studies suggest that therapeutic benefit in more advanced MS may be limited to patients with certain disease characteristics, although subgroup analyses from the different studies are not entirely consistent. In the initial analysis of the European Secondary Progressive MS study the treatment effect was found in patients with and without relapses, while the SPECTRIMS study provided some indication for a better treatment effect in patients with superimposed relapses. Combined analysis of the European and North American interferon beta-1b secondary progressive MS studies showed that the most robust predictors of a favourable response were relapse activity and greater-than-average EDSS progression in the 2 years preceding inclusion (>1 step in the EDSS). Age,

### Table 20.3 Major randomized controlled studies of interferon beta in MS

<table>
<thead>
<tr>
<th>Effect on exacerbation and MRI lesion rates</th>
<th>Exacerbations</th>
<th>MRI active lesion rate*†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapsing-remitting or early MS</strong></td>
<td><strong>Exacerbations</strong></td>
<td><strong>MRI active lesion rate</strong></td>
</tr>
<tr>
<td><strong>Drug and study</strong></td>
<td><strong>Doses studied</strong></td>
<td><strong>Plac</strong></td>
</tr>
<tr>
<td>Interferon beta-1b [5,6,52]</td>
<td>Placebo, 1.6 MIU, 8 MIU, on alternate days</td>
<td>1.31</td>
</tr>
<tr>
<td>Interferon beta-1a [53-55]</td>
<td>Placebo, 0.82 30 µg, once weekly</td>
<td>0.67</td>
</tr>
<tr>
<td>Interferon beta-1a (CHAMPS) [56]</td>
<td>Placebo, 50% 35% 30 µg, once weekly</td>
<td>0.52</td>
</tr>
<tr>
<td>Interferon beta-1a [40,41] (PRISMS)</td>
<td>Placebo, 1.28 22 µg, 44 µg, three times a week</td>
<td>0.91</td>
</tr>
<tr>
<td>Interferon beta-1a [57,58] (ETOMS)</td>
<td>Placebo, 0.43 22 µg, once weekly</td>
<td>0.33</td>
</tr>
<tr>
<td>Drug and study</td>
<td>Doses studied</td>
<td>Placebo dose</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Interferon beta-1a&lt;sup&gt;[50]&lt;/sup&gt; (OWIMS)</td>
<td>Placebo, 1.08</td>
<td>1.08</td>
</tr>
<tr>
<td>Secondary progressive MS</td>
<td>Exacerbations</td>
<td>MRI active lesion rate&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Interferon beta-1b&lt;sup&gt;[60,63–64]&lt;/sup&gt;</td>
<td>Placebo, 8 MIU, on alternate days</td>
<td>0.57</td>
</tr>
<tr>
<td>Interferon beta-1b&lt;sup&gt;[42]&lt;/sup&gt;</td>
<td>Placebo, 8 MIU, 5 MIU/m&lt;sup&gt;2&lt;/sup&gt;, on alternate days</td>
<td>0.28</td>
</tr>
<tr>
<td>Interferon beta-1a&lt;sup&gt;[45,61]&lt;/sup&gt;</td>
<td>Placebo, 22 µg, 44 µg, three times a week</td>
<td>0.71</td>
</tr>
<tr>
<td>Interferon beta-1a&lt;sup&gt;[62]&lt;/sup&gt;</td>
<td>Placebo, 60 µg, once weekly</td>
<td>0.30</td>
</tr>
</tbody>
</table>
### Treatment effect expressed as relative rates versus placebo

<table>
<thead>
<tr>
<th>Drug and study</th>
<th>Doses studied</th>
<th>Exacerbations</th>
<th>MRI active lesion rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interferon dose 1/ placebo</td>
<td>Interferon dose 2/ placebo</td>
<td>Interferon dose 2/ dose 1</td>
</tr>
<tr>
<td>Interferon beta-1b[^5,^6,^52]</td>
<td>Placebo, 0.87</td>
<td>0.69</td>
<td>0.79</td>
</tr>
<tr>
<td>Interferon beta-1a[^53–^55]</td>
<td>Placebo, 0.82</td>
<td>30 µg, once weekly</td>
<td>0.67</td>
</tr>
<tr>
<td>Interferon beta-1a[^56]</td>
<td>Placebo, 0.70</td>
<td>30 µg, once weekly</td>
<td>0.54</td>
</tr>
<tr>
<td>Interferon beta-1a[^40,^41]</td>
<td>Placebo, 0.71</td>
<td>22 µg, 44 µg, three times a week</td>
<td>0.68</td>
</tr>
<tr>
<td>Interferon beta-1a[^57,^58]</td>
<td>Placebo, 0.77</td>
<td>22 µg, once weekly</td>
<td>0.67</td>
</tr>
<tr>
<td>Interferon beta-1a[^59]</td>
<td>Placebo, 1.00</td>
<td>22 µg, 44 µg, three times a week</td>
<td>0.81</td>
</tr>
</tbody>
</table>

### Secondary progressive MS

<table>
<thead>
<tr>
<th>Drug and study</th>
<th>Doses studied</th>
<th>Exacerbations</th>
<th>MRI active lesion rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interferon dose 1/ placebo</td>
<td>Interferon dose 2/ placebo</td>
<td>Interferon dose 2/ dose 1</td>
</tr>
<tr>
<td>Interferon beta-1b[^60,^63,^64]</td>
<td>Placebo, 0.74</td>
<td>8 MIU, on alternate days</td>
<td>0.43</td>
</tr>
<tr>
<td>Interferon beta-1a[^50]</td>
<td>Placebo, 0.71</td>
<td>8 MIU,</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Interferon Placebo, 0.70 MIU/m² on alternate days
Interferon beta-1a 22 µg, 44 µg three times a week
Interferon Placebo, 0.67 MIU/m² on weekly

Table 20.4 Studies comparing different products, doses, frequencies, and routes of administration of interferon beta

<table>
<thead>
<tr>
<th>Study (Name, sources)</th>
<th>Drug, doses schedule compared</th>
<th>Included/ followed up (n)</th>
<th>Design, duration</th>
<th>Annualized relapse rate (% reduction versus baseline)</th>
<th>Percent with relapses</th>
<th>Percent with confirmed progression</th>
<th>Percent with active scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Dose comparison[44,60]</td>
<td>Interferon beta-1a a 30 µg once weekly intramuscularly versus 60 µg once weekly intramuscularly</td>
<td>402/318 400/316</td>
<td>Double-blind, 36 months</td>
<td>0.77 (−41.0) 0.81 (−37.7)</td>
<td>77 77</td>
<td>29 (2nd year), 37(3rd year) 28 (2nd year), 37(3rd year)</td>
<td>73 (2nd year), 77 (3rd year) 66 (2nd year), 61(3rd year)</td>
</tr>
<tr>
<td>EVIDENCE[47,48]</td>
<td>Interferon beta-1a (Rebif) 44 µg subcutaneously three times a week versus interferon beta-1a a 30 µg intramuscularly</td>
<td>339/331 338/328</td>
<td>(Double)- blind, 24/48 weeks</td>
<td>0.63/0.58 (−55)* 0.85/0.68 (−48)*</td>
<td>25/38 37/48</td>
<td>NA NA</td>
<td>31 (week 0–24), 25 (week 25–48) 51 (week</td>
</tr>
</tbody>
</table>

Modified from Rask et al.[48]

'MRI results based on differing methods between studies, and differing parameters reported in publications (e.g. mean versus median); relative rates calculated from parameters; NA, not available
<table>
<thead>
<tr>
<th>Study</th>
<th>Interferon beta-1b 8 MIU on alternate days</th>
<th>Randomized interferon beta-1a a 30 µg once weekly</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCOMING⁴⁹,⁵⁰</td>
<td>96/94 (week 25–48)</td>
<td>0.5 (−76)</td>
<td>49</td>
</tr>
<tr>
<td>Danish trial Koch-Henriksen N, (personal communication)</td>
<td>160/116 (−76)</td>
<td>0.7 (−37)</td>
<td>64</td>
</tr>
<tr>
<td>Khan et al.⁵¹</td>
<td>33/15 (−76)</td>
<td>1.02 (−3)</td>
<td>93</td>
</tr>
<tr>
<td>South Italian trial (Trojano M, personal communication)</td>
<td>234/209 (−76)</td>
<td>(−52/−54)</td>
<td>61</td>
</tr>
</tbody>
</table>
Table 20.5 Four studies of interfered beta in secondary progressive MS: baseline data and key results

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>EUSP M</th>
<th>SPEC M</th>
<th>NASP M</th>
<th>IMP M</th>
<th>EUSP SPEC TRIMS</th>
<th>NASPMS IMP ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Plac ebo</td>
<td>Placebo Plac ebo 8 MID</td>
<td>Placebo Plac ebo 8 MID</td>
<td>Placebo Plac ebo 8 MID</td>
<td>Placebo Plac ebo 8 MID</td>
<td>Placebo Plac ebo 8 MID</td>
<td>Placebo Plac ebo 8 MID</td>
</tr>
<tr>
<td>n</td>
<td>358</td>
<td>204</td>
<td>308</td>
<td>218</td>
<td>360</td>
<td>209</td>
</tr>
<tr>
<td>% female</td>
<td>64</td>
<td>60</td>
<td>60</td>
<td>64</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>40.9</td>
<td>42.7</td>
<td>47.6</td>
<td>47.9</td>
<td>41.1</td>
<td>43.1</td>
</tr>
<tr>
<td>Mean EDSS</td>
<td>5.2</td>
<td>5.4</td>
<td>5.1</td>
<td>5.2</td>
<td>5.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Disease duration (since diagnosis)</td>
<td>13.4</td>
<td>13.7</td>
<td>14.9</td>
<td>10.5</td>
<td>12.8</td>
<td>13.3</td>
</tr>
<tr>
<td>Duration of secondary progressive phase</td>
<td>3.8</td>
<td>4.1</td>
<td>4.1</td>
<td>NA</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Exacerbation free (%)</td>
<td>28.2</td>
<td>52</td>
<td>56</td>
<td>44</td>
<td>31.9</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>Lost to follow-up (%)</th>
<th>Discontintued treatment (%)</th>
<th>Blinding (patients) (%)</th>
<th>Blinding (EDSS-Physicians)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.7</td>
<td>27.1</td>
<td>54</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>9.3</td>
<td>15.6</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>10.4</td>
<td>24.4</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>24.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>25.0</td>
<td>66</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>7.7</td>
<td>17.7</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>21.1</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>13.9</td>
<td>24.9</td>
<td>51</td>
<td>7</td>
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<td></td>
<td>8.9</td>
<td>23.9</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>13.3</td>
<td>28.1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>65</td>
<td>37</td>
<td>27</td>
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<td>---------------------------</td>
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<td>-----</td>
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</tr>
<tr>
<td>Confirmed progression (%)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation-free (%)</td>
<td>36</td>
<td>37</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Median time to first relapse (days)</td>
<td>385</td>
<td>281</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>No MRI activity (new and enlarging 12 lesions) (%)</td>
<td>16</td>
<td>24</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Median change in T2 volume (%)</td>
<td>9.7</td>
<td>10.0</td>
<td>10.9</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>56–58,67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values for previous 3/1 years</td>
<td></td>
</tr>
<tr>
<td>Correct guesses about assigned treatment (%)</td>
<td></td>
</tr>
<tr>
<td>NR, not reached; NA, not available</td>
<td></td>
</tr>
<tr>
<td>*p&lt;0.05–0.001</td>
<td></td>
</tr>
<tr>
<td>§Confirmed at 3 months: EUSPMS, SPECTRIMS; at 6 months: NASPMS, IMPACT</td>
<td></td>
</tr>
</tbody>
</table>

duration of MS, baseline EDSS values, and MRI parameters such as T2 lesion load and gadolinium-enhancing lesions were less consistently associated with therapeutic effect in secondary progressive MS (McFarland and Kappos, in preparation). The reason for reduced efficacy in secondary progressive MS compared with relapsing-remitting MS is not completely clear: accumulating evidence shows that inflammation is less important as a pathogenic mechanism in the later phases of the disease; in addition, destructive and degenerative processes, induced by (autoimmune) inflammation, could continue at least for several months or years after inflammation is turned down. Therefore, a putative stabilizing effect may be detectable only with prolonged follow-up. Well-controlled, long-term follow-up studies have not been feasible up to now, and purely observational studies without real control groups may yield uninterpretable results.

TREATMENT OF CLINICALLY ISOLATED SYNDROMES

Two studies have addressed the effects of interferon beta-1a, initiated at the time of a first clinical demyelinating event (Tables 20.3 and 20.6).[56–58,67] In the study by Jacobs et al. (CHAMPS), 383 patients who had a first acute clinical demyelinating event were randomized to receive weekly injections of interferon beta-1a 30 µg or placebo after initial treatment with high-dose corticosteroids.[56] During follow-up of up to 2 years, the cumulative probability of developing clinically definite MS was significantly lower in the interferon beta-1a group than the placebo group (rate ratio, 0.56; 95% CI 0.38–0.81; p=0.002). Compared with the placebo group, the interferon beta-1a group had a significant reduction in the volume of T2-weighted MRI brain lesions, fewer new or
enlarging T2 lesions, and fewer gadolinium-enhancing lesions at 18 months (see Table 20.3). In a study reported by Comi and colleagues (ETOMS) patients who had had a first episode of neurological dysfunction suggesting MS within the previous 3 months and brain MRI findings suggesting MS were randomized either to interferon beta-1a 22 µg subcutaneously once weekly or placebo.\cite{57,58} Seventy-eight percent of 308 randomized patients received study treatment for 2 years, and 90% were evaluable at study termination. Fewer patients developed clinically definite MS in the interferon group than in the placebo group (34% versus 45%; \(p=0.047\)). The time at which 30% of patients had converted to clinically definite MS was 569 days in the interferon group and 252 days in the placebo group (\(p=0.034\)).

Both studies show that interferon beta-1a treatment at an early stage of MS has significant positive effects on clinical and MRI outcomes. Although reassuring, the results of these two double-blind controlled studies leave certain issues open. First, does delay of the second demyelinating event have an impact on long-term disability progression? Second, can patients at the highest risk of progression to clinically definite MS, or of disease-related disability be defined at the onset? Subgroup analyses identified the number of T2 lesions at the initial scan (nine or more in CHAMPS,\cite{67} eight or more in ETOMS\cite{57}) and the presence of at least one gadolinium-enhancing lesion at baseline (both studies) as the most robust prognostic marker for rapid progression to clinically definite MS. In ETOMS, patients with polysymptomatic onset had a higher risk of developing MS; such patients

### Table 20.6 Comparison of two studies in patients with a first episode suggestive of MS

<table>
<thead>
<tr>
<th></th>
<th>ETOMS\cite{57,58}</th>
<th>CHAMPS\cite{56}</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>309</td>
<td>383</td>
</tr>
<tr>
<td>Mean age</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>% female</td>
<td>64</td>
<td>75</td>
</tr>
<tr>
<td>Time from first symptoms to interferon treatment (mean)</td>
<td>79 days</td>
<td>20 days</td>
</tr>
<tr>
<td>Polysymptomatic onset (%)</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Optic neuritis (%)</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Brain stem or cerebellum involvement (%)</td>
<td>29</td>
<td>28.5</td>
</tr>
<tr>
<td>Spinal cord involvement (%)</td>
<td>27</td>
<td>21.5</td>
</tr>
<tr>
<td>Gadolinium-enhancing lesions on T1-weighted MRI at onset</td>
<td>59</td>
<td>29*</td>
</tr>
</tbody>
</table>
Interferons in relapsing-remitting and secondary progressive

<table>
<thead>
<tr>
<th>Treated with corticosteroids for first episode (%)</th>
<th>70</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon, dosage, route</td>
<td>Interferon beta-1a, 22 µg once weekly, subcutaneously</td>
<td>Interferon beta-1a, 30 µg once weekly intramuscularly</td>
</tr>
</tbody>
</table>

*All patients treated with high-dose corticosteroids were not included in CHAMPS. In ETOMS, severity of first relapse was found to be a negative prognostic factor. Long-term observation of patients included in these two studies as well as the results of an ongoing study of early intervention with interferon beta-1b, 8 MIU on alternate days versus placebo (‘BENEFIT’), planned to provide individual follow-up periods of up to 5 years, will, it is hoped, provide further critical information related to prognostic markers and the significance of early treatment.

**ADVERSE EVENT PROFILE**

When starting treatment approximately 70–80% of patients experience flu-like symptoms, including fever, myalgia, headache, fatigue, and chills. These side effects start approximately 3–4 hours after injection and improve spontaneously within 24 hours. Symptoms have been related to up-regulation of inflammatory cytokines such as IL-6, tumour necrosis factor (TNF)-α and even interferon (IFN)-γ. In more than 80% of patients, flu-like symptoms lessen or entirely resolve during the first 2–3 months of treatment. Gradual stepwise increase in dose and concurrent use of non-steroidal anti-inflammatory drugs or low-dose corticosteroids lessens side effects during the initial months of therapy. Less than 20% of patients need continuing treatment with non-steroidal anti-inflammatory drugs beyond the initial months of interferon beta therapy. Skin reactions occur in more than 50% of patients after subcutaneous administration of interferon beta. Skin necrosis has been reported in up to 5% of patients with subcutaneous injection in the clinical trials. Skin reactions and necrosis have not been reported with intramuscular injection. Meticulous instructions in injection technique, frequent change of injection site, local cooling, and avoiding of excessive exposure to sunlight may reduce skin reactions after subcutaneous injection.

**NEUTRALIZING ANTIBODIES**

Neutralizing antibodies (see chapter 34) have been observed in MS patients treated with interferon beta-1b and interferon beta-1a. A number of reports have addressed their impact on a variety of outcome measures, most suggesting some attenuation of treatment effects. However, it is difficult to draw definite conclusions on the incidence and clinical significance of neutralizing antibody positivity based on available data, especially in light of differences in assay methods, definitions of positivity, sampling rates, and patient populations. The reported frequencies of neutralizing antibody in controlled studies are given in Table 20.7. The lower incidence of neutralizing antibodies
with interferon beta-1a in all but the pivotal trial has been explained by a different manufacturing procedure and less aggregate formation. Antibody formation may also be dependent on the route of administration and dosage.\(^{[73–75]}\) Guidelines for physicians with patients on interferon beta have stated that decisions on treatment should be based on clinical grounds alone.\(^{[76]}\) In the pivotal study of interferon beta-1b in relapsing-remitting MS, neutralizing antibody status was determined in serum drawn every 3 months.\(^{[70]}\) In neutralizing antibody-positive patients, an attenuation of treatment effects was reported with respect to relapse rates, and the T2 lesion load in serial MRIs from month 18 onwards, but mean scores on the EDSS showed a trend toward worsening only among those patients without neutralizing antibodies. Data were then analysed with a more reliable assay, based on the induction of the MXA protein. More sophisticated statistical methods\(^{[77,78]}\) addressed the question of whether change in neutralizing antibody positivity and

<table>
<thead>
<tr>
<th>Table 20.7 Rate of patients with neutralizing antibodies (%)</th>
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<tr>
<td>Interferon beta-1a 30 µg once weekly intramuscularly(^{[71]})</td>
</tr>
<tr>
<td>Interferon beta-1a a 30 µg once weekly intramuscularly(^{[44]})</td>
</tr>
<tr>
<td>Interferon beta-1a 60 µg once weekly intramuscularly(^{[44]})</td>
</tr>
<tr>
<td>Interferon beta-1a 60 µg once weekly intramuscularly(^{[62]})</td>
</tr>
<tr>
<td>Interferon beta-1a 22 µg once weekly subcutaneously(^{[59]})</td>
</tr>
<tr>
<td>Interferon beta-1a 44 µg once weekly subcutaneously(^{[59]})</td>
</tr>
<tr>
<td>Interferon beta-1a 22 µg three times weekly subcutaneously(^{[40,41]})</td>
</tr>
<tr>
<td>Interferon beta-1a 442 µg three times weekly subcutaneously(^{[40,41]})</td>
</tr>
<tr>
<td>Interferon beta-1a 22 µg three times weekly subcutaneously(^{[61]})</td>
</tr>
<tr>
<td>Interferon beta-1a 442 µg three times weekly subcutaneously(^{[61]})</td>
</tr>
<tr>
<td>Interferon beta-1b 8 MIU every other day subcutaneously(^{[70]})</td>
</tr>
<tr>
<td>Interferon beta-1b 8 MIU every other day subcutaneously(^{[60,79]})</td>
</tr>
</tbody>
</table>

negativity during treatment was associated with diminished efficacy. This approach, in which neutralizing antibody-negative and -positive periods are compared within individual patients, did not show a neutralizing antibody-associated attenuation of efficacy for the registered dose of 8 MIU on relapse rates, EDSS or MRI measures. Only
in the cross-sectional analysis was the effect on the rate of relapses attenuated by neutralizing antibodies (Petkau et al, submitted). The two studies with interferon beta-1a also demonstrated trends toward reduced treatment effect on relapses and on MRI activity in neutralizing antibody-positive patients. While only a weak trend was described for the intramuscular interferon beta-1a trial, in the PRISMS 4-year analysis an effect of neutralizing antibody positivity on relapse rates and MRI parameters was described from the third year on treatment. Up to now, no study has demonstrated an effect of neutralizing antibody positivity on disability progression. Recent data in the European Secondary Progressive MS study showed varying effects of neutralizing antibodies on relapse rates, depending on the statistical approach and definition of positivity, but no effect on disability progression. A substantial proportion of neutralizing antibody-positive patients seems to become neutralizing antibody-negative. In a subgroup of participants in the interferon beta-1b pivotal trial, neutralizing antibodies had disappeared at year 10 of treatment. In conclusion, although there are some indications that high titre neutralizing antibody activity has a negative impact on treatment efficacy with respect to relapses and MRI measures of inflammatory activity, it is generally recommended that treatment decisions should be primarily based on clinical grounds.

USE OF INTERFERON BETA IN DAILY PRACTICE—IS THERE A CONSENSUS?

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines recently summarized the available evidence on interferon beta in MS (Table 20.8). There is little to be added to this consensus statement. All three interferons are effective in reducing relapse rate and severity in relapsing-remitting MS patients. In patients with average relapse rates of approximately one per year or two per 3 years, most neurologists would initiate treatment. In patients with less frequent relapses and minimal evidence of disease progression by MRI, the issue is more controversial, with a clear tendency in the last years to extend the indication for treatment. The same is the case for clinically isolated syndromes, in which evidence from two controlled trials supports efficacy of once-weekly interferon. Owing to lack of data on the long-term impact of such treatment, reimbursement for treatment at the time of the clinically isolated syndrome is provided only in a few countries. Recently, the European Commission has recommended reimbursement of once weekly intramuscular interferon beta-1a for patients with a clinically isolated syndrome and more than nine T2-lesions, one of them gadolinium-enhancing, in view of the higher probability of conversion into clinically definite MS in this subgroup of patients.

In very active relapsing MS and where an early effect is mandatory, frequent and higher doses may be preferable. In treatment failures, defined by unchanged relapse rate or accumulating disability, switching from lower dose to higher dose interferons is an option, if systemic side effects of the interferon are not an issue. In such cases, neu-
Table 20.8 Recommendations of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology[81]

1. On the basis of several consistent class I studies, interferon beta has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with MS or with clinically isolated syndromes who are at high risk of developing MS (type A recommendation). Treatment of MS with interferon beta produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression (type B recommendation).

2. As a result, it is appropriate to consider interferon beta for treatment in any patient who is at high risk of developing clinically definite MS, or who already has relapsing-remitting MS or secondary progressive MS and is still experiencing relapses (type A recommendation). The effectiveness of interferon beta in patients with secondary progressive MS but without relapses is uncertain (type U recommendation).

3. It is possible that certain populations of MS patients (e.g. those with more attacks or at earlier disease stages) may be better candidates for therapy than others, although at the moment, there is insufficient evidence regarding these issues (type U recommendation).

4. On the basis of class I and II studies and several pieces of consistent class III evidence, it is considered probable that there is a dose-response curve associated with the use of interferon beta for the treatment of MS (type B recommendation). It is possible, however, that a portion of this apparent dose effect instead may be due to differences in the frequency of interferon beta administration (rather than dose) between studies.

5. On the basis of several class II studies, the route of administration of interferon beta is probably not of clinical importance, at least with regard to efficacy (type B recommendation). The side effect profile, however, does differ between routes of administration. There is no known clinical difference between the different types of interferon beta, although this has not been thoroughly studied (type U recommendation).

6. On the basis of several class I studies, treatment of patients with MS with interferon beta is associated with the production of neutralizing antibodies (type A recommendation). The rate of neutralizing antibody production, however, is probably less with interferon beta-1a treatment than with interferon beta-1b treatment (type B recommendation). The biological effect of neutralizing antibodies is uncertain, although their presence may be associated with a reduction in clinical effectiveness of interferon beta treatment (type C recommendation). Whether there is a difference in immunogenicity between subcutaneous and intramuscular routes of administration is unknown (type U recommendation). The clinical utility of measuring neutralizing antibodies in a patient on interferon beta therapy is uncertain (type U recommendation).
tralizing antibodies against interferon beta should be measured, and if positive, another
disease-modifying compound (glatiramer acetate or an immunosuppressant) may be
preferable. In view of the lower immunogenicity of interferon beta-1a some authors
recommend switching to this treatment after a ‘wash-out’ of 2–3 months.[76] In secondary
progressive disease, treatment with interferon beta seems justified in patients with
additional relapses or evidence of rapid progression of disability, if side effects of
treatment have minor or no impact on the patients’ every day life. Interferon beta-1b has
been approved for this indication in the European Union, and interferon beta-1a three
times a week has been approved in some countries for secondary progressive MS patients
with superimposed relapses. No indication exists for interferon beta treatment in primary
progressive MS.

Ongoing research, including long-term followup of patients participating in controlled
trials and long-term observational studies, if supplemented by sophisticated MRI and
pharmacogenetic studies, using cutting-edge technologies such as cDNA, microarray and
quantitative polymerase chain reaction, will, it is hoped, enlighten our future treatment
decisions by helping to identify responders and non-responders to interferon beta and
expanding our knowledge of the effects of interferon treatment treatment.[82]

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Interferons in secondary progressive multiple sclerosis
Ruth Ann Marrie and Jeffrey A Cohen

INTRODUCTION
Approximately 85% of multiple sclerosis (MS) patients present with a relapsing-remitting course, in which there are acute relapses followed by partial or complete recovery. By definition, clinical manifestations are stable between relapses. In most patients, the course eventually evolves into gradual progression with or without superimposed relapses, minor remissions and plateaus, termed secondary progressive MS. The transition from relapsing-remitting MS to secondary progressive MS is typically rather insidious and occurs over several years. Secondary progressive MS has been distinguished from primary progressive MS, in which patients exhibit gradual worsening from disease onset without relapses (see chapter 35). In primary progressive MS, the patients tend to have an older age of onset, and relatively more men are affected. Magnetic resonance imaging (MRI) demonstrates fewer and less distinct cerebral lesions, a paucity of new lesions over time despite increasing disability, and less gadolinium enhancement.

At the onset of MS, factors predictive of the development of progressive disease include male sex, older age at onset, motor symptoms, polyregional onset, and incomplete remission after first relapse. After 5 years, a high neurologic deficit, the number of affected functional systems, the degree of remission from the last relapse, and the occurrence of polyregional symptoms with the last relapse predict development of progressive disease. However, the predictive ability of these factors, either individually or in combination, is weak. Also, absence of these poor prognostic factors is a weak predictor of a good prognosis. Rather, there is a steady increase in the proportion of patients who convert from relapsing-remitting MS to secondary progressive MS with increasing disease duration. After 10 years, over 50% of patients with initially relapsing-remitting disease develop secondary progressive MS. After 25 years, 90% of patients have converted to secondary progressive MS. Secondary progressive MS is the phase of MS in which significant disability tends to accumulate. The median times from onset of a progressive course to reach a particular Kurtzke expanded disability status score (EDSS) were 1.40 years to a score of 3, 4.50 years to a score of 6, and 24.08 years to a score of 8.

As expected, MRI demonstrates greater evidence of tissue damage in secondary progressive MS than in relapsing-remitting MS, although there is substantial overlap between the two populations. There is a greater total lesion load in secondary progressive MS than relapsing—remitting MS, particularly in the periventricular region, and the lesions are more confluent. The burden of lesions with imaging characteristics thought...
to indicate tissue destruction (e.g. lesion hypointensity on T1-weighted images,[8] reduced levels of the neuronal marker N-acetylaspartate (NAA),[9] and reduced magnetization transfer[10]), is greater in patients with secondary progressive MS as a group. A variety of advanced imaging techniques have also shown widespread abnormality in normal-appearing white matter in MS patients, including T1 and T2 relaxation times,[11] magnetic resonance spectroscopy,[12–17] magnetization transfer imaging,[18–20] and diffusion tensor imaging.[21,22] In patients as a group, the severity and extent of these abnormalities are greater in secondary progressive MS than in relapsing-remitting MS. Global measures of pathology, including cerebral atrophy,[23–25] whole-brain magnetization transfer ratio histograms,[7] NAA,[26] and whole-brain diffusion magnetic resonance histograms,[27] also show greater abnormality in secondary progressive MS. The accumulation of destructive pathology, particularly axonal damage, is thought to account for progressive disability in later stages of MS.[28,29]

The clinical and MRI features of MS that are thought to reflect inflammation most directly continue as patients change from relapsing-remitting MS to secondary progressive MS, although these features become less prominent as disease duration increases. Relapses become less frequent and less distinct.[30] Gadolinium-enhancing lesions are seen on serial MRI in patients with secondary progressive MS as they are in relapsing-remitting MS, but less frequently.[31] More gadolinium-enhancing lesions are seen when there are continued relapses.[32] In the large follow-up study carried out by Confavreux et al.,[33] once patients developed gait impairment, disability progressed at the same rate whether patients had secondary progressive MS with superimposed relapses, secondary progressive MS without superimposed relapses, or primary progressive MS, suggesting that the mechanisms that produce acute relapses and gradual disability progression are distinct. The observations that disability progresses despite decreasing indications of inflammation has led to the hypothesis that MS becomes largely a neurodegenerative disease in its later stages.[34] It remains unclear whether the progressive axonal destruction that is apparently out of proportion to inflammation is due to increased sensitivity of compromised or demyelinated axons to any ongoing inflammation, loss of trophic support, or susceptibility of metabolically challenged (possibly also compromised) neurons attempting to fulfill the function of previously lost neurons.

The immunologic abnormalities in relapsing-remitting MS and secondary progressive MS largely overlap. However, a large variety of immunologic differences between relapsing—remitting MS and secondary progressive MS have been described. For example, patients with secondary progressive MS have been reported to have elevated levels of tumor necrosis factor-α in cerebrospinal fluid more frequently.[35] The pattern of chemokine receptor expression on peripheral blood T cells has been reported to differ, with a significantly higher proportion of cells expressing CCR2 and a lower proportion expressing CCR5 in secondary progressive MS than in relapsing-remitting MS.[36] In secondary progressive MS, T cells can be isolated that are able to act as antigen-presenting cells and to express co-stimulatory molecules.[37,38] These cells are resistant to inhibitory regulation.[37] Proteolipid peptide-specific T-cell clones that are resistant to glucocorticoid-induced apoptosis in vitro have also been demonstrated in secondary progressive MS.[39] Fas (CD95)-triggered programmed cell death in T cells has been reported to be defective in MS patients compared with controls and lower in patients with
progressive MS as compared with those with relapsing-remitting MS.\textsuperscript{[40]} In models of chronic experimental allergic encephalomyelitis, epitope spreading has been shown to occur.\textsuperscript{[41]} Similar epitope spreading has been shown to occur in MS patients, with increasing diversity over time. Thus, it is unclear whether there is a fundamental immunopathologic difference between relapsing-remitting MS and secondary progressive MS, and if so whether the difference is the cause of evolution to a progressive course or merely reflects the chronicity of the immunopathologic process.

**ASSESSMENT OF TREATMENT BENEFIT IN SECONDARY PROGRESSIVE MS**

In clinical trials in relapsing-remitting MS, treatment benefit has been shown most readily using measures of relapses and MRI activity. In secondary progressive MS there are fewer relapses than in relapsing-remitting MS, and MRI demonstrates a greater lesion load and less disease activity. The increasing dissociation between inflammatory activity and progression of impairment and disability makes it more difficult to detect a benefit of treatment. The focus must shift to the effects on progression of impairment and disability.

The most frequently used clinical measure of impairment and disability has been the EDSS.\textsuperscript{[42]} As discussed in Chapters 1 and 2, the EDSS has been criticized because of its poor reliability, suboptimal metric properties, and overemphasis on ambulation in its middle range.\textsuperscript{[43–45]} These issues decrease the responsiveness of the scale and its ability to detect treatment effects in clinical trials. The deficiencies of the EDSS become more problematic in the range represented by subjects in trials of secondary progressive MS.

These concerns led to the development of the Multiple Sclerosis Functional Composite (MSFC), which comprises three component tests:\textsuperscript{[46,47]}

- leg function and ambulation (timed 25-foot walk);
- arm function (nine-hole peg test); and
- cognition (Paced Auditory Serial Addition Test with a three second interstimulus interval, PASAT3).

Anticipated advantages of the MSFC over the EDSS include the following:

1. Throughout the range of MS severity, the MSFC covers cognition, arm function, and ambulation. Measures of vision are under development.
2. The component measures of the MSFC are non-redundant (correlations between the components are modest).
3. The MSFC is practical; it can be administered by a trained technician in 10–15 minutes.
4. The metric properties of the MSFC are advantageous by virtue of being a continuous rather than ordinal scale.
5. The MSFC has been shown to have excellent intra- and inter-rater reliability, substantially greater than that of the EDSS.
6. The MSFC is more sensitive to change and treatment effects than the EDSS.
7. The MSFC has been validated against the EDSS, lesion load and cerebral atrophy on MRI, patient self-report health status, and quality of life. In particular, the predictive validity of the MSFC appears to be greater.
The MSFC was first used as the pre-defined primary outcome measure in the phase III trial of interferon beta-1a in secondary progressive MS discussed below. Experience in that trial confirmed many of the anticipated advantages of the MSFC.

RATIONAL FOR USE OF INTERFERON BETA IN SECONDARY PROGRESSIVE MS

Three forms of interferon beta have been approved in the USA, Canada, and Europe for the treatment of relapsing-remitting MS: interferon beta-1b, intramuscular interferon beta-1a, and subcutaneous interferon beta-1a. Although a large number of biologic effects of interferon beta in vitro and in vivo have been identified (see chapters 19 and 22), the mechanisms of action responsible for the clinical benefit of interferon beta in relapsing-remitting MS remain uncertain.

To the extent that there is overlap between immunopathogenic mechanisms in relapsing-remitting MS and secondary progressive MS, interferon beta should continue to be effective in later stages of the disease. Conversely, the existence of potential immunopathogenic differences in secondary progressive MS as compared with relapsing-remitting MS would be expected to limit the effectiveness of interferon beta (e.g. the decreased role of inflammatory mechanisms sensitive to interferon beta, decreased sensitivity of interferon beta-susceptible immune mechanisms (i.e. ‘resistance’), increased role of degeneration). Patients with advanced MS would potentially be expected to be less able to tolerate side effects of interferon beta. As discussed above, the outcome measures used in MS clinical trials perform less well in more advanced stages of the disease. Finally, greater pre-existing tissue damage may make any further damage (reflecting the partial efficacy of these agents) more apparent. The net result is that the general sense has been that it is more difficult to demonstrate benefit of treatment in secondary progressive MS (see Table 21.1).

PHASE III TRIALS OF INTERFERON BETA IN SECONDARY PROGRESSIVE MS

There have been four phase III trials of interferon beta in secondary progressive MS: the European Study Group on Interferon beta-1b in Secondary Progressive MS (Eu IFNβ1-b), the North American Study Group on Interferon beta-1b in Secondary Progressive MS (NA IFNβ1-b), the Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS), and the International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial of IFNβ-1a (IMPACT). The design and results of these studies are summarized in Tables 21.2 and 21.3.

European study of interferon beta-1b

The Eu IFNβ1-b study enrolled 718 subjects with clinically definite or laboratory-supported MS at 32 European centers. Secondary progression was defined as a period of
deterioration independent of relapses sustained for at least 6 months that followed relapsing-remitting MS.

<table>
<thead>
<tr>
<th>Table 21.1 Putative factors impeding demonstration of treatment benefit in secondary progressive MS</th>
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<tbody>
<tr>
<td>Greater sensitivity to medication side effects</td>
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<tr>
<td>More pre-existing tissue damage and less repair make any ongoing damage more clinically apparent</td>
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<tr>
<td>Greater MRI lesion burden</td>
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<tr>
<td>More cerebral and spinal cord atrophy</td>
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<tr>
<td>Greater axonal loss with comparable lesion burden</td>
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<tr>
<td>New inflammatory activity is more likely to result in increased tissue damage</td>
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<tr>
<td>Decreased sensitivity to immunotherapy</td>
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<tr>
<td>Increasing pathogenic complexity (e.g. antigen spreading or recruitment of additional effector mechanisms)</td>
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<tr>
<td>Decreased sensitivity of susceptible mechanisms to treatment (<code>resistance</code>)</td>
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<tr>
<td>Decreasing role of inflammation</td>
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<tr>
<td>Increasing role of degeneration</td>
</tr>
<tr>
<td>Decreased sensitivity of traditional endpoints</td>
</tr>
<tr>
<td>Relapses</td>
</tr>
<tr>
<td>Fewer in number</td>
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<tr>
<td>Less distinct</td>
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<tr>
<td>Impairment and disability</td>
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<tr>
<td>Gradual change</td>
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<tr>
<td>Decreased responsiveness of scales, particularly EDSS</td>
</tr>
<tr>
<td>MRI</td>
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<tr>
<td>Fewer Gadolinium-enhancing or new or enlarging lesions</td>
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<tr>
<td>Greater pre-existing lesion burden limits ability to detect accrual</td>
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</table>

Patients were 18–55 years old, with EDSS of 3.0–6.5, and a history either of two or more relapses or of an increase of 1 point or more on EDSS in the previous 2 years. Exclusion criteria included previous immunosuppressive or immunomodulatory treatment. The design was block randomized, multicenter, double-blind, and placebo-controlled. Subjects received 0.5 ml (4 MIU) interferon beta-1b or placebo subcutaneously every other day for 2 weeks, which was then increased to 1.0ml (8 MIU). An interim analysis was planned at 24 months and ultimately led to the study being terminated early because of efficacy.

The primary outcome measure was time from baseline to the first scheduled quarterly visit at which the EDSS increased by ≥1.0 point (≥0.5 points for EDSS 6.0–6.5), required to be sustained at the next scheduled visit 3 months later. Other clinical outcome measures included time to becoming wheelchair-bound, proportion of patients with confirmed progression, proportion of patients becoming wheelchair-bound, EDSS at the endpoint, annual relapse rate, time to first relapse, and proportion of patients with
moderate or severe relapses. MRI measures included total T2 volume and change on annual scans. A subgroup of 125 patients had monthly gadolinium-enhanced MRIs.

The treatment groups were well matched at

**Table 21.2 Phase III studies of interferon beta in secondary progressive MS and study design characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Eu IFNβ1-b</th>
<th>NA IFNβ1-b</th>
<th>SPECTRIMS IMPACT</th>
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<td>Randomized</td>
<td>Randomized</td>
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<tr>
<td></td>
<td>Double-blind</td>
<td>Double-blind</td>
<td>Double-blind</td>
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<tr>
<td></td>
<td>Placebo-controlled</td>
<td>Placebo-controlled</td>
<td>Placebo-controlled</td>
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<tr>
<td><strong>Centers</strong></td>
<td>32</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>718</td>
<td>939</td>
<td>618</td>
</tr>
<tr>
<td><strong>Entry criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definite MS</td>
<td>Definite MS</td>
<td>Definite MS</td>
</tr>
<tr>
<td></td>
<td>Secondary progressive course</td>
<td>Secondary progressive course</td>
<td>Secondary progressive course</td>
</tr>
<tr>
<td></td>
<td>Age 18–55</td>
<td>Age 18–65</td>
<td>Age 18–55</td>
</tr>
<tr>
<td></td>
<td>EDSS 3.0–6.5</td>
<td>EDSS 3.0–6.5</td>
<td>EDSS 3.0–6.5</td>
</tr>
<tr>
<td></td>
<td>≥2 relapses or EDSS increase of ≥1.0 step in previous 2 years</td>
<td>EDSS increase ≥1.0 step in previous 2 years</td>
<td>Functional System Score ≥2 EDSS increase ≥1.0 step in previous 2 years</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Interferon beta-1b 8 MIU</td>
<td>Interferon beta-1b 8 MIU</td>
<td>Interferon beta-1a a 44 µg</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Interferon beta-1b 5 MIU/m²</td>
<td>Interferon beta-1a a 22 pig</td>
</tr>
<tr>
<td></td>
<td>Subcutaneously on alternate days</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneously on alternate days</td>
<td>Subcutaneously three times a week</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Time to EDSS progression: 1.0 step for EDSS 3.0–5.5 or 0.5 step for EDSS 6.0–6.5 sustained for 3 months</td>
<td>Time to EDSS progression: 1.0 step for EDSS 3.0–5.5 or 0.5 step for EDSS 5.5–6.5 sustained for 3 months</td>
<td>Time to EDSS progression: 1.0 step for EDSS 3.0–5.0 or 0.5 step for EDSS 5.5–6.5 sustained for 3 months</td>
</tr>
</tbody>
</table>

2-year change in MSFC
Table 21.3 Phase III studies of interferon beta in secondary progressive MS and baseline characteristics and results

<table>
<thead>
<tr>
<th></th>
<th>Eu IFNβ1-b</th>
<th>NA IFNβ1-b</th>
<th>SPECTRIMS</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>41</td>
<td>47</td>
<td>42.8</td>
<td>47.6</td>
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<tr>
<td>Mean MS duration (years)</td>
<td>13.1</td>
<td>14.7</td>
<td>13.3</td>
<td>16.5</td>
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<tr>
<td>Mean pre-study relapse rate (per year)</td>
<td>0.87 (2 years)</td>
<td>0.41 (2 years)</td>
<td>0.45 (2 years)</td>
<td>0.47 (3 years)</td>
</tr>
<tr>
<td>Mean baseline EDSS</td>
<td>5.1</td>
<td>5.1</td>
<td>5.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Mean placebo on-study relapse rate (per year)</td>
<td>0.64</td>
<td>0.28</td>
<td>0.71</td>
<td>0.30</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Positive (EDSS)</td>
<td>Negative (EDSS)</td>
<td>Negative (EDSS)</td>
<td>Positive (MSFC)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Relapses T2 lesion burden</td>
<td>Relapses T2 lesion burden</td>
<td>Relapses T2 lesion burden</td>
<td>Relapses T2 lesion burden</td>
</tr>
<tr>
<td>Positive</td>
<td>New or enlarging T2 lesions</td>
<td>Gadolinium-enhancing lesions</td>
<td>New or enlarging T2 lesions</td>
<td>Gadolinium-enhancing lesions</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life EDSS</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Baseline. A total of 57 patients discontinued from the study, approximately equally in the treatment and placebo groups, and for similar reasons. Treatment was stopped in 130 patients, but follow-up was maintained. Significantly more subjects discontinued interferon beta-1b because of adverse events and non-compliance, while significantly more subjects discontinued placebo because of perceived worsening. The trial was stopped after a planned interim analysis at 24 months demonstrated a consistent treatment benefit across a number of endpoints. At that point, mean follow-up was 892 days in the placebo group and 901 days in the interferon beta-1b group, representing approximately 85% of the anticipated EDSS data for a planned 3-year study.

Benefit was demonstrated in favor of interferon beta-1b on the primary outcome, time to confirmed EDSS progression ($p=0.0008$). There was a relative reduction of 21.7% in...
the proportion of patients with progression, with a treatment effect detectable after 9 months ($p=0.059$) that became significant after 12 months ($p=0.003$). The time to becoming wheelchair-bound was delayed (odds ratio 0.66, 95% CI 0.47–0.93). Mean annual relapse rate was reduced by 31% in the interferon beta-1b group ($p=0.002$), and time to first relapse was prolonged from a median of 403 days to 644 days ($p=0.003$).

Baseline total T2 lesion volume was similar in the placebo and treatment groups. Significant benefit favoring interferon beta-1b was seen at year 1, year 2, and year 3; at the last scan benefit was seen for absolute change and percentage change from baseline in total lesion volume. There was an increase of 15% from baseline to last scan in the placebo group and a reduction of 2% in the interferon beta-1b group. There was a significant reduction in the number of new or enlarging T2 lesions in the interferon beta-1b group at all annual time points compared with placebo.

In general, interferon beta-1b was well-tolerated. Adverse events seen more frequently in the active treatment arm included injection-site reactions, constitutional symptoms, muscle hypertonia, hypertension, and abnormal values of liver enzymes and white blood cell counts. Overall, 27.8% of interferon beta-1b-treated subjects were positive at some point for antiinterferon beta neutralizing antibodies.

Subsequent analysis using the data set at study termination confirmed the previously reported findings. Post hoc analysis showed treatment effects were greater in patients who had had two or more relapses in the 2 years before the study (although not in those with relapses versus those without) and in those with $>1.0$ point change in EDSS in the 2 years before the study, longer disease duration, and longer time since evidence of disease progression. There was no effect relating to the sex of the patients.

**North American study of interferon beta-1b**

The NA IFNβ1-b study\textsuperscript{[53]} has been presented at meetings but has not yet been published in detail. This study enrolled 939 subjects from 35 centers with clinically definite MS for 2 or more years, a progressive course for 6 or more months, an increase in EDSS of 1 or more points during the 2 years before the study, age 18–65, and EDSS of 3.0–6.5. The study was randomized, doubleblind, and placebo-controlled. Subjects were randomized to receive either interferon beta-1b 8 MIU, interferon beta-1b 5 MIU/m$^2$, or placebo subcutaneously every other day for 3 years. Clinical evaluations occurred every 12 weeks for 3 years. MRI was done at baseline and annually for all patients. A subgroup of 163 patients had MRI every 4 weeks.

The primary outcome measure was time to neurologic progression defined as an increase of $\geq1.0$ EDSS point over baseline for EDSS of 3.0–5.5 or $\geq0.5$ EDSS points for EDSS of 6.0–6.5, sustained for 6 months. Other outcomes included annual relapse rate, mean change from baseline in EDSS score, change in a composite neuropsychologic score, MRI activity, and MRI lesion burden (T2 lesion area).

The three groups were balanced for demographic and baseline clinical parameters. There was no significant difference between the treatment groups in time to confirmed EDSS progression ($p=0.71$). This result was unaffected by the presence or absence of relapses during the 2 years before the study or during the study. Secondary clinical and MRI endpoints did demonstrate a benefit of treatment. There was a reduction in annual relapse rate by 43% in the 8 MIU group ($p=0.004$) and 29% in the 5 MIU/m$^2$ group.
Both treatment groups showed effects on median percentage change in lesion area on T2-weighted MRI \((p=0.0001)\). There was an 11% increase in the placebo group with a change of only 0.4% in the 8 MIU group and 0.8% in the 5 MIU/m² group. There was a reduction of 64% in the number of new enhancing lesions in the 8 MIU group \((p=0.03)\), and of 76% in the 5 MIU/m² group \((p=0.002)\).

There was no consistent dose effect comparing the 8 MIU and 5 MIU/m² doses. However, the 5 MIU/m² dose averaged 9.6 MIU, not substantially different from the fixed dose.

**SPECTRIMS (interferon beta-1a)**

SPECTRIMS\(^{[54,55]}\) enrolled 618 subjects with clinically definite MS and a secondary progressive course at 22 centers in Europe, Canada, and Australia. Subjects were required to have progressive deterioration of disability for at least 6 months with an increase of at least 1.0 EDSS point over the 2 years before the study with or without superimposed relapses, following an initial relapsing-remitting course. Subjects were 18–55 years old, with EDSS of 3.0–6.5, and a pyramidal functional system score ≥2. Exclusion criteria included immunosuppressive or immunomodulatory treatments during the previous 3–12 months (depending on the drug), previous treatment with interferon or total lymphoid irradiation, corticosteroid use or a relapse in the previous 8 weeks, severe concurrent illness, and pregnancy or lactation. This was a randomized, double-blind, placebo-controlled study. Subjects were randomized to receive 22 µg or 44 µg of interferon beta-1a or placebo subcutaneously three times a week for 3 years. Clinical evaluations occurred every 3 months and MRIs were performed at baseline and every 6 months. A subset of 283 patients had monthly gadolinium-enhanced scans.

The primary outcome measure was time to confirmed disease progression, defined as an increase from baseline of ≥1.0 EDSS step for EDSS 3.0–5.0 or ≥0.5 step for EDSS of 5.5–6.5, confirmed 3 months later with no intervening score lower than the minimum required level. Other outcomes included the proportion of patients progressing, relapse rate, time to first exacerbation, number of moderate and severe exacerbations, number of corticosteroid courses for MS, number of hospitalizations for MS, and the Integrated Disability Status Score (IDSS). In addition, a composite score was calculated that included time to progression, exacerbation rate, MRI T2 lesion burden, MRI T2 activity, and IDSS. Post hoc subgroup analyses for sex and presence or absence of relapses in the 2 years preceding the study were performed.

Demographics and baseline clinical characteristics were well matched in the three treatment groups. Three years of treatment was completed by 506 subjects (82%). Of the 112 subjects (18%) who discontinued treatment, follow-up was maintained for 65. The reasons for discontinuation of study drug or from the study were similar in the three groups.

There was no difference in the time to sustained EDSS progression between patients receiving 44 µg interferon beta-1a \((p=0.146)\) or 22 µg interferon beta-1a \((p=0.305)\) compared with placebo. Other endpoints, however, did demonstrate treatment effects. Significant benefit was seen on relapses for both doses, including relapse rate, time to first exacerbation, time between first and second exacerbations, numbers of moderate and...
severe exacerbations, corticosteroid use, and hospitalizations. On MRI, total T2 lesion volume increased by 10% in the placebo group but decreased by 0.5% in the 22 µg group and by 1.35% in the 44 µg group ($p<0.0001$). Compared with placebo, the 22 µg group showed a reduction of 70% and the 44 µg group a reduction of 75% in median number of T2 active lesions per patient per scan ($p<0.0001$). Both active treatment groups had 67% fewer active scans than the placebo group. The combined clinical and MRI composite score showed a marked treatment benefit for both doses ($p<0.001$).

Subgroup analyses yielded a number of interesting findings. Women showed a delay in progression compared with placebo at both doses ($p=0.006$ for 44 µg and $p=0.038$ for 22 µg), whereas men did not. This sex difference was largely due to differences in behavior of the males and females receiving placebo. This effect did not appear to be due to imbalances in other demographic or clinical characteristics between the men and women in the study. In contrast, there was no sex effect for the benefit on relapse rate. The benefit on the composite score did show a sex effect.

There was a trend for patients with pre-study relapses to show more benefit from therapy with respect to time to confirmed progression. The subgroup with pre-study relapses was significantly younger, had a shorter disease duration, and deteriorated somewhat faster than the non-relapsing group. The subgroup with pre-study relapses also demonstrated greater treatment benefit for on-study relapses.

In general, both doses of interferon beta-1a were well-tolerated. There were somewhat greater side effects (constitutional symptoms, skin necrosis, and liver abnormalities) with the 44 µg dose. There were no expected adverse effects. Neutralizing antibodies at a titer $\geq 20$ developed in 20.6% of subjects receiving 22 µg interferon beta-1a and 14.7% receiving 44 µg interferon beta-1a.

**IMPACT (interferon beta-1a)**

IMPACT$^{[48,49]}$ was carried out at 42 sites: 31 in the USA, four in Canada and seven in Europe. The study enrolled 426 subjects with clinically definite secondary progressive MS and disease progression over the previous year with or without relapses. Subjects were 18–60 years old, with an EDSS of 3.5–6.5, and cranial MRI demonstrating lesions consistent with MS. Subjects were excluded if they had a primary progressive course, if they were unable to perform the component tests of the MSFC at baseline, or if they had previously been treated with interferon beta. The design was randomized, double-blind and placebo-controlled. Subjects received 60 µg interferon beta-1a or placebo intramuscularly once weekly. A half-dose was given for the first four doses.

The primary outcome measure was the between-group difference in MSFC change from baseline to 24 months. Subgroup analyses were planned on the basis of the presence or absence of relapses in the year before enrollment, baseline EDSS of 3.5–5.5 versus 6.0–6.5, and presence or absence of gadolinium-enhancing lesions on the baseline MRI scan. Secondary outcome measures included time to sustained EDSS worsening (1.0 step for baseline EDSS 3.5–5.5 and 0.5 step for EDSS 6.0–6.5, sustained for 3 months), relapse rate, rate of corticosteroid treatment, health-related quality of life measured by the Multiple Sclerosis Quality of Life Inventory, number of new or enlarging T2 hyperintense lesions, number of gadolinium-enhancing lesions, volume of gadolinium
enhancement, proportion of subjects with one or more gadolinium-enhancing lesions, and total T2 lesion volume.

The two treatment groups were well matched at baseline on demographic characteristics, clinical features, and MRI measures. Fifty-two subjects failed to complete 24 months of follow-up. The only between-group difference in reason for study discontinuation was subject request (six placebo subjects versus 16 interferon beta-1a subjects, \( p<0.05 \)).

Interferon beta-1a treatment reduced median MSFC worsening by 40.4% (\( p=0.033 \)), the primary outcome measure. Benefit on the overall composite appeared to be driven mainly by benefit on the nine-hole peg test and, to a lesser extent, the PASAT3. Similar benefit of treatment on MSFC progression was seen in subjects with and without pre-study relapses, in the low and high EDSS ranges, and with and without gadolinium-enhancing lesions on baseline MRI. In contrast, there was no difference between the treatment groups in time to sustained EDSS worsening (\( p=0.90 \)), mean 24-month EDSS change, or the proportions of subjects categorized as improved, stable, or worse based on 24-month EDSS change. There was a 33% reduction in annual relapse rate (\( p=0.008 \)), and the mean annual rate of corticosteroid treatment was 0.27 courses per year for the placebo subjects and 0.19 for the interferon beta-1a subjects (\( p=0.030 \)). There was significant benefit of interferon beta-1a on eight of 11 Multiple Sclerosis Quality of Life Inventory subscales. The interferon beta-1a group improved on 10 of 11 subscales from baseline to 24 months, but the placebo group worsened on 10 of 11 subscales.

On MRI there was a reduction of the number of new or enlarging T2-hyperintense lesions at 12 and 24 months (\( p<0.001 \) for both). The mean number of new or enlarging lesions was reduced by 52.9% in the interferon beta-1a group relative to the placebo group at 12 months and by 45.6% at 24 months. The number of gadolinium-enhancing lesions was reduced at 12 and 24 months in the interferon beta-1a group compared with the placebo group (\( p<0.001 \) for both). The volume of gadolinium-enhancement (\( p<0.001 \)) and proportion of subjects with one or more gadolinium-enhancing lesions showed similar benefit (\( p<0.001 \) for both). Median change from baseline in total T2-hyperintense lesion volume was reduced in the interferon beta-1a group compared with the placebo group by 78.4% at 12 months and by 69.1% at 24 months (\( p<0.001 \) for both).

Weekly intramuscular injection of 60 µg of interferon beta-1a was well tolerated by the majority of subjects. However, more interferon beta-1a subjects withdrew from the study or discontinued the study drug because of adverse events (8% versus 4%) or intolerance of study drug (6% versus 0) (\( p<0.05 \) for both). More placebo subjects discontinued because of perceived disease worsening (11% versus 3%, \( p<0.05 \)). There were no unanticipated adverse effects. The only adverse events occurring with a 5% or greater incidence among interferon beta-1a-treated subjects were flu-like syndrome, fever, chills, vomiting, and injection site inflammation. The incidence of neutralizing antibodies at a titer \( \geq 20 \) at any time during the trial was 3.3% among interferon beta-1a-treated subjects.

**Overview of phase III trials**

These studies confirmed that, in general, interferon beta was well-tolerated in secondary progressive MS. The adverse effects seen and their overall frequency and severity were
similar to the experience in relapsing-remitting MS. These studies also showed that interferon beta was of benefit in secondary progressive MS. Treatment with interferon beta reduced relapse rate by approximately 30% and decreased MRI activity; the magnitude of the treatment effect on both endpoints was comparable to that seen in relapsing-remitting MS. The results on disease progression in the four studies, however, were somewhat discrepant. The Eu IFNβ-1b study demonstrated benefit on EDSS progression. The NA IFNβ-1b study, SPECTRIMS, and IMPACT yielded negative results on EDSS progression. It is likely that these conflicting findings were due to differences in study populations. Subjects in the Eu IFNβ-1b study were younger with a shorter duration of disease and substantially higher pre- and on-study relapse rates. It may have been more difficult to demonstrate a beneficial treatment effect on EDSS progression in the NA IFNβ-1b study, SPECTRIMS, and IMPACT because the subjects were at a more advanced stage of secondary progressive MS.

Benefit on disease progression in secondary progressive MS was shown in IMPACT through utilization of the MSFC. IMPACT was the first study to use the MSFC as the pre-defined primary outcome measure. The greater sensitivity of the MSFC relative to the EDSS resulted from its high degree of reliability, advantageous metric properties as a continuous scale, and assessment of arm function and cognition in addition to ambulation. These attributes allowed the MSFC to detect a beneficial treatment effect when the EDSS failed. Other studies have suggested that quantitative functional measures are more sensitive to change than the EDSS.[47,56–58]

Although interpretation of the results of studies using the MSFC should be based on the overall composite score, one advantage of the MSFC is that the individual components can be directly compared. In IMPACT, benefit of interferon beta-1a treatment on the MSFC appeared to be driven largely by an effect on arm function and, to a lesser extent, cognition. One interpretation of this observation is that progressive gait impairment in advanced secondary progressive MS is less responsive to treatment than other neurologic manifestations are. Interestingly, a previous study of oral methotrexate in progressive MS[59] also showed benefit of treatment on upper extremity function (measured by the nine-hole peg test, or the box and blocks test) and cognition (including the PASAT3) but not ambulation (measured by the EDSS or Ambulation Index).

An alternative explanation is that differences in MSFC component tests or how they were analysed accounted, at least in part, for the pattern of the results. The timed 25-foot walk worsened over 2 years in the majority of subjects, suggesting that it was a responsive measure. There was a trend to greater worsening in the placebo subjects. However, the timed 25-foot walk distribution was the most skewed of the MSFC components, with substantially greater within-subject and between-subject variability, owing to some subjects having markedly prolonged walking times. Possible scores on the PASAT3 were restricted from 0 to 60, and use of the inverse of the time on the nine-hole peg test reduced the skewing of its distribution. Further studies will be necessary to determine whether the differential treatment effect on the MSFC components resulted from decreased ability of interferon beta-1a to preserve ambulation versus other neurologic domains in secondary progressive MS or whether MSFC analytic methods can be optimized to detect treatment effects better.

Subgroup analysis in SPECTRIMS suggested greater benefit in women. This sex effect was not anticipated and was not seen in the other three studies. Subgroup analyses
in SPECTRIMS also showed greater benefit on EDSS and relapses for subjects with pre-study relapses. Results in the Eu IFNβ-1b study also suggested this effect in some but not all analyses. Finally, in SPECTRIMS there was an interferon beta-1a dose effect for some but not all endpoints. There was no dose effect in the NA IFNβ-1b study, although the 5 MIU/m² dose was not very different than the 8 MIU dose. The Eu IFNβ-1b study and IMPACT included only one dose of interferon beta.

As in studies of relapsing-remitting MS, all of the interferon beta preparations stimulated the production of neutralizing antibodies, although to differing degrees. The rate of neutralizing antibody positivity for each preparation in secondary progressive MS was roughly comparable to that reported for relapsing-remitting MS. As in studies of relapsing-remitting MS, the clinical consequences of neutralizing antibodies were not obvious. However, these studies were not powered to detect an effect on the clinical outcomes comparing neutralizing antibody-positive and -negative subgroups. More importantly, they were not designed to detect sequelae of neutralizing antibodies, which would be expected to manifest themselves after their appearance.

CONCLUSIONS

All four phase III studies of interferon beta in secondary progressive MS showed reductions in relapse rate, MRI activity, and MRI lesion accrual. The magnitude of the treatment effect on these endpoints appeared to be similar to that seen in relapsing-remitting MS. However, these manifestations of MS become less prominent at later stages of the disease. Benefit on disease progression was less clear-cut and differed among the studies. It may have been more difficult to demonstrate benefit on progression in secondary progressive MS compared with relapsing-remitting MS, owing to biologic differences. However, this difficulty appeared to result, at least in part, from decreased performance of the EDSS as an endpoint at this stage of the disease. Benefit on disease progression could be shown using the MSFC, and the magnitude of this benefit was comparable to that on relapses. Patients with secondary progressive MS as a group tolerate interferon beta therapy. Thus, interferon beta appears to be a reasonable treatment to consider for patients with secondary progressive MS, particularly those with recent relapses. Interferon beta-1b has been approved in Europe for the treatment of secondary progressive MS. The three interferon beta preparations are under consideration by the Food and Drug Administration in the USA for this indication.

The Eu IFNβ-1b study and the NA IFNβ-1b study illustrated why it is difficult to make inferences about the relative efficacy of agents by comparing the results of different studies. These two trials tested the identical agent in studies with very similar entry criteria and endpoints. Despite similar entry criteria, different study populations were enrolled, owing to the different clinical environment in which the studies were conducted. Whereas the European study demonstrated benefit on the EDSS, the North American study did not.

Experience in IMPACT confirmed the feasibility of using the MSFC in a large-scale multinational study, its excellent reproducibility, its greater sensitivity to change over time compared with the EDSS, and its greater ability to demonstrate treatment effects.
Further studies are need to optimize the component tests in the MSFC and how MSFC data are analysed.

ACKNOWLEDGMENT

This work was supported in part by a Physician Fellowship Award from the National Multiple Sclerosis Society and a Potiker Fellowship to RAM.

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Biological responses to type I interferons: relationship to therapeutic effects in multiple sclerosis
Richard M Ransohoff

INTERFERONS: THE BASICS

In 1957, interferons were originally described as factors that interfered with viral replication in vitro. Now recognized as an integral part of the host defense apparatus, interferons (IFNs) are separated into two classes, designated as type I and type II. Type I IFNs, a family of related proteins, include IFN-α, IFN-β, IFN-ω, IFN-τ and IFN-δ. Type II IFN is IFN-γ, which has limited homology to type I IFNs. There are 14 non-allelic IFN-α genes, with one IFN-β or IFN-ω gene. IFN-τ is expressed in trophoblasts of ruminants. Despite binding to different cell-surface receptors, type I and type II IFNs exhibit antiviral and antiproliferative activities in common.

It is considered axiomatic that IFNs, which are transcriptional regulators, exert their effects by inducing gene expression and that the products of the interferon-inducible genes are the effectors of the IFN response. Perhaps because of this postulate, IFNs have been studied using each new generation of methodology for examining differential gene expression, from separating metabolically labeled proteins on two-dimensional gels to differential hybridization and display, and more recently with microarray techniques. IFN-inducible genes, by the microarray techniques, number in the hundreds. Major unanswered questions remain concerning how IFNs mediate their diverse activities, despite extensive characterization of IFN-mediated signaling pathways, receptor structure, and IFN-regulated gene expression.

Type I IFNs and the type I IFN receptor

Virtually all nucleated cells produce type I IFNs after appropriate stimulation. A common characteristic of IFNs is species-specificity; only rarely and unpredictably do type I IFNs elicit biological responses across species barriers. It is has been postulated that a common ancestral gene gave rise to archetypical type I IFNs at least 250 million years ago. IFN-α subtypes arose gradually over the past 85 million years. Genes encoding IFN-αs are clustered on the short arm of chromosome 9, while IFN-β and IFN-ω are encoded by single genes located elsewhere on the same chromosome. Members of the IFN-α superfamily exhibit more than 80% sequence homology, while IFN-β is 29% homologous with IFN-αs. Therefore, although IFN-α subtypes and IFN-β share membership in the type I IFN family, they are not highly homologous. Mature, secreted human IFN-αs and IFN-β consist of 165 or 166 amino acids. Type I IFNs are acid-stable proteins, two of which (IFN-α2 and IFN-β) are glycoproteins. In both cases, biological activity is not absolutely dependent on glycosylation, although effects on stability have
been reported.\cite{7,8} Bespeaking their genetic relatedness, genes encoding the IFN-αs and IFN-β are intronless. It is uncertain why so many type I IFN genes have been maintained and expressed over millennia of evolution, given their apparent duplicative function. Speculation has centered on the possibility that numerous type I IFNs have been selected against a stable, fixed receptor structure, to permit the evolution of subtle but functionally distinct cell type-specific effects.

The α-helix is the dominant feature of the secondary structure of type I IFNs, which are accordingly classified as globular, α-helical proteins.\cite{9} Several lines of evidence suggest that the tertiary structures of type I IFNs are similar and consist of five distinct α-helices, designated as A, B, C, D and E, linked by regions of random coils or loops.\cite{10} The IFN-α family of proteins generally has two conserved disulfide bonds (cys1-cys99 and cys29-cys139) whereas IFN-β has only one (cys-33-cys116), and disulfide bonds are critical for correct protein folding and activity for most IFNs.

Type I IFN antiproliferative, antiviral activities and species-specificity can be modified by selective amino acid substitutions.\cite{11} Activity-sensitive ‘hot spots’ have been identified by examination of crystal structure data for IFN-β.\cite{10} For human IFN-α2, single substitutions at positions 121, 125, or 132 increased activity towards mouse cells by a factor of 400-fold.\cite{12}

Type I IFNs interact with a specific high-affinity cell-surface receptor composed of two transmembrane proteins termed IFNAR1 and IFNAR2c.\cite{13} These proteins are not pre-associated on the cell surface but assemble in a ligand-dependent manner. Binding of the IFN ligand drives aggregation of these receptor chains via interactions with their extracellular domains, probably in a 1:1:1 stoichiometry. Assembly of the type I IFN receptor complex is necessary for activation of IFN-dependent signaling and gene expression.

IFN-αs and IFN-β utilize the same receptor chains (IFNAR1 and IFNAR2c), but assemble them differently, suggesting that the detailed protein-protein interactions between receptor chains and type I IFNs are defined by the specific ligand being used.\cite{14} Therefore, variations in the activity of type I IFNs may be anticipated, because of differences in the ligand-induced assembly of the type I IFN receptor complex.

Transcriptional regulation by type I IFNs has been intensively studied.\cite{2,9,13} Interaction of IFN with its cognate receptor initiates JAK-STAT signaling, commencing with tyrosine phosphorylation and activation of two receptor-associated Janus kinases (JAKs), JAK1 and TYK2, with subsequent phosphorylation of cytoplasmic tyrosine residues of the IFN-receptor subunits, IFNAR1 and IFNAR2c.\cite{9} The major signaling output of the ligand-stimulated IFN receptor consists of activated transcription factors called STATs (signal transducers and activators of transcription). Activated STAT oligomers accumulate within the nucleus, associate with regulatory DNA elements in sequence-specific fashion, and upregulate transcription initiation. Type I IFNs activate STAT1, STAT2 and STAT3. The majority of IFN-stimulated genes (ISGs) are activated by the transcription factor IFN-stimulated gene factor 3 (ISGF3), consisting of STAT1-STAT2 heterodimers in association with a 48 kDa DNA binding protein, interferon regulatory factor (IRF)-9. ISGF3 binds to IFN-stimulated response elements (ISREs) located within the promoter regions of ISGs.

Numerous additional signaling proteins, beyond JAKs and STATs, undergo ligand-dependent association with the cytoplasmic domains of type I IFN receptor chains, and
these proteins link the IFN receptor to a large array of intracellular signaling pathways. These include phosphatases such as SH-PTP1, MAP kinase, the adapter protein CrkL and phosphoinositol 3-kinase (PI3K).

The association of insulin receptor substrate (IRS)-1 with the IFN receptor has been extensively studied. IRS-1 undergoes IFN-dependent tyrosine phosphorylation and is a plausible adaptor for coupling PI3K to the receptor, in some cells. In Daudi B-lymphoma cells, phosphorylated STAT3 appears to act as an adaptor to couple PI3K to the IFN pathway. In HT 1080 fibrosarcoma cells, PI3K associates directly with IFNAR-1 and is activated by a mechanism independent of STAT3. The inference from this conservation of PI3K activation by discrepant mechanisms is that such activation plays an important, although enigmatic, role in the biological response to type I IFN.

In some cases, IFN-mediated signaling is quite cell-type specific. For example, in human T-lymphocytes, the transmembrane phosphatase CD45 couples to IFNAR1 after T-cells are stimulated with IFN-α, suggesting that type I IFNs might modulate the signaling output of antigen engagement by the T-cell antigen receptor. It is tempting to speculate that variation in IFN signaling is linked to the differential usage of such proteins. However, relevance of these accessory signaling events for the IFN-mediated transcriptional response (and thus for biological effects) has not been established.

The cardinal biological responses to type I IFN

Antiviral effects of type I IFNs

Both type I and type II IFNs elicit potent and specific antiviral activities against numerous RNA and DNA viruses. Based on this fact and supported by studies in gene-targeted mice, it is considered likely that the primary role of IFNs is to limit viral replication at sites of infection and to orchestrate the adaptive immune response to viral challenge. The mechanisms by which IFNs induce cellular resistance to viral replication involve activation of multiple enzymatic activities including the 2–5 oligoadenylate-synthetase-RNase L system, dsRNA-dependent protein kinase (PKR) and induction of Mx proteins. As might be anticipated, individual viruses are susceptible to individual antiviral activities. This principle is well demonstrated by the example of the murine Mx proteins, which selectively mediate resistance to orthomyxoviruses, among others. IFNs also upregulate diverse components of the adaptive immune response to virus infection. These activities and effectors include MHC class I determinants, elements of the antigen-processing machinery and functional maturation of CD8+ T-cells. In summary, IFNs prime the host to resist virus infection at the cellular and organismic levels.

Antiproliferative effects of type I IFNs

Although it is clear that IFNs exhibit potent antiproliferative effects on cells, the mechanisms by which IFNs inhibit cell growth are not well understood. Antiproliferative effects of IFNs are dependent on IFN-induced gene expression, and several genes that mediate these effects have been isolated by ingenious lethal selection strategies that entail expression of cDNA libraries by retroviral transduction.
Type I IFNs exhibit their antiproliferative activities selectively, depending on the type of IFN studied and the cell type of interest. For example, sensitive Daudi B-lymphoma cells are 10–100 times more sensitive to the antiproliferative effects of IFN-α than a resistant subline of the same cell-line, and the observed differential antiproliferative effects are not susceptible to the trivial explanation of different binding affinities for IFN.[15]

EFFECTS POTENTIALLY RELEVANT TO MS TREATMENT

Overview

IFNs exert modest but definite therapeutic effects for MS patients, primarily during the early relapsing-remitting phase of the illness. Barriers to understanding these effects are numerous and formidable. First, the pathophysiology of MS is unknown. Second, it is possible that there are several pathogenic subtypes of disease, each of which might be modified differently by IFN treatment. Third, the genuine impact of treatment on disease is only moderate at best, and weak biological effects are relatively impervious to elucidation.

IFN-α subtypes and mixtures have been examined less extensively in the treatment of MS, because the clinical trials of these agents were performed before clinical trial methodologies were mature. Therefore, these clinical trials produced apparently negative results. Recent limited studies show benefit for MS patients receiving IFN-α2A.[16] These effects were similar in magnitude and character to those mediated by IFN-β treatment. Head-to-head clinical and immunological comparisons have not been performed. Therefore, it is uncertain which of the demonstrated effects of IFN-β treatment may be subtype-specific.

It is difficult to ascertain how IFNs exert biological effects, even in simple systems where the responses are unmistakable and easily assayed. As a simplifying generalization, IFNs are postulated to generate biological responses by the induction or suppression of gene expression at the transcriptional level. There are at least 100 IFN-inducible genes. In the case of MS, it is not known which genes (or in which cell type) therapeutic benefits might be established. Clinical studies can, of course, be conducted only by studying accessible cells, primarily those obtained by venepuncture.

Given this situation, one might wonder, ‘Why bother?’ As one answer, physicians are uncomfortable administering treatments for which the mechanism is entirely mysterious. Beyond this psychological motivation, it is highly important to understand the therapeutic mechanisms of IFNs in MS, if possible. Clarification of the mechanism is certainly the most direct route to enhancing efficacy or designing rational combination therapies. Further, such information would aid enormously in addressing nagging questions related to possible dosage effects or selection of patients for therapy. The question of the proper dose of IFN-β for MS has been a vexing one,[17,32,33] with a great deal of argument on both sides of the question whether more is better, with much of the contention motivated by attempts to optimize marketing strategies. However, it is not unimportant to establish the correct dose of IFN-β for MS. Without knowing what elements of the IFN response program are most relevant, this task is formidable. In tissue culture systems in which the
assay variable is gene induction or antiviral state, IFN-β-mediated biological effects follow a sinusoidal dose-response curve, which attains a plateau when receptors (which typically number in the tens of thousands per cell) have been saturated. However, the time course of transcriptional induction, post-transcriptional stabilization, and ultimate message levels differ widely, even for a small set of ISGs that were studied in an early differential hybridization experiment. Therefore, it is virtually impossible to predict on first principles what the optimal dose of IFN-β for treating MS should be. The only conceivable means of resolving this question would be either to define operationally a dose at which all patients respond, or to identify one or more markers that correlate uniformly with response and then to perform dose-response and kinetic studies.

To simplify this challenging task, investigators have chosen to begin with the known characteristics of MS, and searched to determine whether IFN treatment causes cellular effects that might be plausibly implicated in therapeutic benefit. One may consider four salient IFN effects that could conceivably contribute to therapeutic properties in MS: first, antiviral (either against a unique, chronic MS pathogen, or against common viral episodes that could stimulate relapses); second, anti-inflammatory; third, modulation of the adaptive immune response; and fourth, neurotrophic effects, either direct or induced. There is evidence in favor of all these possibilities, indicating perhaps how far we remain from a definitive answer. Each is considered below.

**Antiviral or immunomodulatory?**

IFNs were selected for clinical trials in MS during the 1970s, in part on the basis of the hypothesis that a slow or chronic viral infection might underlie the disease, and the choice of IFN as a proposed treatment was supported by experiments showing diminished secretion of IFN-like activities from the cultured cells of MS patients. The emphasis on antiviral properties of IFNs during this phase of the research can be inferred from the fact that IFNs of multiple subtypes (α, β, γ) were considered equally suitable for investigation.

Upon observation of therapeutic benefit from treatment with interferon beta-1b it was initially unclear whether IFN-β exerted its MS-specific therapeutic effects by immunomodulation or by antiviral properties. At the time it was posed, this question arose from the fact that compelling epidemiological studies had associated approximately 25% of attacks of MS symptoms with intercurrent viral infections. Therefore, the inhibitory effects of IFN-β on MS disease activity could potentially reflect the reduced occurrence of viral infections in treated patients. Two observations militated against this interpretation. First, patient diaries, supplemented by antiviral serologies, failed to disclose reduced incidence of common viral upper respiratory infections in IFN-β-treated patients who participated in two pivotal clinical trials. Second, IFN-β was shown to reduce the number and severity of relapses of experimental autoimmune encephalomyelitis (EAE), a purely autoimmune small-animal model of MS. Of course, the search for a unique pathogenic etiology for MS continues; therefore, it remains possible that resistance to such a putative pathogen underlies treatment responses to IFN. This debate will remain spirited until the disease is definitively explained. Despite these unresolved issues, it is likely that a purely antiviral mechanism could not explain the ameliorating properties of IFN-β in MS. Against that background, immunologists
have begun in earnest to address the immunomodulatory and anti-inflammatory properties of IFN-β.

It is not unwarranted to suggest that interest in the immunomodulatory properties of type I IFNs was reanimated by reports of therapeutic efficacy of IFN-β in MS. In contrast to the low level of interest seen in previous years, a current Medline search readily detects several hundred references to studies of the immunomodulatory effects of IFN-β since 1993, when the first IFN-β product for MS, interferon beta-1b, became available in the USA. Recent studies have largely focused on immunomodulatory functions of IFN-β that might plausibly be associated with the mechanism of action in MS patients.

**Effects on leukocyte trafficking**

MS is unequivocally an inflammatory disorder, reflected in cerebrospinal fluid (CSF) pleocytosis, foci of blood-brain barrier disruption detected by gadolinium-enhanced magnetic resonance imaging (MRI), and leukocyte infiltrates in affected tissues. IFN-β causes a rapid, dramatic, and reproducible reduction in the numbers of gadolinium-enhanced lesions on MRI. This effect is widely regarded as highly significant. Furthermore, in one clinical trial IFN beta-1a treatment produced a significant reduction of the likelihood of CSF pleocytosis, when patients receiving active drug and placebo were compared. Although type I IFNs have been known for more than 20 years to produce alterations in leukocyte trafficking, specific mechanisms to explain the IFN-β-mediated reduction in gadolinium-enhanced MRI lesions have been sought. Three categories of molecules are associated with leukocyte transgression of the blood-brain barrier: leukointegrins that bind endothelial adhesion ligands, chemokines, and matrix metalloproteinases (required for degrading basement membrane).

IFN-β treatment modulates the expression and function of trafficking determinants, occasionally in ways that could relate to the reduction of gadolinium-enhanced MRI lesions. Pertinent observations include reduced lymphocyte expression of the 92 kDa gelatinase matrix metalloproteinase 9 (MMP9). Initially described in tissue culture studies, this effect was also demonstrated in cells isolated from IFN-β-treated MS patients. Lymphocytes with reduced MMP9 activity are less competent to transmigrate across fibronectin-coated membranes, an in vitro blood-brain barrier model. Other effects of IFN-β that may account in part for suppression of gadolinium-enhanced MRI lesions include reduced expression of the integrin very late antigen (VLA)-4 on mononuclear cells. In model systems, VLA-4 is required for entry of T cells into the central nervous system (CNS) and its blockade by a monoclonal antibody caused decreased gadolinium-enhanced MRI brain lesions. A complementary effect is increased shedding of the VLA-4 ligand, VCAM-1, with the potential result that soluble VCAM-1 could occupy free VLA-4 on circulating cells. Interestingly, increased levels of soluble VCAM-1 in serum correlated with reduced gadolinium-enhanced MRI lesions.

IFN-β effects on chemokine expression are complex and multiple. In tissue culture systems, IFN-β upregulates expression of numerous chemokines, differentially contingent on cell type. This result is unsurprising, given the status of chemokine genes as early to immediate elements of the response to most cytokines. The most convincing investigations of MS patients’ cells have found relatively little or no effect on chemokine
expression. Further, where effects on the chemokine system have been detected, reports have been divergent.\(^{56,57}\)

In conclusion, IFN-\(\beta\) treatment produces in vivo anti-inflammatory effects that are plausibly related to disease amelioration. Most directly related to clinical benefit are reduced gadolinium-enhanced MRI lesions and concomitant diminished CSF cell count. Mechanisms underlying these properties remain to be defined, but it seems that therapeutic manipulations of leukocyte trafficking determinants are worthy of investigation.

**Antiproliferative and pro-apoptotic properties**

Effects on leukocyte trafficking might help account for a rapid-onset reduction in gadolinium-enhancing MS lesions. Entirely different categories of IFN-\(\beta\) effects have been adduced to explain diminished disease activity during chronic treatment. Although it has long been known that IFN-\(\beta\) is antiproliferative towards T lymphocytes (both in vivo and in vitro),\(^{58}\) recent reports further suggest that activation-related T-cell apoptosis may also be enhanced by IFN-\(\beta\).\(^ {59}\) Supporting this possibility were studies showing that IFN-\(\beta\) treatment enhances pro-apoptotic and suppresses anti-apoptotic cellular components.\(^ {59,60}\) However, it is not universally accepted that IFN-\(\beta\) induces T-cell apoptosis in MS\(^ {61}\) or in the EAE model system.\(^ {62}\) The horizons of this research were widened by a recent report that macrophages may be a relevant target for the pro-apoptotic properties of IFN-\(\beta\) in the treatment of MS.\(^ {63}\) One can state securely that the status of IFN-\(\beta\)-induced leukocyte apoptosis in MS is uncertain. However, given the documented importance of lymphocyte apoptosis in regulating intrathecal immune reactions, further investigation is clearly indicated.\(^ {64}\)

**‘Immunomodulation proper’: effects on T-helper cell polarization**

Much recent research has been engaged with the hypothesis that MS is a disease driven by T-helper type 1 (Th1) lymphocytes. Significant support for this concept came from the stimulation of MS disease activity by administration of the cardinal Th1 cytokine, IFN-\(\gamma\), in phase I clinical trials.\(^ {65}\) In searching for mechanisms to explain treatment benefits, it has been reported that IFN-\(\beta\) augments expression of both immunosuppressive and Th2 cytokines (that restrain Th1 cell activity).\(^ {66–69}\) These cytokines include interleukin (IL)-10 and transforming growth factor-\(\beta\).\(^ {59,70–73}\) Increased expression of the Th2 cytokine IL-6 may be associated with immunoregulatory benefits, but is also thought to cause flu-like side effects.\(^ {74}\)

The most elaborate and specific hypothesis holds that IFN-\(\beta\)-treatment for MS alters the ratio of two regulatory cytokines, IL-12 and IL-10, with consequent profound effects on the generation of Th1-polarized T cells.\(^ {75–80}\) There is support for this hypothesis from studies that used IFN-\(\beta\) to treat EAE as well.\(^ {81}\) Reports have recently focused on IFN-\(\beta\) effects on the antigen-presenting cells (either afferent or efferent) that prime Th1 and Th2 cells to explain these results.\(^ {82,83}\) This hypothesis has been elegantly discussed,\(^ {84,85}\) and recent results support the feasibility of the concept.\(^ {86}\)

In several studies, concomitant reduction of Th1 cytokines, including IL-12, tumour necrosis factor-\(\alpha\), and IFN-\(\gamma\), was also described. Indeed, the clearest therapeutic
The distinction between IFNs in MS was the augmentation of disease activity with IFN-γ and its amelioration with IFN-β. For some years, it has been known that several genes that are IFN-γ-responsive are inhibited by co-treatment or pre-treatment with IFN-β. The most completely studied of these cases involves the MHC class II determinants, which are implicated both in antigen presentation and in activation of CNS macrophages. Although this effect has been demonstrated in vivo in MS patients, its transience calls into question its relevance for sustained immunomodulatory effects of IFN-β in disease treatment. Recent reports using cells from MS patients who received IFN-β showed that type I and type II IFNs counter-regulate additional genes of potential pathogenetic relevance. Ultimately, the complex mix of pro- and anti-inflammatory properties of the type I IFNs may exert variably beneficial effects for MS patients.

Could IFNs be neuroprotective?

The demonstration that MS-associated inflammation causes axonal pathology, producing transection and, possibly, resistance to remyelination, has provoked interest in the neuroprotective properties of current therapies, and the neurobiology of cytokines in general has come under detailed scrutiny. There is some evidence that IFN-β may induce biological responses consistent with neuroprotective properties. For example, type I IFN reduces astrocytic production of nitric oxide and hence inhibits neuronal damage in an in vitro cell-culture paradigm. There is also evidence that IFN-β induces the expression of nerve growth factor (NGF) by astrocytes. Curiously, human NGF was examined as a potential neuroprotective agent in a marmoset EAE model and found to modulate local Th1 cytokine expression in the CNS, with consequent pronounced suppression of neurological symptoms and inflammation. The concept that IFN-β might produce neuroprotective responses in the CNS are all somewhat dependent on showing an intraparenchymal biological effect of systemic cytokine. Certainly, the converse of this possibility is that IFN-β could produce neuropathological consequences, and increased spasticity in patients with secondary progressive MS who receive IFN-β supports such a concern. Nevertheless, although current findings leave the mechanistic situation unclear, they do provide some hope that IFNs may exert unanticipated benefits for MS patients.

Can we learn anything from adverse reactions to IFN-β treatment for MS?

Given the attention paid to immune mechanisms in the analysis of IFN-β effects on MS, it is worthwhile to speculate whether anything could be learned from considering the immunological side effects of treatment. Early and detailed immunological studies of MS patients who received IFN-α showed pronounced stimulation of natural killer cells, as well as strong immunoglobulin production in response to a protein contaminant of the preparation. This result exemplified the difficulty in sorting the wheat from the chaff in such studies.

More recently, studies have focused on the incidence of immune-mediated hypothyroidism in patients receiving IFN-β. Both Graves’ disease and hypothyroidism have been described in these studies. Additional questions focused on the
pertinent question of whether MS patients have abnormalities at baseline that might predict the occurrence of thyroid autoimmunity, with negative results.\[107\] Interestingly, a high incidence of thyroid autoimmunity occurred during clinical trials of a wholly different immunomodulatory treatment, anti-CD52 monoclonal antibodies.\[108\] This report, along with the known association of MS with thyroid autoimmunity,\[109\] irrespective of treatment, leads one to conclude that the linkages between MS and thyroid autoimmunity tells more about the immunogenetic background of the patient population than it does about the mechanisms of IFN action.

Hepatic autoimmunity, along with appearance of anti-smooth muscle antibodies, also has been reported and can produce fulminant hepatic failure,\[110\] although it is thankfully rare.\[111\] Other uncommon reactions, which may be immune-mediated, include urticaria, nephrotic syndrome, and capillary leak syndrome.\[101\] The mechanisms are uncertain, and prospective surveys are difficult, owing to the frequent and non-immune-mediated occurrence of transient, mild abnormalities of hepatic transaminases. In the cases of both autoimmune thyroid and hepatic disease, it might be useful to define autoantibody isotypes and to characterize the T-helper cell response in order to find clues about the cytokine environment in which they were generated.

The development of neutralizing antibodies constitutes a distinct category of immunological phenomenon that has garnered attention in the context of MS treatment with IFN-β. Given that other immunological complications of IFN-β treatment are antibody-mediated, it seems apparent that neutralizing antibodies represent an authentic cytokine-driven response to the same extent that they represent a passive reaction to injected protein. Accordingly, it would be useful to the understanding of MS and of IFN biology if information could be developed about the immunological characteristics of patients who are predisposed to develop anti-IFN antibodies. The issue of the importance of neutralizing antibodies has been a contentious one, with considerably more heat than light expended on the topic.\[112,113\] Certainly, there is no doubt that antibodies that preclude interaction between IFN-β and its unique receptor will inactivate IFN-β, as no other functional cellular binding site has been described.\[9\] There is nonetheless a robust database of information about the occurrence rates of anti-IFN neutralizing and non-neutralizing antibodies, as well as their specificity for epitopes on IFN-β.\[114–120\] Furthermore, their occurrence clearly and consistently differs among the interferon products marketed for MS, owing to the formulation or to the route or timing of administration.\[121\] Recent work showed nicely that antibodies of the immunoglobulin G4 subclass were significantly more likely to neutralize IFN effects than those of other subclasses.\[122\] Extension of work along these lines is clearly indicated.

**SUMMARY AND CONCLUSIONS**

A considerable body of information can be brought to bear on the problem of the therapeutic effects of IFN-β in MS. These data include extensive characterization of the signaling outputs of the receptor and a near-complete accounting of the ISGs in some cell types. From the MS perspective, there are the reasonable points of departure: reduced gadolinium-enhanced lesions, reduced capacity of T-cells to transmigrate across an endothelial monolayer, and alteration of a polarized Th1 cytokine expression by
circulating cells. Antiviral effects, induction of apoptosis, and neuroprotective properties all remain plausible, although with less evidence in support. Even so, formidable obstacles remain, as described above. The promise of such studies is enticing: understanding how IFN-β ‘works’ may tell us much about the pathogenesis of MS and give us clues towards effective treatment.

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INTRODUCTION

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) characterized by multifocal inflammation, demyelination, and axonal injury. The exact etiological factors or agents causing MS remain a mystery, although polygenic determinants and exposure to an unknown environmental trigger are likely. One class of potential environmental triggers is an antigen of viral or bacterial origin. Small peptide fragments of microbial components, with amino acid sequences similar to antigenic segments of myelin proteins, could induce a cross-reactive immune attack on the self by a process of molecular mimicry.[1]

Important insights into the mechanisms of immune-mediated myelin damage have come from animal models. For example, immunizing an animal to antigenic myelin components or peptide fragments can trigger experimental allergic encephalomyelitis (EAE), a form of CNS demyelination. Effective antigens in EAE induction include the major myelin proteins, myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG). It is known that patients with MS and normal subjects have potentially autoreactive T cells that are specific to these myelin antigens in their peripheral circulation.[2–7]

The possibility that MS at certain stages is driven by similar immune mechanisms has led to extensive studies of antigen specific immune-modulating strategies. Recent recognition that axonal injury and axonal transection occurs early in MS and may correlate with permanent neurological deficits has provided additional motivation to find more effective treatments to slow or halt the disease process.[8]

When the Food and Drug Administration (FDA) in the USA approved copolymer 1 for relapsing-remitting MS in 1997, the generic name, glatiramer acetate (GA), was created. The trademark name of the drug is Copaxone®. This unique, synthetic copolymer drug has a long and interesting history leading to its use as a therapeutic agent for MS.

HISTORY OF GA

The development of GA is a fascinating story of scientific ingenuity and serendipity. As an immune-mediated, CNS disease, MS presents inherent barriers for human research.
The development of animal models of demyelination has been an important step in unraveling the immune mechanisms underlying MS. One model, EAE, is a T-cell-mediated disease that can be induced in susceptible animals by inoculating them with CNS in complete Freund’s adjuvant. Certain purified protein components of myelin, such as MBP, can also be encephalitogenic or capable of producing EAE when injected into susceptible animals.[9,10]

Three decades ago, Ruth Arnon and colleagues at the Weizmann Institute in Israel were interested in the structural mechanisms of EAE induction by such protein antigens. They synthesized a family of eleven different copolymers (copolymer 1 through copolymer 11) as potential encephalitogens. The copolymers were synthesized with amino acid compositions chosen to be similar to MBP. None of the copolymers proved capable of inducing EAE, but several had the property of preventing the development of EAE or of reducing disease severity in animals inoculated with MBP. Copolymer 1 (GA), composed of L-glutamate, L-lysine, L-alanine, and L-tyrosine, was the most potent and reduced the incidence of EAE in MBP-challenged guinea pigs from 20% to 75%.[11,12]

Cross-reactivity of GA and MBP was shown at both the T-cell level and the B-cell level. The degree of cross-reactivity with MBP in assays of lymphocyte transformation, delayed hypersensistudies correlated well with the ability of GA to tivity, and by monoclonal antibody binding suppress EAE.[13] Furthermore, the immune modulating effect of GA seemed to be restricted to responses induced by myelin antigens and was not due to general immunosuppressive properties.[14]

An important series of experiments showed that GA could suppress the development or reduce the severity of EAE in a variety of animals, including mice, rats, guinea pigs, rabbits, and primates.[15–19] Studies in primates were of particular relevance to the treatment of MS in humans. It was known that Rhesus monkeys and baboons were very sensitive to MBP-induced EAE and typically died of the disease within 2 weeks of the onset of symptoms. GA treatment was found to reverse EAE in these animals after the appearance of symptoms. Toxicity testing in animals did not reveal mutagenic or other serious adverse effects, and the stage was set for GA to enter clinical testing in humans.

**IMMUNOLOGY AND MECHANISM OF ACTION**

The immune pathology in MS could in part be driven by specific T-cell responses to myelin antigens. Possible myelin autoantigens in MS include MBP, MOG, and PLP.[20] Evidence from animal models for a potential role of these antigenic proteins in demyelinating diseases such as MS derives from their use as encephalitogens in the induction of EAE. In fact, the early interest in GA was related to its ability to suppress the induction of EAE by MBP, PLP, and MOG.[21–23] GA inhibits cell-mediated immune responses to MBP and cross-reacts with MBP at both the cellular and humoral levels.[13,24–26]

There are at least four proposed mechanisms of action by which GA might exert therapeutic benefit in MS.[27] These include: competitive binding to molecules of the major histocompatibility complex (MHC) in preference to myelin protein antigens; preferred binding of GA-MHC complexes over MBP-MHC complexes to appropriate T-
cell receptors (TCR); induction of tolerance in MBP-specific T cells; and induction of GA-specific T cells expressing T-helper type 2 (Th2), anti-inflammatory cytokines.

The avid binding of GA to MHC class II sites on antigen presenting cells (APCs) interferes with antigen presentation to T cells.\textsuperscript{[28,29]} With other antigens, binding to MHC class II molecules can require preprocessing by proteolytic enzymes secreted by the APCs. Such preprocessing is not needed for GA binding, and protease inhibitors do not interfere with GA binding to MHC class II sites on various APCs, including monocytes, splenic macrophages, and B cells transformed by Epstein-Barr virus.\textsuperscript{[30]} Binding of GA to MHC class II sites blocks interactions with MBP, PLP, and MOG.\textsuperscript{[23,31]} However, D-GA, made from D-isomer amino acids, also binds to MHC class II sites but does not have significant effect in treating or preventing EAE.\textsuperscript{[26]} This finding demonstrates that competition at MHC sites alone does not explain the therapeutic effects of GA in EAE or MS.

GA might have an antigen-specific T-cell interaction, since MHC binding of the drug does not seem to block immune responses to non-myelin antigens. TCR antagonism was suggested in a study that showed that GA-MHC complexes could function as a competitive antagonist to MBP peptide(82–100)-MHC complexes.\textsuperscript{[32]} In this model, GA could be an altered peptide ligand for MBP fragments. Another study that used different T-cell clones found no partial agonist or antagonist activity associated with GA interactions with TCR.\textsuperscript{[33]} This mechanism of action would require the presence of GA-MHC complexes in the same compartment in which MBP fragment-MHC interactions with TCR occur and, thus, is considered unlikely.

Patients treated with GA for a few months develop an increase in GA-specific T cells. With continued drug administration the frequency of these cells decreases.\textsuperscript{[34]} Possible mechanisms for this reduction in GA-specific T cells include the induction of anergy or apoptotic cell death.\textsuperscript{[33,35]} Binding of GA-MHC complexes with the TCR of MBP-specific T cells could lead to differential signaling and the induction of unresponsiveness in these cells. This mechanism of action would also have GA functioning as an altered peptide ligand, and it is appealing because the process could occur in the peripheral circulation.

Finally, there is considerable evidence that GA administration leads to the creation of GA-specific T cells that secrete cytokines with a Th2, anti-inflammatory profile. The GA-specific, Th2-polarized T-cell phenotype appears to recognize myelin antigens in a non-specific way and mediate bystander suppression. This mechanism of action was suggested in EAE studies.\textsuperscript{[36]} Helper T-cell lines induced by MBP secrete cytokines with a pro-inflammatory, T-helper type 1 (Th1) profile (interleukin (IL)-2, interferon (IFN)-γ), but GA-induced T-cell lines progressively shifted to a Th2 secretion profile.\textsuperscript{[25]} When exposed to MBP, these GA-specific T cells also responded by secreting the Th2 cytokines, IL-4, IL-6, and IL-10. Adoptive transfer of the GA-specific T cells suppressed the development of EAE induced by whole mouse spinal cord homogenate (MSCH). Since MSCH-induced EAE includes MBP as a major encephalitogenic antigen, it was possible that the amelioration of EAE by GA was related more to suppression of the MBP antigen responses than to other antigenic components of myelin. A follow-up study demonstrated that GA-specific T cells secreting Th2 cytokines suppressed EAE induced by antigens to which the cells did not cross-react. Adoptive transfer of GA-specific T cells improved EAE induced by PLP and PLP epitopes p139–151 (relapsing-remitting EAE) and p178–191 (chronic progressive EAE).\textsuperscript{[37]}
Activated T cells that are specific to any antigen are capable of crossing the blood-brain barrier. In support of this observation, GA-specific T-cells secreting the Th2 profile of cytokines have been demonstrated in the CNS of mice treated with GA. In this study, highly reactive GA-specific T cells secreting IL-4, IL-5, IL-6, IL-10, and transforming growth factor were isolated from the brains and spinal cords of SJL/JxBALB/c mice. Adoptively transferred, labeled GA-specific T cells were found in brain sections at 7 and 10 days after peripheral injection. To the extent that the treatment effects of GA on EAE and MS are similar, this study supports the role of GA-specific Th2 suppressor cells, which can cross the blood-brain barrier and accumulate in the CNS. Stimulation of these cross-reacting cells by MBP or MBP fragments could then result in secretion of immunomodulatory Th2 cytokines in situ.

In a study of eight MS patients initiating therapy with GA, T-cell lines were categorized by their proliferative responses to GA and MBP antigens and profiled according to cytokine production. A high percentage of lymphocytes in the pretreatment samples responded to GA. As in previous studies, continued treatment with GA resulted in a decrease in the number of responsive T-cell lines. Using the ratio IFN-γ:IL-5 as a measure of Th1 to Th2 proclivity, GA-reactive lymphocytes had a significant Th2 bias compared with MBP-reactive cells. While IFN-β treatment reduces the expression of IFN-γ by T-cells, GA-treated MS patients are not different in their T-cell expression of IFN-γ compared with untreated subjects. A recent study showed that the CD4+ T-cell response to GA was similar in both MS patients and normal controls. However, pretreatment CD8+ T-cell responses were significantly lower in MS patients and increased to the normal range after GA therapy. GA may have different mechanisms of action in CD4+ and CD8+ T-cells, operating on each population in a separate but synergistic manner to alter the immunological pathways involved in MS.

GA-specific T-cell lines isolated from three patients with MS and one control produced TNF-α, IFN-γ, IL-4, IL-6, and IL-10. MBP-specific T-cells produced the same cytokine profile, except for IL-6. The GA-specific cell lines also inhibited the proliferation of MBP-specific cell lines in co-culture experiments. GA injected daily could therefore interact with lymphocytes in regional lymph nodes and suppress autoreactive T-cell production. Activated GA-specific T-cells could also cross the blood-brain barrier to modulate inflammation in the CNS.

Several studies have examined the production of antibodies to GA. A group of 130 patients from GA clinical trials were studied for drug-induced, humoral immune responses. All patients developed GA-reactive antibodies peaking at 3 months of therapy, then declining to near baseline. Immunoglobulin (Ig)G1 levels were two to three times higher than IgG2 levels, suggesting a Th2 response. Antibody responses to GA were not associated with loss of efficacy or with side effects.

The migration properties of T cells isolated from GA-treated MS patients were reduced compared with T cells from untreated patients but not to the extent of patients treated with IFN-β. Furthermore, in contrast to IFN-β, GA does not seem to inhibit expression of adhesion molecules on vascular endothelium.

Thus, GA functions as an antigen and induces proliferation of T-cell lines from controls and patients with MS. Repeated daily injections result in loss of proliferative responses and induce the production of the Th2 cytokines. GA induces a Th1 to Th2 shift in cytokine expression; in addition approximately 25% of GA-specific T-cell clones
secrete IL-5 in response to MBP or MBP antigenic fragments. The MBP antigens may function as partial agonists inducing the expression of Th2, immunoregulatory cytokines.\[51]\) GA is the first known treatment of an autoimmune disease that functions by binding to the TCR. In addition, the GA-induced Th1 to Th2 shift seems to be GA-specific.\[52]\) These results support bystander suppression as a potential mechanism of action of GA in the treatment of multiple sclerosis.

Recent evidence suggests a potential role for the immunomodulatory effects of GA in the inhibition of graft rejection.\[53]\) Skin and thyroid transplants in mice had improved survival and function with GA treatment. GA administration induced Th2 cytokine responses to graft cells and inhibited Th1 responses.

GA-specific T cells demonstrated a neuroprotective effect in a rat optic nerve crush injury model. Adoptive transfer of GA-specific T cells also demonstrated the protective effect.\[54]\) It is possible that GA-specific Th2-like T cells secrete neurotrophic factors in addition to the anti-inflammatory cytokines.

The picture emerges that GA copolymers bind efficiently to MHC class II molecules on peripheral APCs and displace other potential myelin antigens. Subsequent interaction with T cells and their specific receptors in a trimolecular complex leads to induction of GA-specific T-cells. These T-cells are suppressor in nature and cross the blood-brain barrier, where they can be reactivated in situ by the cross-reacting antigens originating from myelin proteins. The reactivated Th2 cells secrete suppressor cytokines, producing bystander suppression of the immune response directed against myelin. Whereas MBP specific T suppressor cells either maintain some Th1 properties or can shift back to a Th1 profile when reactivated in vivo, GA-specific Th2 cells appear to be confined to their suppressor profile. This mechanism may be critical in diseases such as EAE and MS, where epitope spreading has been demonstrated.\[20,55]\)

**CLINICAL TRIAL DATA**

**Preliminary clinical studies**

The first human use of GA was in three patients with acute disseminated encephalomyelitis and four patients in the terminal stages of MS.\[56]\) A small, phase I, open-label clinical trial was then carried out by Bornstein et al. at the Albert Einstein College of Medicine to begin to assess efficacy of GA in MS and to study further the toxicity and safety of GA.\[57]\) GA was well tolerated, and no toxicities or adverse effects were noted.

**Pilot trial of GA in relapsing-remitting MS—1987**

The first randomized, double-blind study of GA in MS was also conducted by Bornstein and colleagues at the Albert Einstein College of Medicine.\[58]\) The primary endpoint of the pilot trial was the proportion of relapse-free patients on treatment. The trial was also designed to characterize toxicities and significant side effects. The study enrolled 48 patients in 24 pairs matched for age, sex, and disability, stratified in three disability status scale (DSS)\[59]\) ranges: 0–2, 3–4, and 5–6. Two additional unmatched patients were also
enrolled. One member of each pair was randomly assigned to drug, the other to placebo. All patients had active MS defined as exacerbations in the previous 2 years and were between 20 and 35 years of age. After an initial visit at month 1, each patient was assessed every 3 months for a total period of 2 years. A blinded neurologist performed a neurological examination at each visit. In addition, patients were seen for suspected exacerbations, defined as new or worsening neurological symptoms persisting for at least 48 hours or more and producing objective changes on examination leading to a 1-point increase in their DSS. Subjective symptoms alone, such as sensory changes, were not considered as exacerbations. About 75% of exacerbations in both placebo and treatment groups were treated with corticosteroids.

Seven patients did not complete the full 2 years of the trial. Two of these patients were in the placebo group and were excluded from the final analysis. Partial data available from the other patient was included in the analyses. Twenty-two patient pairs (44 patients) were compared in a matched analysis of the primary endpoint. Four other patients were included in an unmatched analysis. Discordant pairs were those in which one patient had exacerbations on GA or placebo, while the matched patient in the other treatment group had none. There were 12 discordant pairs, involving 10 patients on GA who had no exacerbations while their placebo matches did, and two patients on placebo who had no exacerbations while their GA-treated matches did. Statistical analysis showed a significant difference in discordant pairs in favor of fewer relapses in the GA-treatment group compared with the placebo group \( p=0.039 \). The unmatched analysis also reached statistical significance for the occurrence of fewer exacerbations on GA \( p=0.045 \).

There were a total of 16 exacerbations in the 25 patients receiving GA and 62 exacerbations in the 23 patients receiving placebo (Fig. 23.1). Data stratified by entry DSS showed that patients in the lower disability ranges who were receiving GA tended to have fewer relapses than patients with higher DSS at entry. More patients on GA completed the trial relapse-free, and placebo-treated patients were more likely to have had three or more relapses. Each of these results reached statistical significance. Survival curves showed a marginally significant slowing of progression of disability \( p=0.05 \) at the end of 24 months, defined as an increase of 1 full point on the DSS sustained for 3 months (Fig. 23.2).

No abnormalities were noted in any laboratory measures during the study. Two patients had an unusual, transient post-injection reaction to GA, which consisted of flushing and chest tightness, sometimes accompanied by anxiety and dyspnea. The symptoms resolved in 5–30 minutes without sequelae. One of the patients with these symptoms developed uncomfortable urticaria and pruritus after restarting the medication and was treated with epinephrine and corticosteroids.

**Trial in chronic progressive MS—1991**

One clinical trial of GA has been completed for patients with chronic progressive MS. Patients were required to have documented progression of disability by one of four expanded disability status scale (EDSS) criteria, persisting for at least 3 months. Of 169 patients followed for 6–15 months, 106 showed such progression and were entered into the study. The primary study endpoint was the time to confirmed progression of 1 point on the EDSS for patients with baseline EDSS of \( \geq 5.0 \) and 1.5 points for patients
with baseline EDSS of <5.0. Survival curves for the probability of progression in each treatment arm are shown in Fig. 23.3. There was a trend for less progression in the GA group compared with placebo (17.6% versus 25.5%), which did not reach statistical significance.

**Phase III double-blind, placebo-controlled trial—1995**

Following publication of the positive pilot study of GA in relapsing-remitting MS, there was great interest in confirming safety and efficacy of the drug in a larger, phase III trial. The further devel-
Fig. 23.1 Relapses occurring during the 2 years of the pilot relapsing-remitting MS trial. Each line represents a patient and each circle an
exacerbation. Patients are grouped according to their EDSS score on entry. The numbers of pretrial exacerbations are indicated to the left. Discontinued lines represent patients who withdrew before completion. The open circle indicates an exacerbation occurring after withdrawal that was included as a study event. Patients who were not included in the matched-pair analyses are indicated by an asterisk.

Development and testing of GA was assumed by Teva Pharmaceuticals, Ltd of Petah Tikva, Israel, and considerable effort was put into standardizing manufacturing methods to provide the kilogram quantities of drug needed to conduct such a trial. The final product was approved by the FDA and consisted of random, synthetic polypeptide chains ranging in molecular weight from 4 to 13 kDa. The four amino acids L-alanine, L-glutamate, L-lysine, and L-tyrosine were combined in molar ratios of 4.2, 1.4, 3.4, to 1.0. A dose of 20 mg administered by daily subcutaneous injection for 24 months was selected as the study dose for a double-blind, placebo-controlled trial.

The trial began in October 1991, at 11 university-based MS centers in the USA. The primary endpoint of the study was the mean number of MS relapses in GA-treated subjects compared with subjects on placebo. Relapses were defined as the appearance or reappearance of one or more neurological abnormalities persisting for at least 48 hours. A relapse was not confirmed unless the patient was stable or improving for the previous 30 days. Prospectively defined secondary endpoints included:

- the proportion of relapse-free patients;
- time to first relapse after initiation of therapy;
**Fig. 23.2** Curves representing the probability of no worsening from the baseline EDSS score. Worsening was determined when first observed but was counted only if it continued for 3 months.
Fig. 23.3 Trial in progressive MS. Probability of progressing to confirmed progression.

- mean change in EDSS and ambulation index from baseline to study completion; and
- proportion of patients with sustained progression, defined as an increase of 1 full point on the EDSS persisting for at least 3 months.

Patients were given a 30-day supply of the study drug at monthly visits, at which they reported adverse events, changes in their condition, or use of concomitant medications. Every 3 months each patient underwent a detailed assessment by two neurologists, one a blinded examiner who performed the EDSS evaluation and other objective assessments without information pertaining to symptoms or adverse events. The second neurologist acted as the treating physician, assessing symptoms and adverse events and treating relapses with corticosteroids as needed. A nurse co-ordinator at each site performed nursing assessments and collected blood and urine samples for laboratory analysis. All patients and study personnel, including the neurologists and co-ordinators, were blinded to the individual study drug assignment.

Patients enrolled in the study were clinically stable, without use of corticosteroids, for the preceding 30 days. No patient had previously received GA, immunosuppressive therapy or total lymphoid irradiation. Other exclusion criteria included pregnancy, positive HIV or human T-cell leukemia virus-1 serology, insulin-dependent diabetes mellitus, or chronic need for aspirin or non-steroidal anti-inflammatory drugs. Women of child-bearing potential were required to use an appropriate method of contraception.

A total of 251 patients were randomized to GA or placebo. The two groups were well matched for age, sex, duration of disease, mean relapse rate in the preceding 2 years,
EDSS, and ambulation index. The mean age of the subjects was 34 years, and 73% were women. All had clinically definite or laboratory supported MS with EDSS scores ranging from 0 to 5.0. The proportion of patients in different EDSS ranges is shown in Table 23.1.

There were 161 confirmed relapses in the GA-treated group and 210 in the placebo group. Confirmation of relapse required that symptoms be accompanied by objective abnormalities on neurological examination resulting in a minimum half-step increase in the EDSS, a 2-point increase on one of seven FSS, or a 1-point change on two or more FSS. The mean annualized relapse rate was 0.59 per year for the GA-treated patients and 0.84 per year for the placebo group, a 29% reduction ($p=0.007$). Patients with EDSS scores between 0 and 2 at study entry had a reduction in relapse rate of 33% (Fig. 23.4).

Several of the secondary trial endpoints were designed to evaluate the effects of GA on progression of neurological disability. The results of analyses for these endpoints are shown in Table 23.2. Mean EDSS change from baseline was significantly lower for the treatment group compared with placebo ($p=0.023$). Changes in ambulation index and the number of progression-free patients, defined as an increase of 1 or more points on the EDSS sustained for 3 months, showed little difference between groups. A categorical analysis of patients as being the same, better, or worse during the trial showed a statistical benefit for GA (Table 23.2, Fig. 23.5).

Treatment with GA was not associated with any hematological, metabolic, urinary, or cardiac

### Table 23.1 Pivotal trial of GA in relapsing-remitting MS. Entry EDSS ranges for patients randomized to study drug or placebo

<table>
<thead>
<tr>
<th>EDSS range</th>
<th>Copolymer 1</th>
<th>Placebo</th>
<th>Total fraction (n=251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2.0</td>
<td>20%</td>
<td>27%</td>
<td>47%</td>
</tr>
<tr>
<td>&gt;2.0 to 4</td>
<td>23%</td>
<td>18%</td>
<td>41%</td>
</tr>
<tr>
<td>&gt;4.0 to 5.0</td>
<td>7%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>
Fig. 23.4 Changes in relapse rate observed over 2 years, by baseline EDSS score. The numbers above each bar represent the mean 2-year relapse rate for each group.

abnormalities. Mild erythema, stinging, and induration at injection sites were the most common adverse events reported. The transient post-injection reaction, first observed in the pilot trial, occurred in 15% of GA-treated patients, usually within seconds or minutes of an injection. Variable combinations of flushing, chest tightness, sense of shortness of breath, palpitations, and anxiety characterized the reaction. Typical episodes lasted between 30 seconds and 30 minutes, and no patient experienced serious sequelae. Four patients in the GA group and one in the placebo group discontinued therapy because of this reaction. Three women became pregnant while enrolled in the trial, and all were taking active drug. One had a therapeutic abortion and the other two discontinued treatment and delivered normal infants.

This 2-year pivotal trial confirmed that daily, subcutaneous injections of GA were effective in reducing the relapse rate in patients with
Table 23.2 Disability experience measured by EDSS and ambulation index of GA and placebo groups (secondary endpoints)

<table>
<thead>
<tr>
<th></th>
<th>Copolymer 1</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with a change in disability between baseline and conclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved (EDSS decrease ≥1)</td>
<td>24.8%</td>
<td>15.2%</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>54.4%</td>
<td>56.0%</td>
<td>0.037*</td>
</tr>
<tr>
<td>Worse (EDSS increase ≥1)</td>
<td>20.8%</td>
<td>28.8%</td>
<td></td>
</tr>
<tr>
<td>EDSS change from baseline (mean±SD)</td>
<td>−0.05±1.13</td>
<td>0.21±0.99 0.023†</td>
<td></td>
</tr>
<tr>
<td>Proportion of progression-free patients</td>
<td>78.4%</td>
<td>75.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Ambulation index (mean±SD)</td>
<td>0.27±0.94</td>
<td>0.28±0.93 NS</td>
<td></td>
</tr>
</tbody>
</table>

EDSS, Expanded Disability Status Scale; NS, not significantly different.
* Categorical repeated measures.
† Repeated-measures analysis of covariance.

relapsing-remitting MS. Secondary endpoint analyses showed benefit for GA in slowing the progression of disability. On the basis of the 24-month trial data, the FDA approved GA for use in relapsing-remitting MS in December 1997.

Extension of the phase III trial—1998

Early in the course of the phase III trial, a decision was made to continue all patients on blinded study medication until the last patient enrolled in the trial had completed 24-month follow-up. Some patients were on blinded medication for up to 35 months, resulting in an average of 5.5 months of additional double-blind study data. Conditions of the extension period of the study with respect to blinding and protocol were unchanged. The 24-month core study and extension phase data were combined in a second report of the safety and efficacy of GA. [62]

The characteristics of the patients continuing in the double-blind extension period of the trial are shown in Table 23.3. Approximately equal numbers of patients in the GA arm (n=19) and the placebo arm (n=17) of the 24-month core study dropped out after nearly equal periods of time. A total of 215 patients completed 24 months of the core study and were eligible to continue in the extension phase. Of these, 203 (94.4%) elected to enter the extension phase. Near the end of the 24-month core study period,
Fig. 23.5 Percentage of patients who improved, were unchanged, or were worse by 1 or more EDSS steps between baseline and the last (24-month) measurement (repeated-measures ANCOVA). The numbers above the bars represent the percentage of patients in the respective GA or placebo group.

interferon beta-1b became the first FDA-approved drug for the treatment of relapsing-remitting MS. All patients in the GA trial were notified of this development and signed a new informed consent to continue in the trial. The availability of interferon beta-1b was the most common reason patients gave for dropping out after the core study and not continuing in the extension phase. There was no evidence that any bias was introduced into the extension phase data by the subgroup of patients opting not to continue. Their characteristics are also summarized in Table 23.3.

The mean relapse rate was the primary endpoint of both the core and extension phases of the trial. The core plus extension period data showed that the annualized mean relapse rate was 0.67 per year for the GA-treated cohort and 0.99 per year for the placebo group, a reduction of 32% ($p=0.002$). This result compared well with the 29% reduction in relapse rate observed in the core trial. At the end of the extension phase of the trial, 23.6% of the placebo group and 33.6% of the GA group were relapse-free from study initiation ($p=0.035$). The numbers of patients having no relapses, one or two relapses, or
three or more relapses during the study are shown in Table 23.4. Placebo-treated patients were more likely to have had multiple relapses during the trial ($p=0.008$).

Compared with the 24-month core trial data, more of the secondary measures of progression of disability showed significant benefit with GA treatment. A categorical analysis based on change by 1 or more EDSS steps demonstrated that more GA-treated patients improved compared with placebo-treated patients, who were more likely to worsen ($p=0.001$) (Fig. 23.6). Time to worsening by 1.5 or more steps on the EDSS was evaluated using a Kaplan-Meier approach. In order to eliminate bias due to higher EDSS scores during relapses, the period of time from each relapse onset to stable recovery or plateau of disability for 30 days was determined. All EDSS data from these relapse intervals were removed before the survival analysis was performed. Excluding the relapse interval, 21.6% of GA-treated patients worsened by 1.5 or more EDSS steps, compared with 41.6% of the placebo-treated patients (Fig. 23.7). This was a significant difference of almost 50% ($p=0.001$). At the end of the extended trial, 25 of 125 placebo patients and 16 of 125 GA patients were worse by 1.5 points or more on the EDSS. This result differs from the Kaplan-Meier analysis, where patients who reach the progression endpoint of 1.5 or more EDSS steps are, by definition, excluded from further analysis. Some patients who reached this endpoint in the Kaplan-Meier analysis improved at

Table 23.3 Characteristics of patients in the initial and extended GA study

<table>
<thead>
<tr>
<th>Initial 24-month study</th>
<th>Extension study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized</strong> (n=251)</td>
<td><strong>Completed 24 months</strong> (n=215)</td>
</tr>
<tr>
<td>Glatiramer acetate (n=125)</td>
<td>Glatiramer acetate (n=126)</td>
</tr>
<tr>
<td>Age (y) 34.58 ± 5.97</td>
<td>34.33 ± 6.49</td>
</tr>
<tr>
<td>Duration of disease (y) 7.25 ± 4.85</td>
<td>6.64 ± 5.09</td>
</tr>
<tr>
<td>Prior 2-year relapse rate 2.91 ± 1.26</td>
<td>2.93 ± 1.13</td>
</tr>
<tr>
<td>Baseline EDSS 2.82 ± 1.19</td>
<td>2.42 ± 1.12</td>
</tr>
</tbody>
</table>

EDSS=Expanded Disability Status Score.
Table 23.4 MS relapse experience (24-month core and extended trial periods)

<table>
<thead>
<tr>
<th></th>
<th>Glatiramer acetate</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core study (24 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of relapses per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>60</td>
<td>55</td>
<td>0.023</td>
</tr>
<tr>
<td>≥3</td>
<td>23</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Core and extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of relapses per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>53</td>
<td>51</td>
<td>0.008</td>
</tr>
<tr>
<td>≥3</td>
<td>30</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

later times, resulting in fewer patients showing this level of progression at the end of the extended study than reaching the endpoint at any time during the study.

Safety and tolerability of GA was confirmed in the extension period. There were no laboratory abnormalities associated with GA use. Mild injection reactions of erythema and pain occurred in approximately two-thirds of patients injecting GA and one-third of patients injecting placebo. At the end of the extension phase, 19 patients had had at least one transient, self-limited injection reaction. One patient experienced a total of seven such reactions in 30 months yet continued on treatment. Overall, this unusual reaction occurred in about one in every 840 daily injections.

Comparative trial—2001

A prospective study compared interferon beta-1a, interferon beta-1b, and GA in relapsing-remit-
Fig. 23.6 Percentage of patients who improved, were unchanged, or were worse by 1 or more EDSS steps between baseline and the last measurement. Repeated measures analysis (RMA) and baseline (BL) to last visit observations are shown. The RMA and the p value of 0.024 refer to a repeated measures analysis of the proportion of patients in each of the three categories (improved, no change, or worsened) at each time point (every 3 months). As shown by the numbers above the bars, 27.2% of patients treated with GA and 12% of patients receiving placebo showed an improvement at study termination. The p value of 0.001 is derived from the Cochran-Mantel-Haenszel test on the $2 \times 3$ contingency table (two treatment groups by the three categorical changes of improved, no change, or worsened).
The study was designed to approximate the clinical practice setting and showed that over 12 months and 18 months, GA and interferon beta-1b were more effective in reducing relapse rates than interferon beta-1a. However, this study was open-label and not randomized and, therefore, was subject to potential bias. Additional, better-designed comparative trials would be needed to clarify the results of this small study.

**Fig. 23.7** Time to increased disability determined by 1.5 or more EDSS steps (Kaplan-Meier analysis). In the placebo group, 41.6% of patients worsened by 1.5 or more EDSS steps during the extended trial, whereas for those receiving GA, only 21.6% worsened ($p=0.001$; $x^2$ test). EDSS scores determined during the period of recovery after each relapse (the relapse-remission interval) was excluded from the analysis.
LONG-TERM OPEN-LABEL USE OF GA IN MS

At the end of the extension period of the phase III trial of GA in relapsing-remitting MS, patients who had been on GA or placebo for up to 35 months were offered GA treatment in an open-label study. Of the total of 251 patients enrolled in the original double-blind trial, 152 were followed for 6 years in the open-label study—77 from the GA treatment group (group A) and 75 from the placebo group (group B). Baseline characteristics of the patients completing 6 years of open-label GA are shown in Table 23.5. These patients were followed at 6-month intervals and they reported to the study centers for evaluations of relapses and adverse effects, as they had done in the phase III trial (Fig. 23.8). Neurological assessments for EDSS were recorded at each visit, along with safety data.

At completion of the pivotal double-blind trial, this cohort of 152 patients had a relapse rate of 0.88 per year in the placebo group and 0.56 per year in the GA group. The patients who were on GA from study outset showed a steady yearly decline in relapse rate. By the end of year 6, the relapse rate for this subgroup of patients was 0.23 (Fig. 23.9). This rate corresponds to one attack every 4–5 years. Group A was analysed as improved by 1 or more EDSS steps, unchanged, or worsened by 1 EDSS or more steps (Fig. 23.10). Approximately 69% of these patients were the same or better by these criteria, and 31% were worse. A similar categorical analysis for each year of the study showed that the neurological disability of patients always on

![Fig. 23.8](image)

**Fig. 23.8** Design of USA pivotal trial of GA in relapsing-remitting MS. Both double-blind and open-label phases are shown.
Table 23.5 Patient characteristics at entry into the open-label phase

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=101)</th>
<th>Group B (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>29 (29)</td>
<td>25 (23)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>72 (71)</td>
<td>82 (77)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±sd</td>
<td>37.5±5.8</td>
<td>36.9±6.6</td>
</tr>
<tr>
<td>Range</td>
<td>22–49</td>
<td>22–48</td>
</tr>
<tr>
<td>Age onset of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±sd</td>
<td>27.3±6.0</td>
<td>27.6±6.5</td>
</tr>
<tr>
<td>Range</td>
<td>14–42</td>
<td>11–42</td>
</tr>
<tr>
<td>Relapses reported during 2 years before entry into the open-label phase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±sd</td>
<td>1.21±1.42</td>
<td>1.74±1.81</td>
</tr>
<tr>
<td>Range</td>
<td>0–6</td>
<td>0–7</td>
</tr>
<tr>
<td>EDSS score at entry into the open-label phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±sd</td>
<td>2.70±1.62</td>
<td>2.76±1.80</td>
</tr>
<tr>
<td>Range</td>
<td>0–7</td>
<td>0–7</td>
</tr>
</tbody>
</table>

*p=0.022; sd, standard deviation.

GA for 6 years has been relatively stable (Fig. 23.11). In comparison, 43% of patients in group B who spent up to 35 months on placebo before initiating treatment with GA had worsened by 1 or more EDSS steps. When examined yearly, the

*Fig. 23.9 Open-label GA study.
Relapse rate in each year of the 6-year study for patients in group A (always on GA) compared with group B (on placebo for 24–35 months then changed to GA).
placebo-active treatment patients from group B consistently had a higher percentage of worsened disability and never caught up to the patients in group A who had always been on active treatment (Fig. 23.12). A categorical analysis of

**Fig. 23.10** Open-label GA study. Categorical distribution by EDSS change from baseline to last observation over 6 years for patients in group A, always on GA.

**Fig. 23.11** Open-label GA study. Yearly EDSS change from baseline by year of study for patients in group A.
Fig. 23.12 Percentage of patients who worsened by 1.0 or more EDSS steps from baseline in each year of the open-label study. (Group A, always on drug versus group B, placebo and then active treatment.)

Relapse-free patients at 6 years showed that only 11% of subjects in group A showed worsening by 1 or more EDSS steps (Fig. 23.13). This observation suggests that the group A patients without relapses did not make a transition to secondary progressive MS. Approximately 68% of the patients who entered the open-label trial were still using GA at 8 years of follow-up, consistent with an ongoing benefit and tolerability. Many of the patients have now completed 10 years in the open-label phase, the longest organized study of treated MS patients. There are inherent limitations to measuring drug efficacy in open-label studies. The absence of a placebo arm for comparison is important. However, there is no practical or ethical way to obtain long-term efficacy data using a placebo group when effective treatments for a disease are available. Comparisons can be made to natural history data or to placebo groups from other clinical trials, but such comparisons are hazardous because studies are conducted differently and enroll diverse types of patients and because the outcome measures can be difficult to compare across trials. Additionally, patients who drop out of open-label studies may introduce a bias, especially if the reason is disease activity and progression of disability. In general, patients who elected not to continue in the open-label phase showed more progression of their MS in the double-blind phase than those who did enter the open-label phase. The patients who continued in the open-label study tended to be patients who tolerated GA and who responded to the drug over the long term.
Despite these difficulties, carefully designed open-label studies remain the best alternative to placebo-controlled trials for obtaining long-term safety and efficacy data. Open-label extensions of phase III clinical trials can enhance the confidence of patients and clinicians in their choice of therapy. It would be sensible for future phase III treatment trials in MS to plan for ongoing open-label studies after the initial double-blind study has been completed.

MAGNETIC RESONANCE IMAGING DATA SUPPORTING GA EFFICACY

Magnetic resonance imaging add-on study

The phase III trial of GA in relapsing-remitting MS did not include center-wide, serial magnetic resonance imaging (MRI) data as secondary endpoints of efficacy. Twenty-seven patients in the study at one center underwent frequent MRI scans. A subsequent analysis of images from this site suggested a decrease in gadolinium-enhancing activity and reduced atrophy progression in GA-treated patients compared with those on placebo.[66]

Italian MRI study—1998

A second small study followed monthly MRI changes in a group of 10 patients with relapsing-remitting MS.[67] The patients received monthly gadolinium-enhanced MRI scans for a period of 9–27 months before starting therapy with GA. Six of the subjects had scans for 25–27 months before initiation of treatment. Each patient then had monthly MRI scans for 10–14 additional months while on GA. The incidence of new gadolinium-enhancing lesions was decreased in the GA-treated patients (0.92 per month) compared
with their scans before treatment (2.20 per month). This represented a 57% reduction but was significant only at the $p=0.1$ level by Wilcoxon signed rank test.

**European-Canadian MRI Study—2001**

In 1997, a large, randomized, double-blind, placebo-controlled MRI trial was initiated at 35 centers in Canada and Europe. Patients were randomized to GA or placebo for 9 months followed by an open-label phase for an additional 9 months. MRI scans were performed monthly for the first 9 months and every 3 months for the remaining 9 months. The design of this study, which aimed at investigating the effects of GA on MRI lesion load and new lesion formation is shown in Fig. 23.14. Patients were required to have a diagnosis of relapsing-remitting MS with one or more relapses in the 2 years preceding entry into the trial and one or more gadolinium-enhancing lesion on a screening MRI scan. A total of 485 patients were screened, and 239 were enrolled in the study. There were no significant demographic or MRI differences in the placebo and treatment groups at study entry. The primary outcome measure was the number of gadolinium-enhancing lesions on T1-weighted images. Secondary endpoints included:

- the proportion of patients with gadolinium-enhancing lesions;
- gadolinium-enhancing lesion volume;
- the number of new gadolinium-enhancing lesions;
- the total number of lesions on T2-weighted images;
- the number of new lesions on T2-weighted images; and
- the volume of hypointense lesions (‘black holes’) on T1-weighted images.

The 9-month double-blind data showed a 29% reduction in the mean number of gadolinium-enhancing lesions in the GA-treated group (25.96) compared with the
placebo group (36.8) \((p=0.003)\). The change in volume of gadolinium-enhancing lesions from baseline in the GA cohort was less than placebo \((p=0.01)\). Examined monthly, the cumulative gadolinium-enhancing lesion volume in GA-treated patients began to separate from the placebo group around month 5 and reached statistical significance in the third trimester (Fig. 23.15). The mean number of new gadolinium-enhancing lesions was reduced by 33\%, and the mean number of new T2-weighted lesions was reduced by 33\% \((p \leq 0.003 \text{ for both})\) in the treated cohort. Change in total T2-weighted image lesion volume from baseline was lower for the GA-treated patients \((p=0.006)\). The reduction in relapse rate was 33\% \((p=0.012)\), consistent with the pivotal phase III trial extension data. Although GA significantly reduced MRI disease activity and lesion burden, the effects took several months to develop and paralleled the observed evolution of clinical effects. Compared with IFN-\(\beta\)s, the effect of GA on gadolinium-enhancing MRI lesions is modest, yet similar on clinical endpoints. The best explanation for these data is the different mechanism of action for the two classes of immunomodulators.

An interesting analysis of MRI scans from the

**Fig. 23.15** Cumulative median enhanced lesion volume from randomization. Statistically significant differences emerged during the third trimester.

European-Canadian MRI Study\(^{[68]}\) examined the proportion of new MS lesions evolving into ‘black holes’.\(^{[69]}\) In this study 1722 new MRI lesions from 239 patients were evaluated. New lesions were defined as T2 lesions in an area of previously normal white matter with gadolinium-enhancement on a corresponding T1-weighted image. The evolution of each lesion was then followed to determine the persistence of a T1 black hole and the frequency of re-enhancement. Over 9 months of the double-blind phase, these lesions could be tracked for changes up to 8 months from initial identification of the new lesion. GA-treated patients had fewer lesions that evolved into black holes than placebo patients at 7 months (18.9 versus 26.3\%; \(p=0.04\)) and at 8 months (15.6 versus
31.4%; \( p=0.002 \). Typically, about 40% of new MS lesions result in persistent black holes on T1-weighted MRI and correlate with more severe tissue damage in the lesions.\(^{[70–73]}\) Further analysis of data from the European-Canadian MRI Study assessed treatment effects on brain volume changes.\(^{[74]}\) Image sets from 113 of 119 patients randomized to GA and 114 of 120 patients randomized to placebo were segmented for brain volume measurements from seven contiguous periventricular slices. Scans of these subjects were analysed at baseline, at the end of the 9-month double-blind phase, and at the end of the 18-month study. Although a trend was observed for a treatment effect on slowing the progression of brain atrophy at 9 months, no statistically significant effects were noted. Treatment effects on relapse rate and new MRI lesion activity are significant in this time frame,\(^{[68]}\) and the lack of a significant effect on brain volume measures reinforces the possibility that control of inflammatory MS activity is only partly related to the subsequent development of brain atrophy.

**SUMMARY**

GA is a novel preparation of synthetic copolymers with proven therapeutic benefit in MS. It is perhaps the only drug currently available for use in MS that was truly derived from studies of the more than one hundred compounds shown to prevent or ameliorate EAE. Patients with MS have a life-long disease for which no cure is currently available. Treatments are needed with sustained efficacy, which slow the progression of disability and the frequency of relapse. Patient tolerability is an important aspect of any treatment for a chronic illness. Although the IFN-\( \beta \)s are generally well tolerated, a significant proportion of patients have problems with flu-like side effects such as malaise, low-grade fever, chills, and myalgias. GA has no flu-like side effects. It is regarded as the most tolerable of the available immunomodulator treatments for MS, a characteristic important for patients who may require therapy for decades. Transient post-injection reactions occur infrequently and have never been associated with serious sequelae. Injection site reactions are typically minor and are rarely a cause for discontinuing therapy. Since the mechanism of action of GA is different from that of the IFN-\( \beta \)s, patients and their physicians have the option to use a different drug when lack of efficacy or side effects of one agent mandate a change. Relapse rate reduction and slowed progression of disability make GA a legitimate first-line choice for the treatment of relapsing forms of MS.

Since the recognition that both GA and the IFN-\( \beta \)s are effective in the treatment of MS, the thought of combining the two drugs for potential synergy has been considered. To date no controlled trials of combined therapy have been completed, leaving the clinician with little objective evidence to support such an approach. A small in vitro study found that mitogen-induced T-cell activation was suppressed better by GA and interferon beta-1b together than by either drug alone.\(^{[75]}\) However, in another study, C57BL/6 F1 or SJL/J mice were given GA or saline before induction of EAE, and then treated with murine IFN-\( \beta \). Mice receiving either GA or IFN-\( \beta \) alone showed amelioration of EAE severity. Those receiving combination therapy developed EAE with a severity similar to untreated animals.\(^{[76]}\) At the time of this writing, a clinical trial of combination therapy with interferon beta-1a and GA is being organized. A safety study called CombiRx showed that adding daily injections of GA to weekly injections of interferon beta-1a was
well tolerated, and no negative interactions were suggested by gadolinium-enhanced MRI data.\textsuperscript{[77]}

The development of GA and the IFN-\(\beta\)s as treatments for MS represents a critical milestone in the care of patients with this disabling disease. Clinicians and patients now have proven therapeutic options, which clearly modify the disease course and offer the realistic hope of delaying progression. Most patients with clinically definite MS and a history of relapses should be considered for treatment with one of these agents, while the search for better agents and a cure continues.

REFERENCES


Glatiramer acetate as therapy for multiple sclerosis


63 Khan OA, Tselis AC, Kamholz JA et al. A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFNbata-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol* 2001; 8:141–148.

64 Khan OA, Tselis AC, Kamholz JA et al. A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFN beta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. *Multiple Scler* 2001; 7:349–353.


INTRODUCTION

Mitoxantrone (1,4-dihydroxy-5,8-bis((2-hydroxyethyl-amino)-ethyl)-amino) 9,10-anthracenedione hydrochloride), molecular weight 517 Da, is a synthetic antineoplastic agent first discovered in 1978. It has proven therapeutic efficacy in advanced breast cancer, non-Hodgkin’s lymphoma, acute lymphoblastic leukemia, chronic myeloid leukemia, liver carcinoma, and ovarian carcinoma.[1–5] Soon after its introduction as a cytotoxic agent in cancer chemotherapy, it was found to be immunosuppressive. Wang and colleagues showed that in vitro alloreactivity was almost completely abrogated by mitoxantrone.[6,7] The drug interfered only with lymphocytes capable of proliferating in response to newly presented antigens without affecting precursor populations. The effects were remarkably long-lasting. This prompted evaluation of mitoxantrone in experimental transplantation, where it was found to prolong greatly the survival of heterotopic cardiac transplants.[8] This evidence stimulated other investigators to examine whether mitoxantrone could modulate the course of experimental autoimmune encephalomyelitis (EAE). In these studies, mitoxantrone suppressed both actively and passively induced EAE in mice and guinea pigs.[9–12] At the same time, the contribution of macrophages in effecting myelin damage in EAE was established. Watson et al. demonstrated a blocking effect of mitoxantrone on in vitro myelin breakdown by macrophages retrieved from mice with EAE.[13]

Mitoxantrone was first tested as a potential disease-modifying therapy in multiple sclerosis (MS) in 1990.[14] Benefit on clinical and magnetic resonance imaging (MRI) parameters was initially shown in single-arm, unblinded trials.[14–17] Subsequently, on the basis of two controlled efficacy studies[18,19] and an open safety study,[20] in October 2000 the US Food and Drug Administration (FDA) approved mitoxantrone for worsening relapsing-remitting MS, secondary progressive MS, and progressing relapsing MS.

MECHANISMS OF ACTION

Cytotoxic actions

Mitoxantrone has several cytotoxic activities. It arrests the cell replication at the G2-M and S interphase. It has been shown to induce DNA protein cross-links and protein-concealed single-and double-strand breaks in DNA as well as non-protein-associated
strand breaks.\textsuperscript{[1,21]} Once cells are arrested in the G2 phase, they may enter cell-death pathways. Mitoxantrone was shown to induce programmed cell death of certain leukemia cells.\textsuperscript{[22,23]} This evidence was corroborated by the demonstration that natural resistance of acute myeloid leukemia cells is associated with the lack of apoptosis.\textsuperscript{[24]}

Mitoxantrone inhibits DNA topoisomerase II, an enzyme that promotes efficient condensation-decondensation of chromatin and segregation of replicated daughter chromosomes at cell division. Topoisomerase II changes the topology of DNA strands by the introduction of transient double-strand breaks through which an intact helix can pass. Topoisomerase II also engages in a non-covalent protein-DNA complex that equilibrates with a so-called ‘covalent-cleavable’ complex.\textsuperscript{[25,26]} The cleavable complex formed between DNA and topoisomerase II is stabilized by mitoxantrone, thereby preventing religation of transient double-strand DNA.\textsuperscript{[25,27]}

Mitoxantrone may induce aggregation and compaction of DNA by electrostatic cross-binding.\textsuperscript{[28]}

Mitoxantrone evokes the generation and release of highly reactive oxygen species to induce non-protein-associated DNA strand breaks.\textsuperscript{[3,29]} Metabolic oxidation of mitoxantrone to reactive 1,4-quinone and 5,8-diiminequinone intermediates may be an important mechanism of activation of this agent and a prerequisite for its covalent binding to DNA.\textsuperscript{[28,30,31]} Oxidation may take place in vivo through the action of nitrogen dioxide radicals.\textsuperscript{[30]}

\textbf{Immunosuppressive and immunomodulatory actions}

In alloreactive mixed lymphocyte cultures, the proliferative response of lymphocytes to antigen is curtailed in the presence of mitoxantrone. It also abolishes the generation of cytotoxic T cells.\textsuperscript{[6,7]} T-helper cell activity is diminished while T-suppressor cell function is enhanced.\textsuperscript{[32]} Further, mitoxantrone profoundly inhibits B-cell function and antibody secretion.\textsuperscript{[33]} Mitoxantrone inhibits macrophage-mediated myelin degradation ex vivo.\textsuperscript{[15]} Gonsette followed patients’ lymphocyte subsets for 3 years in an open trial of mitoxantrone in MS\textsuperscript{[34]} and noted an immunosuppressive effect on CD4\textsuperscript{+} cells and an average reduction of the number of B cells, HLA-DR2\textsuperscript{+}, and interleukin-2 receptor-positive cells of approximately 60\%. This reduction in the number of B cells and the decreased CD4:CD8 ratio was maintained for the duration of mitoxantrone therapy. Similar effects have been observed by others.\textsuperscript{[35]}

\textbf{PHARMACOKINETICS}

Pharmacokinetic studies have shown that mitoxantrone is eliminated according to a threecompartment model with successive half-lives of 6–12 minutes, 1.1–3.1 hours, and 23–25 hours.\textsuperscript{[2]} Mitoxantrone can be identified in high concentration in autopsy tissues obtained more than 1 month after drug administration.\textsuperscript{[36]} These pharmacokinetic data provide a rational basis for an intermittent dosing schedule. Seventy-eight percent of the drug is bound to plasma proteins and the relationship between dose and area under the curve is linear. Clearance of mitoxantrone is reduced in cases of marked liver dysfunction.
Early uncontrolled studies of mitoxantrone in MS are summarized in Table 24.1. In a study by Gonsette and Demonty, 16 patients with relapsing-remitting MS and six patients with secondary progressive MS with frequent and disabling relapses and progression of 1.0 or more points on the expanded disability status scale (EDSS) over 1 year were treated with mitoxantrone.[14] Patients were first induced with infusions of 14 mg/m² every 3 weeks for three cycles and then received infusions of 14 mg/m² every 3 months for up to 2 years. Twenty patients were evaluable at 2 years, at which time 16 patients (80%) were progression-free. Mean annual relapse rate was reduced from 1.2 to 0.16. There were no serious adverse events, and treatment was generally well tolerated. Amenorrhea was observed in 15% of female patients. There were no instances of clinically significant cardiac dysfunction. Similar results were observed in 20 of 21 patients who were followed for 3 years.

Kappos et al. treated 14 patients with rapidly progressing MS with mitoxantrone 10 mg/m² every 3 weeks (for three to five courses).[15] Three of eight patients who were followed for longer than 3 months improved, and five remained stable. MRI activity decreased from 139 gadolinium-enhancing lesions at baseline to 4 gadolinium-enhancing lesions at 6 months.

Mauch et al. treated 10 patients (six with relapsing-remitting MS and four with secondary progressive MS with mitoxantrone 12 mg/m² every 3 months).[16] All patients had experienced rapid deterioration of at least 1 point on the EDSS over the 12 months preceding therapy. Eight of nine patients were followed for 1 year and showed an improvement in disability. The total number of gadolinium-enhancing lesions was 169 at baseline, which declined to 40 lesions at 3 months, five at 6 months, one at 9 months, 10 at 12 months, and five at 24 months.

Noseworthy et al. treated 13 patients with progressive MS with mitoxantrone 8 mg/m² every 3 weeks for a total of seven infusions.[17] Only three of 13 patients showed an increase of >0.5 EDSS steps after 18 months. The authors felt this level of progression was consistent with the natural history of the disease. On gadolinium-enhanced MRI, 43 new lesions were observed before treatment, one new lesion at 6 months, and six new lesions at 18 months.

Table 24.1 Single-arm studies of mitoxantrone in MS

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Type of MS</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonsette and Demonty[14]</td>
<td>16</td>
<td>Relapsing-remitting</td>
<td>14 mg/m² every 3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 Progressive</td>
</tr>
<tr>
<td>Kappos et al.[15]</td>
<td>14</td>
<td>Rapidly progressive</td>
<td>10 mg/m² every 3 weeks</td>
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</table>
The phase II Italian multicenter controlled trial of mitoxantrone in relapsing-remitting MS

This randomized, single-masked, placebo-controlled trial conducted in eight Italian centers, evaluated the efficacy of mitoxantrone over 2 years in a group of 51 patients with relapsing-remitting MS. Entry criteria included EDSS scores of 2.0–5.0 and two or more exacerbations in the previous 2 years. Patients were randomly assigned to monthly treatment with mitoxantrone (8 mg/m$^2$) or placebo for 12 months. Baseline clinical characteristics were similar for both groups (Table 24.2). Patients were evaluated before treatment and at 12 and 24 months by a treating neurologist (unmasked) and by an evaluating physician (masked) who determined an EDSS score at each visit. Exacerbations were documented by the treating neurologist. T2-weighted MRIs were performed at months 0, 12, and 24. The primary endpoint of the study was the proportion of patients with a progression of 1 or more EDSS points.

Over 2 years, nine of 24 (37%) placebo patients and two of 27 (7%) mitoxantrone-treated patients worsened by 1 point or more on the EDSS ($p=0.02$) (Table 24.3). Treatment benefits were also observed on secondary endpoints (see Table 24.3), including annual exacerbations ($p<0.001$) and the proportion of exacerbation-free patients ($p<0.01$). Mean EDSS worsened in placebo recipients from baseline to month 24 (from 3.5 to 4.2, $p<0.01$). In contrast, mitoxantrone recipients showed no change in EDSS (3.6 versus 3.5, $p=NS$). Twenty-three mitoxantrone recipients and 19 placebo recipients completed the annual MRI for 2 years. There was a 52% reduction in new T2 lesions in the mitoxantrone group compared with the placebo group (7.3 versus 3.5, $p=0.05$). There was no difference in the number of enlarging lesions between treatment groups.

The most common adverse event was nausea. This generally was mild and easily controlled with antiemetics. Five of 17 women developed amenorrhea that resolved rapidly after cessation of therapy. There were no signs of cardiotoxicity on electrocardiogram or echocardiogram, no serious infections, no moderate or severe alopecia, and no severe hematological adverse reactions.

### Table 24.2 Italian mitoxantrone trial: baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Number of patients (males/females)</td>
<td>10/17</td>
<td>6/18</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>30.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>23.7</td>
<td>24.3</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>5.7</td>
<td>5.3</td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>range</td>
<td>2–5</td>
<td>2–5</td>
</tr>
<tr>
<td>median</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Mean relapses in previous 2 years</td>
<td>2.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Table 24.3 Italian mitoxantrone trial: clinical outcomes measures

<table>
<thead>
<tr>
<th>Percentage of patients with EDSS progression by ≥1.0 point</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>7% versus 25% (p=0.08)</td>
</tr>
<tr>
<td>Year 2</td>
<td>0% versus 25% (p=0.01)</td>
</tr>
<tr>
<td>Total</td>
<td>7% versus 37% (p=0.02)</td>
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<table>
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<tr>
<th>Percentage of patients exacerbation-free 2 years</th>
<th></th>
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<tr>
<td></td>
<td>63% versus 21% (p=0.006)</td>
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<table>
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<tr>
<th>Mean number exacerbations over 2 years</th>
<th></th>
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<tr>
<td></td>
<td>0.89 versus 2.62 (p=0.0002)</td>
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TRIALS IN SUPPORT OF APPROVAL OF MITOXANTRONE FOR USE IN WORSENING RELAPSING-REMITTING MS, SECONDARY PROGRESSIVE MS, AND PROGRESSIVE RELAPSING MS

The phase II French and British multicenter controlled trial of mitoxantrone in relapsing-remitting MS or secondary progressive MS

Forty-two patients with relapsing-remitting or secondary progressive MS were enrolled in this trial.[18] Entry criteria included two relapses with sequelae or progression of 2 or more EDSS points in the preceding 12 months. All patients initially received 3-monthly infusions of methylprednisolone (MP) 1 g and had 3-monthly gadolinium-enhanced MRI scans. Patients who had at least one new active lesion on the baseline scans were randomly assigned to therapy, mitoxantrone 20 mg plus MP 1 g or MP 1 g alone, monthly for 6 months (Fig. 24.1). Patients who started therapy completed monthly gadolinium-enhanced and T2-weighted scans. Lesion activity was evaluated by radiologists, who were masked to treatment assignment. Monthly clinical evaluations were performed by physicians who were aware of treatment assignment.

At baseline, clinical characteristics were similar in both groups (Table 24.4). Six patients in the control group and four patients in the mitoxantrone group had secondary progressive MS. Five MP recipients discontinued treatment. These five patients experienced progression of EDSS and active disease as shown by MRI. No recipients of both mitoxantrone and MP discontinued treatment. A significant treatment effect was observed on the primary endpoint, the proportion of patients by treatment group without new gadolinium-enhancing MRI lesions (Fig. 24.2). As summarized in Table 24.5, treatment benefits were also observed on secondary end-points, the mean number of new gadolinium-enhancing lesions at 6 months (p<0.01) and the mean number of new T2 lesions from baseline to the end of treatment (p<0.01). Globally there was an 85% reduction of new lesions in the group receiving both mitoxantrone and MP (Fig. 24.3).
**Fig. 24.1** French-British mitoxantrone (mitox) trial: trial design (IV, intravenously). Edan et al. [18]

**Table 24.4** French-British mitoxantrone trial: baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone plus methylprednisolone</th>
<th>Methylprednisolone alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6/15</td>
<td>10/11</td>
</tr>
<tr>
<td>(males/females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>31.4</td>
<td>32.2</td>
</tr>
<tr>
<td>Mean duration of disease (years)</td>
<td>6.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Mean EDSS at month –2</td>
<td>4.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean relapses in previous 12 months</td>
<td>3.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Edan et al. [18]
Fig. 24.2 French-British mitoxantrone (mitox) trial: percentage of patients with new gadolinium-enhancing MRI lesions. Edan et al.\cite{18}

Fig. 24.3 French-British mitoxantrone (mitox) trial: mean number of new gadolinium-enhancing MRI lesions. Edan et al.\cite{18}

Unblinded clinical assessments of the patients showed a benefit for mitoxantrone recipients (Table 24.6). Improvements in mean EDSS from month 0 to months 2–6 were
significant for mitoxantrone recipients. In contrast, the MP recipients generally deteriorated (Fig. 24.4). During the 2-month baseline period, the combined-treatment recipients and the MP-alone recipients had had annualized relapse rates of 3.1 and 2.9, respectively. These rates were similar for the 12 months preceding therapy (3.1 versus 2.4). During the treatment period, there were fewer relapses in the combined-treatment group than in the MP-alone group (seven versus 31 relapses). This effect was even more pronounced during the last 4 months of the treatment (one versus 19 relapses). During the treatment period, the proportion of exacerbation-free patients was 67% in the combined-treatment group and 33% in MP-alone group.

Adverse effects are summarized in Table 24.7. Minor and transient alopecia occurred in seven patients (all in the combined-treatment group). Eight of 15 women (all in the combined-treatment group) developed amenorrhea between months 2 and 6. Amenorrhea was transient for seven women and persistent for one woman, aged 44. As expected, all patients in the mitoxantrone group experienced a pronounced neu-

<table>
<thead>
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<th>Table 24.5 French-British mitoxantrone trial: MRI outcomes</th>
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<tbody>
<tr>
<td>Mitoxantrone plus methylprednisolone (n=21)</td>
</tr>
<tr>
<td>Patients without new gadolinium-enhancing lesions at 6 months (%)</td>
</tr>
<tr>
<td>Mean number of new gadolinium-enhancing lesions at 6 months</td>
</tr>
<tr>
<td>Mean number of new T2 lesions</td>
</tr>
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</table>

Edan et al. [18]

<table>
<thead>
<tr>
<th>Table 24.6 French-British mitoxantrone trial: clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone plus methylprednisolone (n=21)</td>
</tr>
<tr>
<td>Pre-study annualized relapse rate</td>
</tr>
<tr>
<td>Total on-study relapses</td>
</tr>
</tbody>
</table>
Mean annualized relapse rate 0.7 3
Relapse-free patients 14 (67%) 7 (33%) <0.05
Number of patients with ≥1.0 point EDSS change
Improved 12 3
Stable 12 8 <0.01
Worse 1 6
Edan et al.[18]

tropenia beginning 2 weeks after injection, but resolving within a few days. At the next monthly injection, minor leukopenia was noted in four patients; this did not require a dose adjustment. Nine patients received concomitant treatment for nausea. There was no evidence of cardiotoxicity or serious side effects.

The phase in randomized, double-blind, placebo-controlled, multicenter trial of mitoxantrone in progressive MS

In the multicenter trial Mitoxantrone in Progressive MS (MIMS), 194 patients were enrolled between 1993 and 1997 at 17 centers in Belgium, Germany, Hungary, and Poland, and randomly assigned to treatment with mitoxantrone

![Fig. 24.4 French-British mitoxantrone (mitox) trial: mean EDSS change. Edan et al.[18]](image)
12 mg/m² (n=63) or 5 mg/m² (n=66), or placebo (n=65), administered intravenously every 3 months for 24 months. One hundred and ninety-one patients received at least one dose and 188 patients completed at least one clinical evaluation and were available for efficacy analyses (Fig. 24.5). All patients met the entry criteria: age 18–55 years, documentation of stepwise progression (worsening relapsing-remitting MS) or gradual progression of disability with or without superimposed relapses (secondary progressive MS), EDSS of 3.0–6.0, worsening of 1.0 or more EDSS points over the 18 months before enrollment, and no clinical relapse or treatment with glucocorticoids within 8 weeks of enrollment. Severe relapses were prospectively defined as the occurrence of new symptoms lasting for more than 48 hours, with a change in Functional System (FS) score of more than 2 points or a deterioration of existing symptoms with a change of more than 1 point in at least one of the pyramidal, brainstem, cerebellar, or visual systems.

EDSS, Ambulation Index (AI),[38] and Standardized Neurologic Status (SNS)[39] scores were determined at each scheduled and unscheduled visit by a neurologist who was masked to treatment assignment (the assessing physician). A separate treating physician, not masked to treatment assignment, performed all medical evaluations, reviewed laboratory data, adjusted the dose of the study drug according to protocol, provided

Table 24.7 French-British mitoxantrone trial: adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Mitoxantrone plus methylprednisolone</th>
<th>Methylprednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Mild alopecia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other gastrointestinal events</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Neurological events (other than MS)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Edan et al.[18]
symptomatic therapies, and diagnosed and graded the severity of clinical relapses.

Baseline clinical and MRI characteristics were similar for evaluable patients across treatment groups (Table 24.8). The primary efficacy outcome consisted of five clinical measures tested in one combined hypothesis of stochastic-ordered alternatives (Table 24.9). A significant treatment effect ($p<0.0001$) was detected with the primary outcome, a multivariate comparison a dose of 12 mg/m$^2$ versus placebo. The pre-planned ordered analyses of each of the five components of the composite outcome showed significant treatment effects for change in EDSS, a change in AI, the number of relapses treated with corticosteroids, the time to first severe relapse (treated with corticosteroids), and a change in SNS. Time to first severe relapse differed significantly between the placebo and 12 mg/m$^2$ mitoxantrone groups ($p=0.0004$, log rank test). The median time to the first severe relapse was 14.2 months for the placebo group but was not reached in 24 months by either mitoxantrone group. A highly significant difference ($p=0.005$) also was demonstrated for the 5 mg/m$^2$ mitoxantrone group compared with the placebo group with the multivariate efficacy analysis.

One-hundred thirty-eight of 188 patients (73%) who were included in the intent-to-treat analysis of efficacy at 24 months (24-month cohort) completed an additional clinical evaluation at 36 months (36-month cohort) for safety.

**Table 25.8 Overview of demographic data and variables at baseline**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (n=64)</th>
<th>5 mg/m$^2$ Mitoxantrone (n=64)</th>
<th>12 mg/m$^2$ Mitoxantrone (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>N (%)</td>
<td>12 mg/m² (n=35)</td>
<td>12 mg/m² (n=42)</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Male</td>
<td>33 (52)</td>
<td>25 (39)</td>
<td>32 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (48)</td>
<td>39 (61)</td>
<td>28 (47)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.02</td>
<td>39.92</td>
<td>39.94</td>
</tr>
<tr>
<td>SD</td>
<td>7.88</td>
<td>8.06</td>
<td>6.85</td>
</tr>
<tr>
<td>Type of MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening RR</td>
<td>29 (45.3)</td>
<td>37 (57.8)</td>
<td>28 (46.7)</td>
</tr>
<tr>
<td>SP</td>
<td>35 (54.7)</td>
<td>27 (42.2)</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Number of relapses (preceding 12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.31</td>
<td>1.42</td>
<td>1.27</td>
</tr>
<tr>
<td>SD</td>
<td>1.14</td>
<td>1.26</td>
<td>1.12</td>
</tr>
<tr>
<td>Duration of MS (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10.27</td>
<td>9.03</td>
<td>9.63</td>
</tr>
<tr>
<td>SD</td>
<td>6.86</td>
<td>6.18</td>
<td>6.94</td>
</tr>
<tr>
<td>EDSS deterioration (preceding 18 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.58</td>
<td>1.62</td>
<td>1.50</td>
</tr>
<tr>
<td>SD</td>
<td>0.85</td>
<td>0.71</td>
<td>0.77</td>
</tr>
<tr>
<td>EDSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.69</td>
<td>4.64</td>
<td>4.45</td>
</tr>
<tr>
<td>SD</td>
<td>0.97</td>
<td>1.01</td>
<td>1.05</td>
</tr>
<tr>
<td>Ambulation Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.63</td>
<td>2.52</td>
<td>2.52</td>
</tr>
<tr>
<td>SD</td>
<td>1.02</td>
<td>0.98</td>
<td>1.14</td>
</tr>
<tr>
<td>SNS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.94</td>
<td>18.88</td>
<td>19.33</td>
</tr>
<tr>
<td>SD</td>
<td>7.67</td>
<td>6.66</td>
<td>8.46</td>
</tr>
</tbody>
</table>

RR, relapsing-remitting; SP, secondary progressive; EDSS, expanded disability status scale; SNS, standardized neurologic status assessment. Comparing disability levels at 36 months relative to baseline, mean EDSS change was 0.10 (sd=1.22) in the 12 mg/m² group and 0.46 in placebo recipients. Six of 42 (16.2%) 12 mg/m² recipients and 16 of 40 (42.1%) placebo recipients deteriorated by at least 1.0 point on the EDSS. Similarly, mean change in AI was 0.61 (±1.78) in the 12 mg/m² group and 1.13 (±1.64) in the placebo group. Mean change in SNS was 0.19 (±10.00) and 3.28 (±9.08),
### Table 24.9 MIMS study: primary efficacy criterion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Mann-Whitney difference (95% CI)</th>
<th>Summary statistic</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global difference (Wei-Lachin test)</td>
<td></td>
<td>0.3016 (0.1667, 0.4366)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDSS change</td>
<td></td>
<td>0.2393 (0.0414, 0.4373)</td>
<td></td>
<td>0.0194</td>
</tr>
<tr>
<td>(last value—baseline) Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.23 (1.01)</td>
<td>0.23 (1.01)</td>
<td>0.0306</td>
<td></td>
</tr>
<tr>
<td>12 mg/m² mitoxantrone</td>
<td>−0.13 (0.90)</td>
<td>−0.13 (0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al change</td>
<td></td>
<td>0.2107 (0.0240, 0.3974)</td>
<td></td>
<td>0.0306</td>
</tr>
<tr>
<td>(last value—baseline) Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.77 (1.26)</td>
<td>0.77 (1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mg/m² mitoxantrone</td>
<td>0.30 (1.24)</td>
<td>0.30 (1.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted total no. of treated relapses</td>
<td></td>
<td>0.3849 (0.1801, 0.5897)</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Placebo</td>
<td>76.77</td>
<td>76.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mg/m² mitoxantrone</td>
<td>24.08</td>
<td>24.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to 1st treated relapse Median (months)</td>
<td></td>
<td>0.4431 (0.1974, 0.6888)</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>Placebo</td>
<td>14.19</td>
<td>14.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mg/m² mitoxantrone</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in SNS (last value—baseline) Mean (SD)</td>
<td></td>
<td>0.2302 (0.0299, 0.4305)</td>
<td></td>
<td>0.0268</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.77 (6.79)</td>
<td>0.77 (6.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mg/m² mitoxantrone</td>
<td>1.07 (8.61)</td>
<td>1.07 (8.61)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
respectively. The number of severe relapses decreased from 66 in the placebo to 26 in the 12 mg/m² recipients.

Significant treatment effects were observed for most of the pre-planned secondary outcomes of efficacy (Table 24.10). Treatment effects for the 5 mg/m² recipients were generally intermediate between those observed in 12 mg/m² recipients.

**Table 24.10 MIMS study secondary efficacy variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Value</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%) with EDSS deterioration (=1 from baseline)</td>
<td>Placebo</td>
<td>16</td>
<td>0.013a</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 5 mg/m²</td>
<td>10</td>
<td>(25.0%)</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 12 mg/m²</td>
<td>5</td>
<td>(8.3%)</td>
</tr>
<tr>
<td>No. of patients (%) with 3-month confirmed EDSS deterioration during study</td>
<td>Placebo</td>
<td>14</td>
<td>0.036a</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 5 mg/m²</td>
<td>9</td>
<td>(14.1%)</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 12 mg/m²</td>
<td>5</td>
<td>(8.3%)</td>
</tr>
<tr>
<td>No. of patients (%) without relapses</td>
<td>Placebo</td>
<td>23</td>
<td>0.021a</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 5 mg/m²</td>
<td>25</td>
<td>(39.1%)</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 12 mg/m²</td>
<td>34</td>
<td>(56.7%)</td>
</tr>
<tr>
<td>Adjusted total no. of relapses regardless of severity</td>
<td>Placebo</td>
<td>129.4</td>
<td>0.0002b</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 5 mg/m²</td>
<td>77.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 12 mg/m²</td>
<td>48.2</td>
<td></td>
</tr>
<tr>
<td>No. of patients hospitalized</td>
<td>Placebo</td>
<td>43</td>
<td>0.002a</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 5 mg/m²</td>
<td>36</td>
<td>(56%)</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 12 mg/m²</td>
<td>24</td>
<td>(40%)</td>
</tr>
<tr>
<td>No. of all hospitalizations</td>
<td>Placebo</td>
<td>89</td>
<td>0.0082a</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone 5 mg/m²</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>
and the placebo recipients. The difference between groups in change in EDSS at 24 months reflected fewer patients demonstrating deterioration of at least 1 point (25% for placebo and 8% for mitoxantrone 12 mg/m², *p*=0.03). Over 24 months, confirmed neurologic progression was observed in significantly fewer patients receiving mitoxantrone 12 mg/m² relative to placebo (five (8.3%) versus 14 (22%), *p*=0.04). Patients in the mitoxantrone 12 mg/m² group showed a significant advantage in the analysis of time to confirmed EDSS deterioration at 3 months (*p*=0.027) and 6 months (*p*=0.034). Annualized relapse rates were significantly lower in the 12 mg/m² group relative to placebo at 1 year (0.42 versus 1.15, *p*<0.0001) and 2 year (0.27 versus 0.85, *p*=0.0001), a reduction by 63% and 68%, respectively. Moreover, significantly more patients in the 12 mg/m² group did not experience any relapse over 24 months relative to the placebo group (5 (8.3%) versus 14 (22%), *p*=0.04). Significantly more patients in the placebo group were hospitalized for reasons other than administration of study medication. Only 15 patients showed progression that required the use of a wheelchair (corresponding to an EDSS of 7.0). No significant difference between groups was apparent, but fewer 12 mg/m² recipients than placebo recipients progressed to an EDSS of 7.0 (three (5%) versus seven (11%), *p*=0.23). Quality of life assessment was conducted with the validated Stanford Health Assessment Questionnaire (HAQ). The placebo group mean score increased (0.26), with significantly less change observed in the 12 mg/m² mitoxantrone group (0.09; *p*=0.024). Moreover, significantly more patients in the placebo group (n=41) showed deterioration in HAQ index relative to the 12 mg/m² mitoxantrone group (n=25, *p*=0.012).

A subset of 110 patients (36 on placebo, 40 on mitoxantrone 5 mg/m² and 34 on mitoxantrone 12 mg/m²) completed annual unenhanced and gadolinium-enhanced MRI scans of the brain. Demographics and clinical features of this subgroup were similar to the total study population at baseline, and mitoxantrone recipients were well matched to placebo recipients. These studies were performed on high-resolution 1.0 or 1.5 Tesla systems. Using 5-mm slice-thickness and a 256×256 matrix, double spin-echo sequences were performed with time of repetition of 2500 ms and time echo of 40 ms and 90 ms. Conventional T1-weighted images following the injection of gadolinium-DTPA (0.1 mmol/kg) were acquired according to European Union Concerted Action Guidelines.[40] Lesion load was estimated using a scoring system described previously,[18,40] with two experienced readers being masked to treatment assignment. MRI outcome criteria included numbers and volume of gadolinium-enhancing lesions, T1-hypointense lesions, and T2-hyperintense lesions. Significantly fewer patients receiving mitoxantrone 12
mg/m\(^2\) demonstrated gadolinium-enhancing lesions at 24 months relative to placebo (0% versus 15.6%, \(p=0.022\)). The mean increase in the number of T2-hyperintense lesions was 0.29 in mitoxantrone 12 mg/m\(^2\) recipients and 1.94 in placebo recipients \((p=0.027)\).\(^{[41]}\)

Cardiac monitoring (electrocardiography with rhythm-control printout and left ventricular ejection fraction (LVEF) assessed by echocardiography or radionuclide scan) was performed before treatment and at months 12, 24, and 36. Study drug administration was discontinued if LVEF decreased by 10% or more compared with baseline, or if the measured value was less than 50%. No significant differences in the numbers of patients who experienced reduced LVEF were detected between the mitoxantrone patients and the placebo group at the end of the first, second, or third year of the study. Over the 3 years, LVEF decreased to less than 50% in one patient in the 5 mg/m\(^2\) group, and in two patients in the 12 mg/m\(^2\) group. No congestive heart failure or other clinically significant cardiac dysfunction occurred during 3 years of monitoring.

With regard to adverse events (Table 24.11), mitoxantrone was generally well tolerated as administered during this study. Nausea, urinary tract infections, menstrual disorder, amenorrhea, and mild thinning of hair were observed more frequently in mitoxantrone recipients. The severity of these adverse events was usually graded as mild or moderate. There were no deaths or

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (n=64)</th>
<th>5 mg/m(^2) Mitoxantrone (n=65)</th>
<th>12 mg/m(^2) Mitoxantrone (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred term</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>33</td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Menstrual disorder</td>
<td>8</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Amenorrhea(^c)</td>
<td>0</td>
<td>(0(^a))</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Urine abnormal</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>ECG abnormal</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>9</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>SGOT increased</td>
<td>5</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

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Back pain 3 5 4 6 5 8 8
Pharyngitis 6 9 5 8 4 6 6
Sinusitis 1 2 2 3 4 6 6
Granulocytopenia 1 2 4 6 4 6 6
WBC abnormal 1 2 5 8 4 6 6
Infection viral 4 6 4 6 6 6 6
Headache 3 5 4 6 4 6 6
Anemia 1 2 6 9 4 6 6

\(^a\) Numbers in parentheses reflect percentage of female patients
\(^b\) Significantly more common in active drug recipients
\(^c\) Secondary amenorrhea (absence of menses for \(\geq 6\) months and persisting to final clinical evaluation)

serious drug-related adverse events. One 5 mg/m\(^2\) recipient developed renal cell carcinoma, believed to be unrelated to the study drug. The drug was discontinued as a result of an adverse event in five mitoxantrone 12 mg/m\(^2\) recipients (because of leukopenia, depression, decreased LVEF, bone pain and emesis, repeated urinary tract infections and hydronephrosis), in none of the 5 mg/m\(^2\) group, and in two placebo recipients (because of hepatitis and myocardial infarction).

Leukopenia was observed in 19% of the 12 mg/m\(^2\) patients and in 9% of the 5 mg/m\(^2\) patients, but not in any of the placebo group. Elevated \(\gamma\)-glutamyltransferase was noted in 15% of the 12 mg/m\(^2\) patients, 3% of the 5 mg/m\(^2\) patients, and 3% of the placebo recipients. Changes in other hematological and biochemistry parameters were not different between groups. At the 36-month evaluation, no significant differences in clinical or laboratory safety parameters, including alopecia, urinary tract infection, amenorrhea, nausea, and leukopenia, were observed between groups for the 138 patients followed up 1 year after dosing completion. Two of 27 female patients receiving 5 mg/m\(^2\) and seven of 25 female patients receiving 12 mg/m\(^2\) experienced secondary amenorrhea (cessation of menses for 6 months or more) during therapy. One year later, amenorrhea persisted in none of 27 mitoxantrone 5 mg/m\(^2\) recipients and in five of 25 mitoxantrone 12 mg/m\(^2\) recipients.

**TOLERABILITY OF MITOXANTRONE IN OPEN-LABEL STUDIES OF PATIENTS WITH MS**

Substantial tolerability data are available from oncology studies, in which mitoxantrone was generally used in combination with cyclophosphamide, fluorouracil, mitomycin, methotrexate, and radiotherapy for leukemia, non-Hodgkin’s lymphoma, and solid tumors and also from MS studies, in which mitoxantrone was used as single-agent therapy.

**Cardiac tolerability**

Cardiac toxicity has been reported in cancer patients who received mitoxantrone as a cytotoxic agent.\(^{[42-46]}\) In these studies, mitoxantrone was typically administered in
combination with cyclophosphamide, fluorouracil, mitomycin, methotrexate, or radiotherapy. In such studies, mitoxantrone-associated cardiotoxicity became evident by changes in the electrocardiogram, indicating possible tachycardia and arrhythmia, by an asymptomatic decrease in measures of LVEF, or by symptomatic congestive heart failure (CHF). Histologic endomyocardial changes associated with mitoxantrone administration include dilatation of the sarcoplasmic reticulum with vacuole formation and myofibrillar dropout. The increased risk of cardiotoxicity is associated with higher cumulative doses of mitoxantrone, prior treatment with anthracyclines, prior mediastinal radiotherapy, and pre-existing cardiovascular disease. The mechanisms of mitoxantrone-associated cardiotoxicity are not completely understood but include formation of free radicals, increased oxidative stress, lipid peroxidation, alterations of adrenergic functions, alterations in sarcolemmal calcium ion transport, and effects of tumor necrosis factor-α and interleukin-2.

At least two mechanisms have been identified by which anthracyclines and anthracendiones, including mitoxantrone, could initiate the formation of reactive oxygen species. First, by chelating iron, mitoxantrone produces highly reactive hydroxyl radicals. Second, by a redox-cycling process, mitoxantrone may produce hydrogen peroxide, which promotes formation of hydroxyl radicals. Hydrogen peroxide is inactivated by two enzymes, catalase and glutathione peroxidase. While the former is lacking in the heart muscle, the latter enzyme is inhibited by mitoxantrone.

The risk of cardiac toxicity after single-agent mitoxantrone therapy for MS has been assessed in two large open-label studies. In a German retrospective study, 452 patients received a mean cumulative dose of 43 mg/m² mitoxantrone. Over a mean follow-up of 48 months, two patients died of clinically significant CHF. One patient, a 39-year-old man with a cumulative dose of 163 mg/m² delivered by a physician who was unaware of previous mitoxantrone administration, died 3 months after discontinuing therapy. The second patient, a 65-year-old woman, developed CHF after a single dose of 9 mg/m² and died 4 years later. In the French Consortium open-label study, 802 MS patients received a mean cumulative dose of 70 mg/m² mitoxantrone. Over a mean follow-up of 29 months (range 1–123 months), no patient experienced clinically significant cardiac dysfunction. LVEF was tested at baseline and during follow-up in 656 of the 802 patients. One of the 656 patients had an LVEF of 49% at baseline. This patient was excluded from the incidence analysis of patients developing an LVEF below 50% after initiating therapy. Of the 655 patients who had LVEF tested at baseline and at follow-up, 13 experienced an asymptomatic LVEF of less than 50%—five at their most recent clinical assessment, five transiently (with return of LVEF to more than 50%), and three with LVEF less than 50% on two or more tests that persisted to their last visit. All 13 patients remained in clinical follow-up. Three patients were clinically asymptomatic for 4.5 to 7.0 years after mitoxantrone therapy was started. The incidence of asymptomatic LVEF of less than 50% was 1.98% (CI 1.28–3.47%) in this cohort.

To minimize clinically significant cardiotoxicity, the authors believe it is mandatory to monitor the LVEF by performing either echocardiography or radionuclide ventriculography. The authors obtain LVEF at baseline and before each infusion once the cumulative dose exceeds 100 mg/m². Cardiology consultation is indicated if the LVEF is less than 50% at any time. Although the cumulative dose employed in these studies was well tolerated, the possibility that permanent subclinical, cardiac injury induced by the
drug could later become clinically evident cannot be dismissed. For this reason, the authors periodically measure LVEF after mitoxantrone therapy has been discontinued.\[57\]

**Bone marrow suppression**

Bone marrow suppression is the most common dose-limiting toxic side effect of mitoxantrone. Generally, granulocytopenia develops 8–14 days after a single large dose and persists for 4–10 days. Full recovery generally occurs by day 24 after drug administration.\[58\] Hemoglobin level, white blood cell count, and platelet count should be performed 3–5 days before each course of mitoxantrone. Generally, absolute neutrophil count should exceed 1500/mm\(^3\) and platelet count should exceed 100000/mm\(^3\) before infusion.

**Therapy-related acute leukemia**

Therapy-related acute leukemia (t-AL) has been reported in patients treated with topoisomerase II inhibitors such as etoposide, anthracyclines, and mitoxantrone. These cases frequently manifest as t-AL without preceding myelodysplastic syndrome. Most patients develop the disease within 2–4 years after chemotherapy has been started. This form of t-AL often exhibits balanced translocations of chromosome bands 11q23 and 21q22,\[59\] has a prognosis similar to that of de novo acute leukemias, and tends to respond to standard antileukemic therapy. A Medline search of all full-length articles and abstracts reporting on the risk of t-AL in cancer patients receiving mitoxantrone identified seven independent studies that provide sufficient information to estimate reliably the incidence of t-AL in cancer patients. These seven reports comprise data from 2973 patients, all treated with mitoxantrone in combination with other chemotherapeutic agents, often in conjunction with radiotherapy. Various cytotoxic regimens were used, including CNF (cyclophosphamide, Novantrone (mitoxantrone), and fluorouracil), MMM (mitoxantrone, methotrexate, and mitomycin), and a prednimustine-containing regimen.\[60\] Each of these agents has been reported to be associated with t-AL.\[61,62\] Of the 2973 patients reported in these seven studies, 31 (1.04\%) developed t-AL. Latency period from the start of mitoxantrone therapy to the development of t-AL was documented in six studies and ranged from 8 months to 7 years. The exact latency period was known in 19 of the 31 cases of t-AL and was always less than 4 years.

Two cases of t-AL in MS were reported as of September 2001. The first was a spontaneous report of acute promyelocytic leukemia following mitoxantrone therapy for MS.\[63\] In this report, a 36-year-old man was treated with intravenous mitoxantrone 10 mg/m\(^2\) monthly for 5 months (total cumulative dose of 50 mg/m\(^2\)). Acute promyelocytic leukemia was diagnosed 5 years after therapy was started. Cytogenetic analysis was normal, but molecular gene rearrangement was consistent with the diagnosis of acute promyelocytic leukemia. The patient achieved a complete remission following treatment with idarubicin and all-trans retinoic acid and remained in complete remission 1 year after completing antileukemic therapy. Although the latency period in this case was longer than that generally observed with topoisomerase II inhibitors, a causal relationship cannot be excluded with certainty. The second patient, a 28-year-old woman who received mitoxantrone 120 mg over 6 months was reported in the French Consortium
open-label study.\textsuperscript{[56]} This woman developed acute leukemia 15 months after discontinuing mitoxantrone. As of September 2001, the annual incidence of t-AL in the French Consortium open-label study was 0.05\% (CI 0.001–0.28\%).

**Gonadal dysfunction**

Although rigorous studies of fertility have not been performed, secondary amenorrhea can be a delayed side effect of chemotherapy.\textsuperscript{[64]} This possibility should be discussed with women considering mitoxantrone therapy for MS. In the Multicenter French Consortium open-label study,\textsuperscript{[56]} among the 448 MS women at risk of loss of menses, 53 episodes of transient amenorrhea (11.8\%) and 48 episodes of persisting amenorrhea (10.7\%) were observed. The risk of persisting amenorrhea was higher in women older than 35 years (14\%) and lower in women less than 35 years old of age (6.5\%).

In men treated for Hodgkin’s disease, mitoxantrone in combination with other chemotherapeutic agents (vincristine, vinblastine, and prednisone) caused significant decreases in sperm counts and mobility, but recovery occurred within 3–4 months after completion of chemotherapy.\textsuperscript{[65]} In contrast to other regimens with alkylating agents (e.g. cyclophosphamide), after cessation of mitoxantrone there generally is complete recovery of the sperm production without morphological changes in vitro or genotoxic effects on germinal cells in vivo.\textsuperscript{[66]}

**Other acute side effects**

Nausea or vomiting occurs in up to 60\% mitoxantrone recipients. This side effect usually is mild or moderate and rarely requires cessation of therapy. Alopecia is infrequent and generally mild.

**DISCUSSION**

Data from phase II and III clinical trials consistently indicate that mitoxantrone is an effective and generally well-tolerated disease-modifying therapy for patients with worsening relapsing-remitting or secondary progressive MS. Benefit has been shown in relapse rate, progression of disability, and MRI activity.\textsuperscript{[14–19,37]} Nonetheless, several important questions remain concerning the safety and use of mitoxantrone in MS, and these questions are discussed below.

**What is the long-term safety profile of mitoxantrone in MS?**

Although mitoxantrone is generally well tolerated and the risk of clinically significant cardiac dysfunction and t-AL have been low in open-label studies, the long-term risk of these potential drug-related side effects needs to be determined. Such data are being collected from 802 patients in an open-label study conducted by the Consortium of French Multiple Sclerosis Centers\textsuperscript{[56]} and from 500 patients followed for 5 years in a multicenter post-marketing study in the USA.\textsuperscript{[67]}
What is the role of mitoxantrone for patients with secondary progressive MS who experience relapses and for those who do not?

The potential relationship between the inflammatory aspects of MS pathology and disease-modifying treatment effects was not appreciated when the MIMS trial was designed. Thus, the relative efficacy of mitoxantrone in patients with and without pre-study relapses could be examined only in post hoc analyses. These analyses (unpublished data) suggest that change in EDSS, AI, and the number of relapses were similar in patients with or without pre-study relapses. It is possible that these treatment effects might reflect the clinical characteristics of patients enrolled in the MIMS trial. Not surprisingly, of the four clinical trials of interferon beta in secondary progressive MS (interferon beta-1b,[68,69] subcutaneous interferon beta-1a,[70] intramuscular interferon beta-1a (not yet published)), patients in the MIMS trial most closely resembled patients in the European interferon beta-1b trial.[68] At baseline, the mean age of placebo recipients in the MIMS study and the European interferon beta-1b trial were 40 and 41 years, respectively, the mean EDSS scores were 4.7 and 5.2, respectively, and the proportion of patients who were free of exacerbations for 1–2 years before enrollment were 25.5% and 28.2%, respectively. The authors believe that the relative efficacy of mitoxantrone in patients with progressive disease who experience superimposed relapses (and in those who do not) can be answered definitively only by a study that is designed to answer that question.

What is the role of mitoxantrone in rapidly worsening MS patients?

The important issue of treating rapidly worsening MS patients (e.g. two or more clinical exacerbations with sequelae or progression of more than 2 EDSS points and gadolinium-enhancing MRI lesions) with mitoxantrone was addressed by the French and British trial[18] and subsequently in open-label studies.[71,72] The strong and rapid reduction in the inflammatory process observed with the monthly combination of mitoxantrone (20 mg/month for 6 months) and MP (1 g/month for 6 months) suggests a potential role for this regimen to treat patients with rapidly worsening MS.

What is the role of mitoxantrone as ‘rescue’ therapy for Avonex®, Betaferon®, Copaxone® (ABC) failures?

Mitoxantrone may provide a new treatment option for patients with relapsing-remitting MS who experience suboptimal treatment response to interferon beta or glatiramer acetate. However, only limited data are available to support this notion. In an open, follow-up, retrospective study of a total of 100 relapsing-remitting patients,[71] 11 patients who received interferon beta administered for at least 12 months and who failed to respond were compared with 50 patients who received no immunosuppressive or immunomodulatory drug before mitoxantrone (Table 24.12). Twelve months before mitoxantrone therapy was started, the 11 non-responders to interferon beta had a mean annual relapse rate of 3.1 and a mean worsening of EDSS of 1.4, whereas for the same time period the 50 untreated patients had a mean annual relapse rate of 2.8, and a mean worsening of EDSS of 2.0.
After receiving mitoxantrone induction therapy (mitoxantrone 20 mg/month and MP 1 g/month for 6 months), the clinical benefit was similar in both groups. One year after mitoxantrone induction, the annual relapse rate was 0.27 versus 0.20 (91% versus 93% reduction), the percentage of patients free of relapse was 80% versus 73%, improvement of 1.0 point on the EDSS was 45% versus 56%, and worsening of 1.0 point on the EDSS was 0% versus 6%.

**What is the long-term clinical efficacy of mitoxantrone in MS?**

In the Italian controlled study[37] and the MIMS study,[19] the clinical and MRI benefits of mitoxantrone were sustained for at least twelve months after stopping the therapy. Longer studies are needed to examine the duration of benefits of mitoxantrone therapy.

**What is the optimal dosing regimen?**

Treatment effects have been observed with 8–12 mg/m\(^2\) monthly for 6–12 months and with 12 mg/m\(^2\) every 3 months for up to 24 months. The optimal dosing regimen for mitoxantrone needs to be determined by clinical trials designed to answer that question.

**Mitoxantrone as a single agent versus induction or combination therapy**

The concept of induction therapy followed by a long-term treatment combining several drugs has been proven effective in infectious diseases and in oncology but has not been investigated in MS.

### Table 24.12 Open study of 100 consecutive rapidly worsening relapsing-remitting MS treated with mitoxantrone 20 mg and methylprednisolone 1 g monthly for 6 months[71]

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>(n=100)</th>
<th>(n=11)</th>
<th>(n=50)</th>
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<tbody>
<tr>
<td>All patients</td>
<td></td>
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<tr>
<td>Interferon beta before mitoxantrone</td>
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<tr>
<td>DMT-naïve before mitoxantrone</td>
<td></td>
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<td></td>
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<tr>
<td>Age (years) at mitoxantrone onset</td>
<td>Mean</td>
<td>32.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Duration of MS (years) before mitoxantrone</td>
<td>Mean</td>
<td>5.3</td>
<td>6.6</td>
</tr>
<tr>
<td>EDSS at mitoxantrone onset</td>
<td></td>
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</table>
Since both interferon beta and mitoxantrone have proven efficacy, sequential administration of these agents offers a good opportunity to test this therapeutic concept in MS. The specific and complementary effects of these two compounds, in term of immunosuppressive activity (global action for mitoxantrone, selective action for interferon beta), in terms of rapid action (strong and immediate action for mitoxantrone, progressive immunomodulation for interferon beta), and in terms of treatment duration (prescription limited to a few months for mitoxantrone with monthly infusion, but available for several years for interferon beta) suggest that these two compounds, when combined in a sequential schedule, might exhibit synergic action in MS. Support for this hypothesis is provided by the French retrospective open-label follow-up study,[71] in which most of the patients (78 of 100) had received other long-term disease-modifying therapy within 3 months after discontinuing mitoxantrone (Table 24.12). In this study, 100 consecutive patients with relapsing- remitting MS patients with active disease (mean annual relapse rate of 3.2, mean worsening of 2.2 EDSS steps prior to mitoxantrone therapy, 84% having an MRI scan with gadolinium-enhancing lesions), were followed for

<table>
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<th>Mean</th>
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<th>4.4</th>
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<td>Number of relapses</td>
<td>Mean</td>
<td>3.2</td>
<td>3.1</td>
<td>2.8</td>
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<td></td>
<td>2.2</td>
<td>1.4</td>
<td>2</td>
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<tr>
<td>EDSS deterioration</td>
<td>Mean</td>
<td>0.3</td>
<td>0.27</td>
<td>0.20</td>
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<tr>
<td>(preceding 12 months)</td>
<td></td>
<td>76</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>No. of relapse (1 year after</td>
<td>Mean</td>
<td>60</td>
<td>45</td>
<td>56</td>
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<tr>
<td>mitoxantrone)</td>
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<tr>
<td>Relapse-free patients (1 year</td>
<td>%</td>
<td>4</td>
<td>0</td>
<td>6</td>
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<tr>
<td>after mitoxantrone)</td>
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<tr>
<td>1-point improvement</td>
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<td>EDSS (1 year after mitoxantrone)</td>
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<td>1-point worsening EDSS (1 year</td>
<td>%</td>
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<td>after mitoxantrone)</td>
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DMT, disease modifying therapy; EDSS, expanded disability status scale
up to 5 years after mitoxantrone induction. Disease activity dropped considerably. Annual relapse rate declined from 3–3.5 to 0.28–0.37 during the following five years, and 43% of this population was still relapse-free 4 years after mitoxantrone induction treatment. Improvement of mean EDSS lasted 4 years.

A consortium of European academic neurologists is conducting a new trial that aims to determine whether a treatment strategy combining induction treatment with mitoxantrone followed by interferon beta-1b can delay disease progression (as compared with interferon beta-1b alone) in patients with a very active relapsing course of the disease suggesting the risk of early or severe disability.

Can the useful lifespan of the drug be extended with dexrazoxane or an alternative treatment protocol?

Over the past few years, efforts have been made to reduce or even prevent cardiotoxicity associated with mitoxantrone. One promising approach is the use of liposomal agents that permit more specific organ targeting of mitoxantrone and prolong the half-life of the drug. A first clinical study using liposomally entrapped compounds in cancer patients is under way.[72] Second, cardiotoxicity may be diminished by chelating agents that remove iron to prevent formation of mitoxantrone-iron complexes, which catalyse the generation of extremely reactive hydroxyl radicals. One chelating agent, dexrazoxane (a member of the bisdioxopiperazine family), has shown encouraging results in reducing the incidence of cardiotoxicity in adult cancer patients. Interestingly, dexrazoxane is the (+S)-enantiomer of the racemate razoxane for which cytotoxic activity in vitro in the G2-M phase of the cell cycle was demonstrated.[73] More recently, in Lewis rat EAE, dexrazoxane monotherapy slightly ameliorated disease severity. When administered in combination with mitoxantrone it was superior to mitoxantrone monotherapy.[74] The effects of a combination of the two drugs, mitoxantrone and dexrazoxane, is currently being explored in a pilot study in patients with worsening MS.[75] In addition to strategies designed to diminish cardiotoxicity, recent technical developments may allow more sensitive tests to be used to screen for MS patients with cardiac dysfunction that is not yet detectable by electrocardiogram or echocardiogram (e.g. blood levels of troponins[24] or P-magnetic resonance spectroscopy).[76]

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Intravenous immunoglobulin to treat multiple sclerosis
Franz Fazekas, Siegrid Strasser-Fuchs, Ralf Gold and Otto R Hommes

INTRODUCTION

Over the past few years, intravenous immunoglobulin (IVIG) has become an important treatment option for various autoimmune-related neurologic diseases.\cite{1–4} Efficacy equal to that of plasmapheresis has been convincingly documented for Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy.\cite{3,5,6} Although it has been less extensively studied, some have similar views about the treatment of myasthenia gravis crises,\cite{7} while the benefits of IVIG, although limited, have to be weighed against quite aggressive therapies such as cyclophosphamide in multifocal motor neuropathy.\cite{8,9} In all these comparisons, the ease of administration, good tolerability, and a reasonable safety profile are factors that are cited in favor of IVIG. The broad range of immunologic activities of the immunoglobulins which are important in maintaining immune homeostasis in healthy people and which have the potential to interfere with immunopathologic conditions in various ways,\cite{4} may offer further advantages over other immunomodulatory therapies. Therefore, an increasing number of controlled trials have been embarked on to determine the efficacy of IVIG for multiple sclerosis (MS), which is the most common neurologic autoimmune disorder of the central nervous system. To outline the present role of IVIG for MS, this chapter reviews the published randomized, placebo-controlled clinical trials and other available study data.

IMMUNOLOGIC PROPERTIES AND SAFETY OF IVIG PREPARATIONS

Immunoglobulins are the carriers of humoral immunity and are able to recognize a broad spectrum of immunogenic structures. The immense variation in their antibody-binding specificities is produced by the contribution of germline diversity and of somatic mutation.\cite{10} A prototypic immunoglobulin molecule is composed of four polypeptide chains (two identical heavy and two identical light chains), which are joined into a macromolecular complex by disulfide bonds. There exist two functional domains—the Fabfragment contains the antigen-binding site of the molecule and bears the recognition function, and the Fc-part is responsible for biological effector functions such as complement fixation or binding to Fc-receptors on inflammatory cells.\cite{10,11}

Commercially available IVIG is prepared from pooled plasma of 3000–10000 healthy donors and contains more than 95% immunoglobulin (Ig)G, less than 2.5% IgA, and a
negligible amount of IgM. IgA can potentially cause anaphylactic reactions in sensitized IgA-deficient people. Although, in principle, the distribution of IgG subclasses corresponds to that of normal human serum, there is some variation between manufacturers according to the size and composition of donor pools used.[4] IVIG preparations also contain trace amounts of soluble CD4, CD8, and HLA molecules and certain cytokines.[12] To minimize the possibility of transmission of infectious diseases such as hepatitis B and hepatitis C, regulations require that only selected donors may be accepted and that plasma donations must be screened for certain viruses. The purification process itself includes various steps to eliminate infectious agents, and this process is constantly updated and improved.[13–15]

Kinetics

The overall half-life of most IgG subclasses contained in IVIG after administration is approximately 18–32 days, which is similar to that of native immunoglobulin. Following intravenous infusion of high doses of IVIG (2g/kg body weight), serum IgG levels have been shown to increase fivefold and then to decline by 50% in 72 hours.[16] These rapid shifts of IgG serum concentration within the first 3 days are a consequence of extravascular redistribution, but they may also reflect increased catabolism.[17] Pretreatment serum levels were reached after 2–4 weeks.[16] High-dose IVIG infusions also lead to an increase in the concentration of IgG in the cerebrospinal fluid (CSF) by as much as twofold within 48 hours.[16] However, it takes only 1 week for IgG levels in the CSF to return to normal.

Mechanisms of action

Multiple immunomodulatory effects of IVIG have been documented. These have been extensively described in numerous reviews.[2–4,17,18] However, so far it has not been possible to identify one single mode of action as the crucial mechanism. It is conceivable that various immunoregulatory effects of IVIG act in concert to equilibrate the disturbed immune network.

Healthy individuals generate IgG antibodies against a wide spectrum of normal human proteins: these antibodies include so-called antiidiotypic antibodies, which attach to the antigenbinding region of the Fab-part of another immunoglobulin. As a consequence, IVIG derived from a large pool of human donors may include anti-idiotypic antibodies which bind to and neutralize pathogenic autoantibodies and prevent the interaction with their autoantigen.[19–21] It has also been suggested that binding of the antiidiotypic antibodies to antigenic determinants and the surface IgM or IgG on B cells would result in a down-regulation of antibody production.[22] With these actions in mind, one certainly has to consider that the efficacy of IVIG preparations could vary with the selection and size of the donor pool. However, such speculations have not yet been substantiated experimentally or clinically.

The Fc-portion of immunoglobulins interacts with many phagocytic cells of the reticuloendothelial system that express Fc-receptors on their cell surface. These Fc-receptors link cellular and humoral immunity by serving as a bridge between antibody specificity and effector cell function.[11] Pathogenic antibodies can bind to the Fc-receptor
and thereby target macrophages. Excess amounts of immunoglobulins may compete with this binding and block or (at least), reduce the damaging effects of inflammatory effector cells.\textsuperscript{[23]} There is corroborating evidence from experimentally induced inflammatory neuropathy in rats that intact human IVIG can reduce disease severity.\textsuperscript{[24]} In addition to the mere blockade of Fc-receptors, immunoglobulins and complexes derived from them can cross-link Fc-receptors and thus mediate apoptosis of B cells\textsuperscript{[17,25]} Recently, it has been recognized that the anti-inflammatory activity of IVIG can be mediated through the inhibitory Fc-\gamma receptor type 2B, either directly or indirectly. Modulation of inhibitory signalling may thus be a potent therapeutic strategy.\textsuperscript{[26]}

Clinical studies also have shown changes of the cytokine profile of patients treated with IVIG. This appears to be due to a modulation of the production and secretion of cytokines by lymphocytes or monocytes.\textsuperscript{[27,28]} Up-regulation of interleukin (IL)-1 receptor antagonists and IL-8 secretion have been induced by IVIG. In addition, IVIG preparations may also influence the cytokine network since they contain traces of interferon (IFN)-\gamma and transforming growth factor-\beta in varying amounts as well as neutralizing antibodies against IL-1\alpha, IL-6, and the class 1 interferons (IFN-\alpha and IFN-\beta).\textsuperscript{[29,30]} In particular, it recently was demonstrated in antigen therapy of experimental encephalomyelitis that IVIG antagonizes tumor necrosis factor-\alpha-mediated cell death.\textsuperscript{[30a]}

Immunoglobulins can also bind complement components with their constant domain and thus prevent tissue damage caused by the complement activation cascade. Direct evidence of the functionality of this mechanism in humans was demonstrated in dermatomyositis.\textsuperscript{[31]} Recent experimental data also speak for an enhanced physiologic cleavage by IgG of C3b-containing complexes,\textsuperscript{[32]} dependent on the presence of factors I and H. These properties may act in concert and may also prevent binding to the oligodendrocyte surface and to myelin proteins.\textsuperscript{[33]}

Apart from its impact on the humoral immune system, IVIG has also been shown to act on T lymphocytes. Changes in both CD8\textsuperscript{+} suppressor-cytotoxic T cells and CD4\textsuperscript{+} helper T cells have been demonstrated after IVIG treatment.\textsuperscript{[34,35]} Antibodies directed against several T-cell surface molecules are present in IVIG, including the T-cell receptor,\textsuperscript{[36]} CD4, and MHC molecules.\textsuperscript{[37]} Neutralizing antibodies against bacterial and viral superantigens that stimulate T cells non-specifically also are contained in IVIG.\textsuperscript{[38]} Furthermore, soluble CD4 or CD4-like activity and soluble HLA molecules are found in trace amounts in IVIG.\textsuperscript{[12]} Induction of T-cell apoptosis by components of the Fas/FasL system\textsuperscript{[39]} or soluble HLA class 1 molecules\textsuperscript{[40]} included in therapeutic preparations of IVIG may exert a regulatory role on T cell functions by eliminating effector cells.

Finally, there is experimental evidence that IVIG might have the capacity to promote remyelination. Following the observation that polyclonal immunoglobulins against spinal cord homogenate were able to enhance remyelination in the inflammatory model of Theiler’s virus encephalitis,\textsuperscript{[41]} further studies showed that more specific antibodies that are reactive with myelin basic protein also bear the capacity to promote remyelination in this model.\textsuperscript{[42]} A monoclonal IgM antibody was identified that could facilitate remyelination and suppress inflammation and that had some effect in a toxic model of demyelination.\textsuperscript{[43]} This monoclonal antibody was shown to be polyreactive, recognizing antigens present on the surface and in the cytoplasm of oligodendrocytes and other glial cells.\textsuperscript{[44]} Assuming that the remyelination-promoting properties of these antibodies relate to the oligodendrocyte surface activity, IVIG could exert a beneficial effect if it contains
such autoantibodies. However, a systematic exploration of effects of polyclonal immunoglobulin on various aspects of oligodendrocyte precursor cell behavior in vitro was completely negative.

TRIALS OF IVIG IN RELAPSING-REMITTING MS

Well-controlled clinical trials to confirm a benefit of IVIG for MS as suggested by largely observational earlier reports were performed first in patients with relapsing-remitting MS. Three prospective, randomized, placebo-controlled trials have been published in full to date. As summarized in Table 25.1, they concentrated on different aspects of efficacy.

The Austrian Immunoglobulin in MS trial—a study on disability

The Austrian Immunoglobulin in MS (AIMS) trial was the largest of these studies (a phase III trial); 150 patients with relapsing-remitting MS were randomized to receive IVIG treatment in a dosage of 0.15–0.2 g/kg body weight or physiologic saline every month for 2 years. Inclusion criteria were a clinically definite diagnosis of relapsing-remitting MS with complete and incomplete remissions, a baseline Kurtzke Expanded Disability Status Score (EDSS) of between 1.0 (minor neurologic signs without disability) and 6.0 (ambulatory with assistance), and a history of at least two clearly identified and documented relapses during the previous 2 years. Patients had to have stopped any immunosuppressive or immunomodulatory therapy at least 3 months before enrollment and were excluded if they had taken corticosteroids within 2 weeks before study entry. A centralized, computergenerated randomization schedule stratified patients by center, age, sex, and progression rate (baseline EDSS divided by the disease duration in years). Patients were seen monthly in their center by the treating physician. Study assessments were performed by a neurologist who was unaware of treatment allocation (and was different from the treating physician) at scheduled intervals (baseline and every 6 months) or in the event of a possible relapse.

Primary outcome measures were the between-group differences in the absolute change of the EDSS score and in the proportion of patients

<table>
<thead>
<tr>
<th>Study design</th>
<th>Fazekas et al. (AIMS)</th>
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<th>Sørensen et al.</th>
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<tr>
<td>n</td>
<td>148</td>
<td>40</td>
<td>21</td>
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<tr>
<td>Study duration</td>
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<td>2 years</td>
<td>2×6 months</td>
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<td>MRI activity</td>
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who improved, remained stable, or worsened in disability, as defined by an increase or a
decrease of at least 1.0 point of the EDSS by the end of the study. Secondary outcome
measures were the number of relapses, the annual relapse rate, the proportion of relapse-
free patients, and the time to first relapse during the study period. A relapse was defined
as the appearance or reappearance of one or more neurologic abnormalities with an
objective change of at least 1 grade in one of the functional scores present for at least 24
hours after a stable or improving neurologic state of at least 30 days. Further analyses
examined the course of disability and relapse rates in both treatment groups over the
study period and examined the impact of baseline variables on treatment efficacy.[53]
Demographic variables and disease characteristics were well balanced between both
treatment groups. Sixty-four patients in the IVIG group and 56 patients in the placebo
group completed 2 years of treatment.

Intention-to-treat analysis showed mild improvement of IVIG-treated patients over the
study period from a baseline EDSS of 3.33 (95% CI 3.01–3.65) to a final mean EDSS of
3.09 (95% CI 2.72–3.46). In contrast, the placebo group deteriorated slightly from a
baseline EDSS of 3.37 (95% CI 2.96–3.76) to 3.49 (95% CI 3.06–3.92). The change in
EDSS (IVIG -0.23, placebo 0.12) differed significantly between the two groups
\( p=0.008 \). A similar and significant difference was maintained when only those patients
who completed the study were analysed. There was an improvement of 1 point or more
on the EDSS in 23 (31%) of the IVIG-treated patients compared with 10 (14%) of the
placebo group. In contrast, deterioration of disability occurred in 12 (16%) of the IVIG-
treated patients and in 17 (23%) of the placebo group \( p=0.041 \). Overall, 24% of patients
did better on IVIG than on placebo when the differences in rate of improvement (17%)
and prevention of deterioration (7%) between the IVIG-treated and the placebo groups
were added.

The number of relapses in IVIG-treated patients was approximately half of that in the
placebo group (62 versus 116). This resulted in a significantly higher proportion of
relapse-free patients receiving IVIG (53% versus 26%; \( p=0.03 \)). IVIG treatment reduced
the annual relapse rate from a pre-study rate of 1.3 (95% CI 1.09–1.51) to a mean of 0.52
(95% CI 0.32–0.72) during the study period. In placebotreated patients, the annual
relapse rate was 1.41 (95% CI 1.21–1.61) before the study and 1.26 (95% CI 0.75–1.77)
during the study. Hence, IVIG treatment was associated with a 59% reduction of the
annual relapse rate compared with placebo \( p=0.0037 \).

The drop in relapse rate with IVIG treatment was detectable within the first 6
months.[53] Over the study period the relapse rate also continuously decreased in the
placebo group. However, monthly relapse rates of IVIG-treated patients were always
significantly lower than those of the placebo patients. The mean EDSS of the IVIG group
improved in parallel (and significantly) from 3.33±1.38 to 3.05±1.73 within the first 6
months of the study \( p=0.002 \); thereafter it remained rather stable. Placebo treatment was
associated with a slight gradual increase of the EDSS, as described above.

Patient evaluation also included two scales for self-rating of the incapacity status and
the environmental status, as proposed in the minimal record of disability by the
International Federation of Multiple Sclerosis Societies.\[54\] Mean rating scores of eight of 16 items of the incapacity status scale improved in IVIG-treated patients, compared with only one area of improvement in the placebo group, and the total mean change of ratings was significantly in favor of the IVIG group ($p=0.01$).\[55\] The same trend was seen with ratings of the environmental status. Furthermore, IVIG treatment was associated with a lower, though not significantly different, number of hospital admissions and fewer days spent in hospital.\[55\]

Side effects were rarely observed in the AIMS trial. They included a transient rash that developed a few days after infusion in two IVIG patients; another patient of the IVIG group experienced deterioration of his depression, which finally led him to terminate the study.

### Study of the effects of IVIG on relapses

A study by Achiron et al. followed 40 patients with clinically definite and magnetic resonance imaging (MRI) confirmed relapsing-remitting MS over 2 years.\[51\] Further inclusion criteria were an average annual relapse rate of 0.5–3.0 in the 2 years preceding the study and an EDSS of between 0.0 and 6.0. Patients were assigned to treatment groups by block-stratified randomization considering annual relapse rate, age, and disease duration. Twenty patients received IVIG at a loading dose of 0.4g/kg body weight per day for five consecutive days. Subsequent booster doses of IVIG in a dosage of 0.4 g/kg body weight once daily were administered every 2 months. Physiologic saline served as placebo. Patients were examined at baseline and monthly thereafter by two independent neurologists. A relapse was defined as the rapid appearance, re-appearance, or worsening of one or more neurologic abnormalities persisting at least 48 hours after a stable or improving neurologic state of at least 30 days. Objective changes on neurologic examination by a neurologist blind to the patient’s treatment was required, and deterioration accompanied by fever was not considered. Relapse severity was graded according to the Kurtzke EDSS. MRI of the brain was performed on a 0.5 Tesla magnet. Primary endpoints of the study were the annual relapse rate, the proportion of relapse-free patients, and the time until first relapse. Secondary outcome measures were relapse severity, neurologic disability (by EDSS and distribution of cumulative disability over time), and annual brain MRI score.

The annual relapse rate of IVIG-treated patients dropped from 1.85±0.26 in the prestudy period to 0.75±0.16 in the first year and 0.42±0.14 in the second year ($p<0.05$ compared with baseline). The annual relapse rate of the placebo group was 1.55±0.17 before the study, 1.8±0.2 in the first year, and 1.42 ±0.23 in the second year of the trial. Hence, in both years of the study the annual relapse rate of the group receiving IVIG was significantly lower ($p=0.0006$). The number of relapse-free patients was also significantly higher after medication with IVIG during both years and the total study period.

There was a trend towards reduced neurologic disability in the IVIG group (baseline EDSS 2.9±0.43, study completion EDSS 2.6±2.2), whereas a minor increase occurred in the placebo group (baseline EDSS 2.8±0.37, study completion EDSS 2.97±1.47). Distribution of the change in disability over time was significantly in favor of IVIG treatment. The proportion of patients who improved by at least 1 point in the EDSS was 23.5% following IVIG compared with 10.8% in the placebo group. The proportion of
patients worsening by at least 1 point was 13.7% and 17.1%, respectively ($p=0.03$). The mean annual severity of relapses in the IVIG versus placebo groups was not significantly different during either study year.

MRI examinations were analysed by generating an MRI score based on the number and diameter of demyelinating plaques. Mean MRI scores were not significantly different between treatment groups. However, by the end of the second year the number of subjects examined had dropped to 30.

The incidence of notable side effects was low. Out of 630 infusions administered throughout the trial, events were recorded in 12 of 316 (3.8%) patients in the IVIG group and seven of 314 (2.2%) patients in the placebo group ($p<0.05$). Side effects in both groups included fatigue, headaches, rash, and low-grade fever. All complaints spontaneously resolved within a few hours.

**IVIG and disease activity as shown by MRI**

Sørensen et al. examined the effect of IVIG on disease activity using frequent gadolinium-enhanced MRI in a cross-over study of 26 patients with relapsing-remitting MS or secondary progressive MS with relapses. Inclusion criteria consisted of disease duration not longer than 10 years, EDSS of between 2.0 and 7.0, two or more acute relapses in the year before entry, and at least five cerebral lesions on T2-weighted images on a screening MRI. In a randomized fashion, one group of patients was first treated with IVIG for 6 months. After a 3-month washout period, these patients were then treated with placebo for another 6 months. The second group was treated in reverse order. IVIG treatment consisted of infusions of 1 g/kg body weight per day for two consecutive days at monthly intervals. Human albumin (2%) administered with an identical regimen served as placebo. MRI was performed using a 1.5 Tesla scanner and a conventional double spin-echo sequence with a slice thickness of 4 mm and no interslice gap. Postcontrast T1-weighted scans were obtained 10 minutes after injection of gadolinium in a dosage of 0.1 mmol/kg body weight. All scans were evaluated blindly by two independent radiologists for the presence of gadolinium-enhancing lesions. Lesion area measurements were obtained from proton-density images. In addition, all patients underwent neurologic examination and neurophysiologic studies with multimodal evoked potentials. Primary study endpoints were the total number of gadolinium-enhancing lesions and the number of new enhancing lesions on serial MRI. Secondary endpoints were the percentage of patients with active scans (scans with gadolinium-enhancing lesions), the total lesion load on T2-weighted MRI, changes in multimodal evoked potentials, number of relapses, number of relapse-free patients, number of severe relapses, changes in neurologic function on the Scripps Neurological Rating Scale, and changes in EDSS ratings. Twenty-one patients were available for intention-to-treat analysis following completion of at least 1 month of follow-up and two MRI scans in the second treatment period. Eighteen patients completed the entire cross-over study and constituted the per-protocol population.

Overall, IVIG treatment significantly reduced the mean number of new and total gadolinium-enhancing lesions by approximately 60% compared with placebo both in the per-protocol population (total numbers: baseline 3.8±8.3, IVIG 1.2±2.2, placebo 3.2±5.9; $p=0.03$) and according to intention-to-treat analysis (total numbers: baseline 3.6±7.7,
IVIG 1.3±2.3, placebo 2.9±5.4; $p=0.003$. Disease activity on MRI decreased after 1 month of treatment with IVIG and then remained stable, whereas no changes in activity were observed during treatment with placebo. The average percentage of per-protocol patients with active scans on 6-monthly serial MRI scans was 37% during IVIG treatment compared with 68% when receiving placebo ($p<0.01$). Four of 18 patients did not have any gadolinium-enhancing lesions during the entire IVIG treatment period but none was free of new gadolinium-enhancing lesions while on placebo. Only four patients had a poor response to active medication, defined as more than 50% active scans during IVIG therapy or more active scans while on IVIG than on placebo (or both). No significant between-group differences were found with regard to the total T2 lesion load.

In IVIG treatment periods, the number of relapses was 42% lower according to intention-to-treat analysis and 27% lower as per-protocol but these differences did not reach statistical significance. However, a significantly greater number of patients were relapse-free when receiving IVIG (71%) than during placebo medication (33%) ($p=0.02$). Although a greater number of patients improved on IVIG than on placebo, no significant differences were found with regard to changes of the EDSS between the two treatment periods. Multimodal evoked potentials also failed to demonstrate significant differences.

In this study, an unexpectedly high number of acute and chronic adverse events occurred. More than 50% of patients experienced one or more adverse events with IVIG treatment. Acute adverse events consisted of headache, nausea, and urticarial rashes. Headache was usually mild, lasting for 1–2 days and controlled by analgesics. A reduction in infusion rate of IVIG significantly decreased the occurrence of post-infusion headache and nausea. Urticarial rashes could be abolished or diminished by administration of an antihistamine drug before the infusion. The most common major chronic side effect was severe eczema, observed in 11 patients during treatment with IVIG. The eczematous reaction developed 2–4 days after infusion and preferentially affected the palms of the hands, although it also spread to the soles of the feet and to the extremities; it became generalized in two patients. In all affected patients the eczema eventually resolved after discontinuation of IVIG therapy, but in some patients it persisted for several weeks after the last infusion. Differences in the concentration of cytokines between commercially available preparations of IVIG may have contributed to this unusual adverse effect profile, because such observations have not been made as frequently in other indications for high-dose treatment. In addition, one patient developed hepatitis C and one experienced deep venous thrombosis and pulmonary embolism.

**MS disease activity and different dosages of IVIG**

A further double-blind placebo-controlled study of IVIG in relapsing-remitting MS has recently been reported in abstract form.\(^{[56]}\) This single-center study performed at the Department of Neurology of the Medical University of Łódź attempted to compare the efficacy of different dosages of IVIG on clinical and MRI outcome measures. A total of 49 patients were randomly allocated to three treatment groups with 0.2 g/kg of IVIG, 0.4g/kg of IVIG, or saline as placebo. All treatments were given at monthly intervals for 1 year. Clinical variables assessed were the number of relapses and changes in EDSS and the Scripps Neurologic Rating Scale. MRI scans, including gadolinium-enhanced scans, were performed every 3 months and served to assess the total T2-lesion volume and the
number of new and gadolinium-enhancing lesions. During the study the annual relapse rate was lower in both IVIG groups (0.88 in the low-dose and 0.86 in the high-dose group), compared with a mean relapse rate of 1.24 in the placebo patients. Disability remained stable following IVIG treatment but deteriorated significantly in the placebo patients. Total lesion volume increased by 13.6% in the placebo patients and by 3.6% in the low-dose IVIG group, and it decreased by almost 4% in the high-dose IVIG group. The mean number of gadolinium-enhancing lesions was lower in the IVIG groups than in the placebo group. The study concluded that these results would indicate a similar efficacy of both dosages of IVIG in relapsing-remitting MS.

**Comparison with other immunomodulating drugs**

Table 25.2 summarizes the results of published trials of IVIG in relapsing-remitting MS with regard to the reduction of disease activity and the progression of disability.[50-52] As can be seen, observed treatment effects all went in the same direction and uniformly were in favor of IVIG. A similar trend also is seen in the reported Polish study.[56] Although these data convincingly demonstrate the capability of IVIG to reduce the frequency of relapses in patients with relapsing-remitting MS, the exact extent to which this may be achieved is more difficult to determine. This is primarily because of the different treatment regimens used and the mostly small numbers of patients studied. The data of the AIMS trial, as the largest study so far, suggest at least a similar effect of IVIG treatment in reducing relapse frequency as the results of studies that have assessed interferon beta[57-59] or glatiramer acetate.[60,61] The effect on progression of disability as

<table>
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<th>Fazekas et al. (AIMS)⁵⁰</th>
<th>Achiron et al.⁵¹</th>
<th>Sørensen et al.⁵²</th>
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<tr>
<td></td>
<td>IVIG n=75</td>
<td>P n=73</td>
<td>IVIG n=20</td>
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<td><strong>Relapses</strong></td>
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<td>Annual relapse rate</td>
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<tr>
<td>at baseline</td>
<td>1.3</td>
<td>1.41</td>
<td>1.85</td>
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<tr>
<td>during trial</td>
<td>0.52</td>
<td>1.26†</td>
<td>0.59</td>
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<tr>
<td><strong>Number of relapses</strong></td>
<td>62</td>
<td>116</td>
<td>–</td>
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<tr>
<td><strong>Number of relapse-free patients</strong></td>
<td>40 26*</td>
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<td><strong>Disability</strong></td>
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<td>EDSS</td>
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<td>at baseline</td>
<td>3.33</td>
<td>3.37</td>
<td>2.9</td>
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<tr>
<td>at end of trial</td>
<td>3.09</td>
<td>3.49†</td>
<td>2.6</td>
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<tr>
<td>Improved§</td>
<td>31</td>
<td>14</td>
<td>23</td>
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<tr>
<td>Stable§</td>
<td>53</td>
<td>63</td>
<td>63</td>
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<tr>
<td>Worse§</td>
<td>16</td>
<td>23*</td>
<td>14</td>
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* p<0.05, † p<0.01, ‡ p<0.001
§percentage of patients with change of EDSS by ≥1.0 point
observed in the AIMS study was also comparable to that achieved with other immunomodulatory drugs.\textsuperscript{[62]} Besides these encouraging aspects, however, the relative paucity of supportive evidence for IVIG in relapsing-remitting MS compared to that which is available for interferon beta and glatiramer acetate has to be acknowledged. This especially concerns the overall small number of patients, the limited length of the observational period, and the lack of more comprehensive outcome variables, including MRI, in successful treatment trials of IVIG so far.

TRIALS OF IVIG IN SECONDARY-PROGRESSIVE MS

Following suggestive evidence for a beneficial effect in relapsing-remitting MS, the application of IVIG to other forms of MS or in a different stage of MS was the next logical step. This appeared all the more important since data on the effects of other immunomodulating drugs were also collected only recently for this group of patients.

The European Study on IVIG treatment in secondary progressive MS

The European Study on IVIG treatment in secondary progressive MS (ESIMS) was a European-Canadian multicenter, double-blind, placebo-controlled, randomized trial (phase III) of two parallel treatment groups.\textsuperscript{[63]} Eligible patients within an age range of 18 to 55 years had to have a clinically and laboratory supported definite diagnosis of MS with a disease duration of at least 3 years and a secondary progressive course for at least 1 year. Secondary progression was defined as a documented deterioration over the preceding 12 months with or without super-imposed relapses following an initial phase of relapsing-remitting MS. The EDSS was required to range from 3.0 to 6.5. Disease activity was defined as a documented deterioration of 1.0 point on the EDSS for baseline EDSS <5.5 or 0.5 points on the EDSS for baseline EDSS $\geq$ 5.5, or two attacks and a documented deterioration of 0.5 points on the EDSS points in the previous 2 years.

Patients were treated with monthly infusions of 10% IVIG in a dosage of 1 g/kg bodyweight up to a maximum of 80 g. Placebo medication consisted of the same volume of 0.1 g albumin. All infusions were administered at the study site. Regular visits for neurologic evaluation occurred every 3 months for a total of 30 months. The primary efficacy parameter of this trial was the percentage of patients with a confirmed treatment failure defined as a deterioration of 1.0 point on the EDSS if the initial EDSS was <5.5 or 0.5 points on the EDSS if the initial EDSS was $\geq$5.5 at two consecutive visits 3 months apart. In sample size calculations it was assumed that the placebo group would show progression in about 45% of patients. A reduction of 40% was assumed to be clinically meaningful so that the treatment failure rate under treatment would be $\leq$27%. From these assumptions it was calculated that at least 300 patients (i.e. 150 per group) were required to detect this difference, with the power of 0.80 in a Fisher’s exact test at $\alpha$=0.05 assuming a drop-out rate of 15%. A confirmed 20% worsening in the nine-hole peg test and the number of relapses were defined as further clinical outcome variables. MRI with and without gadolinium-enhancement was performed at baseline, year 1, and year 2. The major MRI outcome variable consisted of the change in total T2-lesion load. Further MRI outcome variables were the number of new and enlarging or gadolinium-enhancing
lesions. The volume of ‘black holes’ and the brain parenchymal fraction also were analysed. Advanced MRI techniques such as magnetization transfer imaging and three-dimensional atrophy measurements were performed in subgroups of patients.

The study was completed in April 2001. Detailed results are not yet available, but it has been reported that the study failed to demonstrate a significant difference between IVIG and placebo treatment with regard to the primary and most secondary outcome variables of the trial.\[64\]

TRIALS OF IVIG TO REVERSE FIXED DEFICITS OF MS

After 1–2 months of IVIG treatment, van Engelen et al. noted improved visual acuity and color vision in five MS patients with optic neuritis despite long stable visual impairment beforehand.\[65\] This improvement persisted over a follow-up period of 1.2–1.7 years, and it was thought that it most likely represented the effects of remyelination. As outlined above, such speculation can be supported by experimental data, which have found a remyelinating capacity of IVIG or specific IVIG components in addition to its immunomodulatory activities.\[66\] Meanwhile two randomized, double-blind, placebo-controlled trials have failed to confirm the capacity of IVIG to reverse fixed deficits after demyelinating lesions.\[67,68\]

IVIG for established weakness in MS

Noseworthy et al. performed a trial of IVIG in 67 patients with MS and an apparently irreversible motor deficit.\[67\] To be defined as the targeted neurologic deficit for the trial, the weakness had to have been present and stable for between 4 and 18 months and to involve at least one limb with more than 25% loss of power. The primary endpoint was the change from baseline to 6 months in the mean percentage of normal strength of muscles with targeted neurologic deficit. Secondary outcome measures included various disability scales and measures of neurologic functions. MRI studies were also performed in five patients from each treatment group. Treatment consisted of 0.4g/kg IVIG in a 10% solution or placebo (0.1% human serum albumin in 10% maltose) given intravenously for 5 days and every 2 weeks thereafter for 3 months for a total of 11 infusions. Great care was taken to keep patients and examiners blinded to treatment assignment, and only the two non-treating neurologists who reviewed the videotaped examinations at the end of the trial were informed of the nature of the targeted neurologic deficit. The study was terminated after a negative interim analysis.

At 6 months, muscle strength had worsened mildly in both treatment groups and IVIG had failed to improve isometric strength of the muscles representing the targeted neurologic deficit as well as that in other muscle groups. The deterioration in mean percentage of normal muscle strength of targeted neurologic deficit muscle groups from baseline to 6 months was somewhat more pronounced in the IVIG group (−2.5±12.5% versus −0.3±14.2%). This difference, however, was not significant. Analysis of secondary outcome variables including the EDSS, the nine-hole peg test, or the ambulation index also showed no evidence of a beneficial effect of IVIG. Because of the small number of patients examined, it was felt that no meaningful conclusions could be
drawn from the MRI findings. Treatment was well tolerated, and adverse events consisted primarily of a rash, which was seen in eight of 33 IVIG-treated patients and two of 34 placebo patients. Headaches were also slightly more common in the IVIG group.

**IVIG in inflammatory demyelinating optic neuritis**

The potential of IVIG to repair functional deficits in MS was also examined in the visual system. Inclusion criteria of this study included one or more episodes of demyelinating optic neuritis that had occurred in the setting of clinically definite or laboratory-supported definite MS or in the presence of cranial MRI changes consistent with MS. Visual acuity had to be worse than 20/40 for a period of at least 6 months with no change on at least two standardized examinations separated by at least 1 month. Optical disk pallor and an abnormal visual field were further prerequisites. The primary outcome measure was the change in visual acuity from baseline to 6 months. Secondary outcome measures included other tests for visual function, neurologic impairment, and clinical measures of disease activity. Patients received daily 0.4g/kg IVIG in a 10% solution or placebo (0.1% human serum albumin in 10% maltose) intravenously for 5 days, and thereafter at 4-week intervals for a total of eight infusions. Twenty-seven patients were assigned to IVIG and 28 to placebo treatment. Overall, in the full study cohort, no significant differences between groups were noted to suggest that IVIG had reversed pre-existing visual or neurologic dysfunction. Visual acuity was essentially unchanged for both groups at 6 months, and a slight positive trend in favor of IVIG at 12 months was non-significant. Interestingly, there appeared to be a treatment interaction between the change in visual evoked responses at 12 months and the type of disease. Among those with relapsing-remitting MS, 36.9% of the IVIG-treated patients had improved visual evoked responses compared with 9.5% of the placebo group. Conversely, among patients with secondary progressive MS, no IVIG patients had improved visual evoked responses and 33% got worse, whereas 40% of placebo patients had improved visual evoked responses and none got worse. IVIG-treated clinically stable patients also were more likely to show improvement (seven of 11 on IVIG versus three of 13 on placebo; \( p=0.022 \)), while there was a tendency for mild worsening of visual acuity and visual fields at 12 months in IVIG-treated unstable MS patients compared with placebo. This raised concern that IVIG might even have adversely affected patients with active MS.

Side effects consisted primarily of a rash in association with the infusions and of headaches; they were recorded more frequently in IVIG than in placebo patients.

**CURRENT POSITION OF IVIG IN THE TREATMENT OF MS**

At present, all available clinical evidence for a beneficial effect of IVG treatment refers to patients with relapsing-remitting MS only. The results of the ESIMS trial with a comprehensive evaluation of more than 300 patients clearly do not support the use of IVIG in secondary progressive MS, and IVIG failed to restore MS-related stable neurologic deficits in two appropriately designed clinical trials. Despite these negative results, IVIG can still be considered a possible treatment option for relapsing-remitting MS. The ‘diversity’ of the pathophysiologic mechanisms involved in the
evolution of MS are increasingly recognized\cite{69,70} and a different response to IVIG treatment according to the stage of the disease should not be too surprising. Such differences in efficacy have become a common experience with other immunomodulators as well,\cite{71,72} and in the case of IVIG they are further supported by the observation of almost contradictory effects of IVIG on the restoration of visual function in patients with relapsing-remitting MS and those with secondary progressive MS.\cite{68}

Because of the limitations of available scientific evidence and existing uncertainties, such as mode of action and optimal dosage, the use of IVIG in relapsing-remitting MS is presently restricted to individual patients who could especially benefit from the advantages of this product.\cite{73,74} Both the frequency and the routes of administration of interferon beta and glatiramer acetate are not easily acceptable for some patients, and local reactions at the injection site can become a problem, whereas monthly administration of IVIG (such as in the AIMS trial\cite{50}) or every other month (as in the study by Achiron et al\cite{51}) is readily tolerated. Also, the side effects of IVIG at a low dosage as used in these two studies and the recent Polish trial\cite{56} have been uniformly minor and consisted primarily of headaches, malaise, or a transient rash.\cite{75} Treatment failures of interferon beta and glatiramer acetate may also warrant consideration of IVIG as an alternative treatment option. For such decisions a better characterization of the causes for treatment failure (e.g. antibody production following long-term treatment with interferon beta) and an improved understanding of the mechanisms by which IVIG can act differently are urgently needed. The results of the ESIMS trial\cite{63,64} and anecdotal evidence\cite{76} argue clearly against the use of IVIG in more severe forms of MS, and the efficacy of IVIG in these settings obviously does not increase with increased dosage dosage.\cite{64}

**FUTURE RESEARCH**

Future research efforts will concentrate primarily on relapsing-remitting MS. It will be necessary to clarify which low-dosage regimen should be used and further direct and indirect proof of a disease-modifying action of IVIG, including supportive morphologic data, needs to be collected. Preliminary evidence of a beneficial role of IVIG in pregnancy for the prevention of postpartum relapses will have to be confirmed.\cite{77,78} Various clinical studies that address these issues are currently planned or ongoing. Further insight into the exact mechanisms of action of IVIG are needed to allow for a more ‘targeted’ therapeutic approach and to appreciate the possible role of differences in the preparation of the product. Such understanding should also be the prerequisite for considering the potential contribution of IVIG to combination therapies in MS.\cite{79}

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Therapeutic plasma exchange for multiple sclerosis
Brian G Weinshenker and Mark Keegan

INTRODUCTION

Therapeutic plasma exchange (TPE), also known as plasmapheresis or apheresis, has been studied as a treatment for multiple sclerosis (MS) since 1980. The effects of TPE on MS are perhaps best considered by examining two distinct patient groups, those with progressive forms of MS and those with acute, severe attacks of MS and other idiopathic inflammatory demyelinating diseases. Evidence for efficacy is equivocal and modest at best in progressive MS. However, a sizeable proportion of patients with acute, severe attacks experience marked and rapid improvement. Noseworthy reviewed the use of TPE in progressive MS. Since that time, Vamvakas et al. published a review and meta-analysis of six prospective controlled studies. Recently, a controlled clinical trial at the Mayo Clinic demonstrated that TPE is an effective treatment for acute, severe attacks of inflammatory demyelination of MS and other idiopathic inflammatory demyelinating disease in patients who do not respond to conventional treatment with high-dose corticosteroid therapy.

This chapter considers the results of clinical series and controlled trials, adverse effects, and possible mechanisms of action of TPE in neurological and non-neurological diseases. It reviews the meta-analysis by Vamvakas et al. about the efficacy of TPE for progressive MS; however, it focuses on the results of the randomized trial performed at the Mayo Clinic. It reviews data from a retrospective study that included all patients with acute, severe attacks of demyelinating disease at the Mayo Clinic treated with TPE from 1984 to 2000 that identified clinical factors that predict favorable response to TPE. It then considers the possible mechanisms of action of TPE in these inflammatory demyelinating diseases of the central nervous system (CNS).

METHODS, MECHANISMS OF ACTION AND ADVERSE EFFECTS

Plasma exchange consists of withdrawal of blood and separation of cellular elements from plasma by centrifugation, followed by re-infusion of the cellular elements in a replacement solution, usually consisting of albumin. Plasma is rarely used as a replacement solution except in thrombotic thrombocytopenic purpura; in this instance,
plasma contains the active agent that is necessary to treat the disease. Recently, colloidal starch has been recommended as a suitable replacement solution.\[6\]

TPE removes plasma proteins non-selectively, including immunoglobulins of all classes, immune complexes, cryoglobulins, and cholesterol-containing lipoproteins. TPE is especially effective in diseases where the pathological substance is large (≥15000 Da), has a long half-life, (i.e. is not regenerated immediately), and is acutely toxic so that rapid removal is beneficial.\[7\] Only the intravascular component is accessible for removal by TPE. Therefore, removal of the extravascular component by subsequent exchanges is dependent on the diffusion of the substance across the vascular membrane into the intravascular space. Specific substances vary in their percentage reduction by TPE. Studies with immunoglobulins, however, reveal approximately 90% of the total substance is removed by five exchanges over a 7–10-day period.\[7\] Any subsequent recurrence of immunoglobulins arises from continued shift from the extravascular to the intravascular component and by production of new antibody.

TPE effectively treats a number of neurological and non-neurological diseases. Renal, hematological, and dermatological disorders account for most of its non-neurological use. TPE is a life-saving treatment in Goodpasture’s disease and is associated with a reduction in anti-glomerular basement membrane antibodies. It is the standard of care for TTP and for some types of cryoglobulinemia. The main indications in dermatological disorders are pemphigus and bullous pemphigoid, for which reductions in both autoantibody titers and in the level of cytokine interleukin (IL)-6 have been described.\[8\]

The two most common neurological indications for TPE are myasthenia gravis and Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy). Pathogenic autoantibodies occur in both of these disorders (against acetylcholine receptor in myasthenia gravis and against ganglioside moieties in Guillain-Barré syndrome). However, these disorders differ in their presentation. Myasthenia gravis is a chronic disease whereas Guillain-Barré syndrome is typically a monophasic condition. TPE is beneficial in MG with acute crises or in preparation for thymectomy or other surgeries. TPE reduces the titer of acetylcholine receptor antibodies and rapidly improves strength. Guillain-Barré syndrome is particularly relevant to CNS inflammatory demyelinating disease since the pathology consists of macrophage-mediated myelin and axonal injury, not unlike what is encountered in many situations of acute, severe CNS demyelinating disease. In Guillain-Barré syndrome, the improvement is not typically as rapid and dramatic as in myasthenia gravis, but TPE reduces the time to regain independent walking and become ventilator-independent.\[10\] A variety of autoantibodies are associated with Guillain-Barré syndrome, some being specific to the clinical presentation and the response to TPE. For example, antibodies to ganglioside GQ1b are associated clinically with the Miller-Fisher syndrome and a favorable response to TPE, whereas antibodies to ganglioside GM1b appear to be associated with acute motor neuropathy with poor response to TPE.\[11\]

Circulating immune complexes are rarely present in patients with MS who have been reported to benefit from TPE,\[12\] although Stricker et al. reported circulating immune complexes in a patient with acute disseminated encephalomyelitis who appeared to respond to TPE.\[13\] Other circulating factors that may be relevant to the therapeutic actions of TPE include proinflammatory cytokines (e.g. tumor necrosis factor-α, interferon-γ) and complement. Whether the therapeutic effect occurs at the level of the
blood-brain barrier, within the CNS, or possibly in the periphery (e.g. by altering T-cell suppressor function) is unknown. As discussed later, the response described by many investigators in patients who receive TPE for acute attacks of MS is rapid, suggesting that the effect may be physiological rather than anti-inflammatory or resulting from remyelination. Buchwald et al. recently found that IgG from patients with Guillain-Barré syndrome can interfere with neurotransmitter release and post-synaptic activation of muscle. Others have also described neuroelectric-blocking activity in the immunoglobulin fraction of MS sera that is capable of inhibiting the ventral root response in isolated, perfused spinal cords.

TPE is generally well tolerated. The most common adverse effects are hypotension and sodium citrate anticoagulant toxicity (perioral paresthesias). Other treatment-related complications include those resulting from the placement of a central line, which is required by a high proportion of patients who require frequent plasma exchange treatments. Serious complications are those related to central lines, including sepsis. Multifactorial treatment-related anemia is observed frequently. Anemia is caused by hemodilution resulting from the replacement colloidal solution and loss of blood in the dead space of the apparatus. Hemolysis does not ordinarily occur. Platelet levels should be monitored because the use of heparin during the procedures exposes the patient to the risk of developing heparin-associated thrombocytopenia syndrome. Patients using angiotensin converting enzyme inhibitors should discontinue these medications at least 24 hours before plasmapheresis because they may develop anaphylactoid reactions that are probably associated with activation of kinins.

**TPE IN PROGRESSIVE MS**

Noseworthy reviewed seven non-randomized studies and four randomized studies conducted before 1991 in ‘chronic progressive’ MS in an earlier edition of this volume. Studies in progressive MS have been contradictory, although a meta-analysis suggested that TPE may have a weak beneficial effect at 12 months from initiation of treatment to prevent deterioration when combined with other immunosuppressive treatment. As of 1991, when the last of these studies was reported, it was not customary to differentiate between primary progressive MS and secondary progressive MS. Most current studies enroll only patients with secondary progressive MS. Potentially important biological differences have been described between these two subtypes. Patients with primary progressive MS have less inflammation, fewer MRI lesions, and possibly immunogenetic differences, such as an excess of the MHC class II allele DR4. Axonal degeneration may play a more dominant role in primary progressive MS than in secondary progressive MS. Accordingly, one might speculate that trials with a relative excess of patients with primary progressive MS may have been less likely to demonstrate benefit.

Vamvakas et al. reported a meta-analysis of six prospective studies that included patients with clinically definite, progressive MS and had a concurrent comparison group. The design and results of the individual studies were summarized in the paper. Of the six studies, four were randomized and two were double blinded with respect to the use of TPE. One study was multicenter. The treatment regimens were variable (between four and 20 treatments) as was the duration over which
they were administered (2 weeks to 1 year), making comparison between the studies difficult. The homogeneity of the behavior of patients in these studies, (assessed using the Q statistic, Yusuf et al.\textsuperscript{[28]}) allowed for meta-analysis. However, for analysis of mean change in disability status score (DSS), some patients in one study\textsuperscript{[22]} were excluded because the conditions for homogeneity could not otherwise be met, since these patients were ‘outliers’. The results of the meta-analysis are given in Table 26.1. There was evidence for significant, though modest, efficacy in reducing the odds of worsening at 12 months and in enhancing the odds of improving at 6 and 12 months after TPE. Follow-up at 24–36 months revealed significant results only for the relative odds of worsening at 24 months.

The conclusions from this meta-analysis must remain tentative because:

- the ‘control groups’ were not strictly comparable (e.g. in the Canadian Cooperative Study,\textsuperscript{[23]} the ‘control group’ for the purposes of this meta-analysis had received high-dose intravenous cyclophosphamide rather than oral cyclophosphamide, as did the TPE group because the trial was designed to evaluate several therapeutic claims for different regimens, particularly ones including cyclophosphamide, and not expressly to evaluate the efficacy of TPE);
- the effects of TPE and the other immunosuppressive treatments administered in these studies are difficult to disentangle; and
- the TPE regimens differed considerably in terms of the intensity of the exchanges and the durations over which they were applied.

Further investigation of TPE for progressive MS is of questionable benefit because existing studies do not provide any indication of a subgroup that is likely to respond, other possible treatments for progressive MS exist, and TPE is an expensive, cumbersome treatment that is not well suited for long-term management, particularly if other treatments are equally or more effective and if benefit is transient.

### TPE IN ACUTE ATTACKS OF DEMYLELINATING DISEASE

In contrast to the modest and equivocal results in patients with progressive MS, uncontrolled

### Table 26.1 Meta-analysis of effect of plasma exchange in progressive MS

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>Controlled</td>
<td>All</td>
<td>Controlled</td>
</tr>
<tr>
<td>Change in DSS</td>
<td>−0.171</td>
<td>−0.177</td>
<td>−0.212</td>
<td>−0.204</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(−0.149)†</td>
<td>(−0.167)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative odds of worsening</td>
<td>0.746</td>
<td>0.879</td>
<td>0.436*</td>
<td>0.441*</td>
<td></td>
</tr>
<tr>
<td>Relative odds of improvement</td>
<td>1.981*</td>
<td>2.321*</td>
<td>2.129*</td>
<td>2.258*</td>
<td></td>
</tr>
</tbody>
</table>
Based on a review by Vamvakas et al.\textsuperscript{[2]} of six studies, four of which were controlled values shown reflect difference in change in mean DSS or relative odds of worsening/improvement by 1 DSS point in treatment versus control group \( \ast p<0.05 \)
\( \dagger \) after exclusion of four outliers

observations in patients treated with TPE for acute severe attacks suggested that patients may show dramatic recovery from devastating, apparently fixed, neurological deficits after a brief course of treatment. A recent controlled trial established the benefit of TPE for acute, severe, corticosteroid-refractory attacks of MS and other idiopathic inflammatory demyelinating disease.\textsuperscript{[3]} It is instructive to contrast this study with the one previous randomized clinical trial of plasma exchange for acute attacks of MS\textsuperscript{[29]} to analyse why the benefits apparent in the Mayo Clinic trial were not as evident in this earlier multicenter study.

The natural history of acute severe attacks of demyelinating disease has not been extensively studied. Ascertainment of cases in studies that address recovery from acute attacks is based on hospitalized series that are biased to patients with the most severe attacks. The most complete data on this subject comes from the study by Kurtzke et al. of hospitalized US veterans.\textsuperscript{[30]} The strengths of these data include the unbiased ascertainment (high likelihood that military recruits would have been hospitalized for these symptoms), the long duration of ‘in-hospital’ evaluation (mean 105 days), and the fact that most patients were experiencing a first attack. Pseudo-exacerbations caused by physiological perturbations such as fever were less likely to have an impact on this study because pseudoexacerbations occur more frequently in patients with relatively more advanced disability. The outcome for 18 patients with the most severe attacks, whose admission DSS scores were between 7 and 9 (not ambulatory), is shown in Table 26.2.

Fifty-six percent of patients had either no recovery or minimal recovery after a devastating acute attack that rendered them non-ambulatory.

Table 26.2 Outcome of severe attacks of MS

<table>
<thead>
<tr>
<th>DSS at dismissal\textsuperscript{a}</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

| Improvement in DSS at dismissal\textsuperscript{b} | n (%) | |
|--------------------------------------------|-----------------|
| Change in DSS                              | n (%)          |
| 0                                          | 7 (39%)        |
| 1                                          | 3 (17%)        |
Based on data from Kurtzke et al.\cite{46} on 18 US veterans admitted with acute exacerbations and EDSS of 7–9 at baseline.

| $\geq 3$ | 8 (44%) |

*Mean hospital stay 105 days

Although Kurtzke et al. concluded that severe attacks were as likely as or more likely than less severe attacks to improve by 1 DSS point, it is important to point out that improvement by 1 DSS point is trivial for attacks that lead to an acute deterioration by 6 or more DSS points. Other studies conducted on patients with acute attacks support the conclusion that patients with relatively infrequent severe attacks may not recover and that high-dose corticosteroid failure occurs in up to 40% of such patients.

In an earlier edition of this book\cite{31}, the authors summarized the background literature on the use of TPE in acute inflammatory demyelinating disease of the CNS that led to the clinical trial conducted at the Mayo Clinic from 1995 to 1998.\cite{3} That review summarized eleven series with 28 patients that reported favorable results in uncontrolled clinical experience with TPE in diverse idiopathic and, occasionally, in symptomatic, demyelinating disease syndromes (14 patients with MS, nine with acute disseminated encephalomyelitis, two with acute transverse myelitis, and three with neuromyelitis optica). Since that review, several similar reports have appeared. These reports include one of substantial recovery from acute disseminated encephalomyelitis following industrial hog vaccine self-injection in a man with severe cognitive impairment,\cite{32} a second in a pregnant woman with acute disseminated encephalomyelitis,\cite{33} and a third in three patients with malignant forms of MS, two of whom had a locked-in state and a third who had a severe pseudobulbar palsy.\cite{34} In the latter, immunoadsorption was used to remove immunoglobulin, immune complexes and complement specifically, but presumably the mechanism of improvement was similar. Furthermore, a series reporting favorable results with the use of plasma exchange in patients with neuromyelitis optica was reported in abstract form by Rensel et al.\cite{35}

The most influential study published since the last series was the Mayo Clinic randomized clinical trial.\cite{3} This trial was designed to directly assess the experience of Rodriguez et al.,\cite{36} who reported dramatic benefit resulting from between six and nine courses of TPE administered without immunosuppressive treatment in six patients with acute attacks of MS. These patients had failed standard treatment with intravenous corticosteroids. All were paraplegic, hemiplegic, or quadriplegic. In addition, two patients were aphasic and two were ventilator-dependent. The mean improvement at the conclusion of TPE was 3.8 extended DSS (EDSS) points (range 0.5–6.0, median 4.5). Improvement was first evident at a median of 4.8 days (range 2–12 days) after starting TPE. Benefit was sustained over 6–35 months of follow-up.

Weiner et al. reported a randomized, controlled, parallel-design trial of 11 courses of true versus sham exchange over 8 weeks as a supplement to oral cyclophosphamide and adrenocorticotropic hormone (ACTH) in 116 relapsing-remitting or progressive MS patients with acute exacerbations.\cite{29} The primary endpoint was improvement by 1 DSS point. The overall difference between the patients and controls was not significant, but there was a trend in favor of treatment at one month that was most evident in with relapsing-remitting MS patients with the most severe attacks.
The authors do not feel that the study by Weiner et al.\cite{29} either proved or disproved a beneficial effect, even a dramatic one, of TPE for acute attacks of MS. The limitations of this study include the facts that patients with attacks of varying degrees of severity were studied, including patients with mild attacks; patients with progressive MS were also included; all patients received ACTH and cyclophosphamide in addition to being randomized to receive true or sham plasma exchange; and the endpoint was the DSS rather than the deficit targeted to the patient’s specific attack-related neurological deficit. The DSS could be quite insensitive to major improvements of cognitive dysfunction or upper extremity dysfunction if these were the neurological deficits caused by the attack.

Mindful of the differences between the studies of Rodriguez et al.\cite{36} and Weiner et al.\cite{29} the authors developed a randomized, shamcontrolled study focused on the patient subgroup of interest to address the uncontrolled observations by Rodriguez et al.\cite{36} Until these observations could be confirmed in a prospective, randomized, controlled, and blinded fashion, the tentative conclusions of Rodriguez et al.\cite{36} would not achieve widespread acceptance or be incorporated into treatment strategies for MS.

The following principles were intrinsic to the design of the Mayo Clinic study:

1. Enroll patients for whom the diagnosis of demyelinating disease was virtually certain. In equivocal cases, biopsy material was obtained to confirm the diagnosis. The trial included patients with idiopathic inflammatory demyelinating diseases other than MS, such as acute disseminated encephalomyelitis, Devic’s neuromyelitis optica, and focal demyelinating diseases of the brain with or without mass effect. By definition, patients qualifying for this protocol were atypical in having experienced a severe neurological deficit that was unresponsive to corticosteroids. Significant overlap between MS and ‘atypical’ inflammatory demyelinating diseases does exist. Exclusion of such cases would eliminate an important and not uncommon group of patients with severe demyelinating disease who might respond to TPE.

2. Include only patients with a high probability of experiencing severe, permanent neurological deficits. All patients had a profound neurological deficit affecting one or more of the following: power in at least one extremity, language function, cognitive function, or consciousness. All patients enrolled had a neurological deficit for 3 weeks and experienced no or minimal improvement 2 weeks after high-dose intravenous methylprednisolone therapy (minimum 7 mg/kg per day or equivalent for 5 days). An exception was made for patients who had an attack of inflammatory demyelinating disease for a minimum of 12 days who had completed 5 days of intravenous methylprednisolone and experienced continued progression of their neurological deficit.

3. Institute a robust measure of treatment success. The study was interested only in a functionally significant outcome and not in a 1-point change in the EDSS. Functionally important change was the standard required to justify this expensive and cumbersome treatment. Furthermore, the EDSS was not sensitive to some of the targeted neurological deficits, including global cognitive dysfunction and aphasia. Accordingly, the primary outcome was a global assessment of change in the targeted neurological deficits by the two masked evaluating neurologists. Patients with demyelinating syndromes resulting from small lesions such as those that cause optic neuritis or vertigo, for which the prognosis is generally felt to be less ominous, were not enrolled. Objective and established scales were chosen to rate each of the
outcomes, and consensus was reached about the degree of improvement that would be interpreted as mild, moderate, or marked improvement. However, the final decision about the degree of improvement was left up to the global opinion of the evaluating neurologist. This outcome measure was appropriate because it was expected that the masking would be very effective. Common adverse effects of TPE (e.g. hypotension, citrate toxicity) were independent of the active treatment, namely replacement of plasma by albumin. Moderate (functionally important) or marked improvements were required for treatment success in this study. However, perfect improvement (i.e. return to baseline function) was felt to be an excessive requirement.

4. Evaluate TPE alone without concomitant immunosuppression, because Rodriguez et al.\(^{[36]}\) found that TPE alone was effective.

A regimen consisting of seven exchange treatments every other day was chosen, based on the study by Rodriguez et al.\(^{[36]}\) A cross-over protocol was used. Although the cross-over design was controversial because the effect could not be ‘washed out’, recruitment to this sham-controlled study would not be feasible if exposure to the active treatment was not possible for half the patients in a parallel study design. Because the benefit was seen early in the course of treatment in the study of Rodriguez et al.,\(^{[36]}\) it was unlikely that the benefit of TPE in the first treatment period would be detected after cross-over. Furthermore, it was suspected that cross-over would enhance the power of the study. Patients who failed on sham treatment in the first treatment phase but who succeeded on active treatment in the second treatment phase would be particularly informative.

If no carry-over effects occurred, cross-over would increase the power of the study. Patients would cross-over only if they did not experience moderate or greater benefit from TPE. Three outcomes were possible for each patient, as shown in Table 26.3. Each outcome was assigned an arbitrary Z-score.

The difference in the distribution of the Z-scores between the two treatment groups (i.e. ‘active exchange first’ and ‘sham exchange first’) was chosen as the primary outcome. The best outcome, from the point of view of TPE, would be a mean Z-score of +1.0 for the ‘active treatment first’ group and −1.0 for the ‘sham treatment first’ group. The magnitude and direction of the difference is a measure of the effectiveness of TPE. The statistical test applied was a one-sided rank-sum test as the hypothesis was that TPE was effective. Based on the outcome from the first (pre-cross-over) treatment phase, and setting \(\alpha=0.05\) and assuming 70% success with TPE and 20% success with sham, the power to detect treatment effect was 0.8 with the sample size of 22 patients.

Patients were followed over 6 months after treatment to determine if benefit was sustained and whether recurrent episodes of demyelinating disease occurred in the follow-up period. The study included patients between the ages of 18 and 60 who had had a recent (between 3 weeks and 3 months from onset) severe neurological deficit caused by an attack of MS or another inflammatory demyelinating disease of the CNS. Twelve patients with MS were included. Ten patients with other inflammatory demyelinating disease including transverse myelitis, acute disseminated encephalomyelitis, Devic’s neuromyelitis optica, recurrent myelitis, and localized cerebral inflammatory demyelination. The diagnosis of inflammatory demyelination was confirmed at brain biopsy when clinical criteria were insufficient to reach a confident clinical diagnosis of idiopathic demyelinating disease and when the syndrome was caused.
by a brain lesion. Clinical criteria alone were considered for spinal cord lesions, because biopsy of cord lesions was believed to carry greater risks of neurological deficit and because the small amount of tissue that would be obtained offered less diagnostic value for establishing a diagnosis of acute demyelination. Patients with infectious or other inflammatory diseases of the brain or spinal cord, such as vasculitis or sarcoidosis, were excluded. All patients had been treated with high-dose intravenous corticosteroids (typically methylprednisolone). They had not improved after a period of 2 weeks from the initiation of corticosteroid treatment.

Patients were randomly assigned to receive either true or sham plasma exchange, seven exchanges (54 ml/kg or 1.1 plasma volumes per exchange) every other day for 14 days. At the conclusion of 2 weeks, two neurologists, who were masked to the treatment assignment, decided if moderate to marked improvement occurred. Those patients who experienced less than moderate improvement crossed over to the opposite treatment. Neither patients nor physicians were advised of the order of treatment until the study was completed. All patients were followed for 6 months after treatment to assess the durability of the response and recurrent disease activity.

The results of the study are summarized in Fig. 26.1. Nine patients experienced moderate to marked improvement (significant impact on function) during treatment. Eight of nine were receiving the active treatment at the time of improvement. Of 19 courses of true plasma exchange that were administered, eight of 19 resulted in moderate to marked improvement (42% of courses of active treatment). In comparison, one of 17 (5.9%) courses of sham treatment resulted in moderate to marked improvement. Three patients who failed to respond in the first treatment phase experienced moderate or greater improvement in the second treatment phase. The predefined primary analysis was based on the differences in distribution of the Z-scores (see

---

### Table 26.3 Outcome measures in the Mayo Clinic plasma exchange study[3]

<table>
<thead>
<tr>
<th>First treatment</th>
<th>Cross-over</th>
<th>Second treatment</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>No</td>
<td>Success</td>
<td>+1.0</td>
</tr>
<tr>
<td>Failure</td>
<td>Yes</td>
<td>Failure</td>
<td>0.0</td>
</tr>
<tr>
<td>Failure</td>
<td>Yes</td>
<td>Success</td>
<td>−1.0</td>
</tr>
</tbody>
</table>
above) in the study. The analysis was based on strict ‘intention-to-treat’ principles. The frequency distribution of Z-scores (+1, −1, 0) (see Table 26.3) according to the evaluating neurologist who was most removed from monitoring the patients care was 5, 0, and 6 in the active treatment first group, and 1, 3, and 7 for the sham treatment first group. These results were significant (at $p=0.01$) according to neurologist B, who was most removed from frequent patient evaluation (predefined primary outcome). There was only a single instance of disagreement about outcome between the two blinded neurologists; neurologist A rated one patient who was receiving placebo as being moderately improved, whereas neurologist B rated that patient as being mildly improved. The $p$ value was significant at the $p=0.03$ level if the evaluation of neurologist A was considered. Even if the cross-over component to the study were not considered, the results (five of 11 patients improved on active treatment versus one of 11 patients on sham treatment), although not statistically significant, suggested efficacy of the active treatment. The trial was not powered for this consideration.

Favorable responses occurred early in the course of treatment. In only one instance in a patient who improved while on sham treatment, the benefit was not sustained. In all other responders who received active exchange, the benefit was sustained and improvement continued when treatment ended; however, the major improvement
occurred during the treatment phase during which active treatment was being administered.

Of the eight patients who improved on active treatment, four of eight had further attacks during the 6-month follow-up. In some cases, the subsequent attacks were severe. However, the remaining four patients have not had any further attacks, some of whom patients had been followed up to 3 years from TPE treatment. Prevention of subsequent attacks was not a primary or secondary planned outcome of the trial.

Side effects were relatively minor, primarily mild treatment-related hypotension and perioral paresthesias during the treatment, probably related to citrate toxicity. Anemia developed in most patients. In four patients, the anemia was severe (hemoglobin <8.0g/dl), although it produced no serious symptoms in any patient and resolved spontaneously within 1 month of completion of treatment. Roughly half of the patients required central intravenous lines in order to complete the treatments. There were no major complications of this procedure. Two patients developed heparin-associated thrombocytopenia during the course of this study.

There were no statistically significant differences in the baseline characteristics between the group of patients who responded and those who did not respond. However, patients who did respond tended as a group to be younger. Also, patients who responded tended to have somewhat less severe weakness, although all patients were severely weak in one or more limb. Patients who had flaccid areflexic weakness seem to be somewhat less likely to respond.

Compared with the trial by Weiner et al., patients in the Mayo Clinic study had more severe deficits of longer duration and had failed standard treatment with corticosteroids (Table 26.4). No adjunctive treatment was administered. A more robust outcome was required for success. This comparison indicates that a smaller study can be more informative than a larger study if the patients selected for study are unlikely to improve spontaneously and only a single treatment is investigated.

Table 26.4 Comparison of randomized controlled trials for acute attacks of demyelinating disease

<table>
<thead>
<tr>
<th>Weiner et al. [29]</th>
<th>Mayo Clinic Study [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>116</td>
</tr>
<tr>
<td>Attack severity</td>
<td>DSS&gt;1</td>
</tr>
<tr>
<td>Duration</td>
<td>5 days–8 weeks</td>
</tr>
<tr>
<td>Prior steroids</td>
<td>Not permitted</td>
</tr>
<tr>
<td>Design</td>
<td>Parallel, double-masked, sham-controlled</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Decrease in DSS by 1 or 2 points</td>
</tr>
<tr>
<td>Concomitant treatment</td>
<td>ACTH, cyclophosphamide</td>
</tr>
</tbody>
</table>
A retrospective analysis of all patients with acute, severe attacks of CNS demyelinating diseases treated with TPE at Mayo Clinic from 1984 to 2000 was recently reported using the same criteria for success as was used in the prospective clinical trial.[4] This study was done to identify clinical factors predictive of a favorable response to TPE, to examine the frequency of treatment success in a larger patient sample unconstrained by the inclusion and exclusion criteria of the randomized study, and to assess the safety of TPE in a mostly uncontrolled setting. Fifty-nine patients were treated (Fig. 26.2). Most had severe attacks of relapsing-remitting MS (22 patients), neuromyelitis optica (10 patients), or acute disseminated encephalomyelitis (10 patients). Moderate or marked improvement occurred in 44.1% of treated patients, which was very similar to the proportion improved in the randomized study. Improvement occurred in most disease subtypes, but was somewhat more common in neuromyelitis optica and Marburg-variant MS (see Fig. 26.2). Male sex, preserved reflexes, and early initiation of treatment (<20 days after onset) were identified as factors that predicted treatment success. Patients who responded successfully to treatment began to improve early after initiation of TPE despite failing on treatment with high-dose corticosteroids. Failure to observe an early response to TPE was associated with a diminishing likelihood of subsequent response. Seventyfive percent of those with moderate or marked improvement showed objective improvement within the first three exchanges (Fig. 26.3). Adverse events associated with TPE were few but included hypotension (17%), significant anemia (5%), and heparin-associated thrombocytopenia (3%). Central intravenous catheter access was necessary in 44% of the patients. However, complications related to the central line were uncommon.

Whether the use of TPE has any effect on the number of subsequent attacks of demyelinating disease is unknown. There was no suggestion of a reduction of subsequent attacks in the retrospective study. However, follow-up was not satisfactory to address a potential effect, and there was no appropriate control group. There did not, however, appear to be any significant increase in the number of attacks or rebound of disability following treatment.
**Fig. 26.2** Response rate of moderate or marked functional improvement of patients undergoing TPE for acute CNS demyelinating disease at Mayo Clinic (1984–2000) by disease subtype. Response is defined as moderate to marked (functionally important) recovery within 2 weeks of initiation of therapy. RR-MS, relapsing-remitting MS; ADEM, acute disseminated encephalomyelitis; ATM, acute transverse myelitis; NMO, neuromyelitis optica.

![Graph showing response rate of TPE](image)

**Fig. 26.3** Likelihood of treatment response according to whether any objective improvement was noted after each exchange procedure. If no improvement was noted after five exchanges, the chances of subsequent improvement was small.
MECHANISM OF ACTION OF TPE IN CNS DEMYELINATING DISEASES

The mechanism of action responsible for the effect of TPE in the treatment of acute, severe attacks of CNS demyelinating disease is unknown (as is the case for many disorders in which TPE is standard treatment). The search for the mechanism in CNS demyelinating diseases is complicated by a number of factors. First, the cause of and related serological changes associated with MS attacks are unknown. Second, pathological subtypes of MS appear to be heterogeneous. Third, atypical presentations of CNS idiopathic inflammatory demyelinating conditions, such as Devic’s neuromyelitis optica, acute disseminated encephalomyelitis, and Marburg-variant and tumefactive MS may be associated with different serological or pathological findings.

Although it is difficult to identify a single responsible mechanism of action of TPE, a number of considerations will help in the investigation of potential mechanisms. The effects of TPE on antibodies, especially those directed to myelin antigens, are of obvious interest. The characteristics and time course of patient response in acute demyelinating attacks also provide potential clues about the mechanism of effect.

The idiopathic inflammatory demyelinating diseases are pathologically heterogeneous. T-cell mediated autoimmunity has been the dominant model for demyelination in MS. The role of humoral mechanisms in CNS demyelination is becoming increasingly accepted. Immunoglobulin deposition and activation of complement have a prominent role in the pathology in one subgroup of MS patients. It remains to be seen whether this pathological subgroup is more likely to respond favorably to TPE. Terminal components of activated complement are also found in the pathology of neuromyelitis optica. TPE may be particularly effective for acute attacks of neuromyelitis optica. As noted above, although not significant, a trend towards higher response rates in those with Marburg-variant MS and neuromyelitis optica was observed.

Myelin-reactive antibodies, such as those against myelin basic protein and myelin oligodendrocyte glycoprotein, have been described in MS and in other neurological diseases. The presence of antibodies to myelin oligodendrocyte glycoprotein may be more common in severe forms of demyelinating diseases and may be predictive of response to TPE. Other possibilities, such as a reduction in proinflammatory cytokines or removal of conduction blocking substances such as QYNAD pentapeptide have not been investigated, but they offer possibilities for explaining the rapidity of action of TPE in these disorders. Ongoing studies in this area may help to identify the suspected mechanisms of action in TPE to determine better those patients who are most likely to respond to TPE.

SUMMARY

The role of TPE in the treatment of MS remains undefined. There is equivocal evidence from a meta-analysis for benefit of TPE as a supplement to immunosuppression for progressive forms of MS, but TPE has not been evaluated as a standalone therapy. It is a
cumbrous and expensive long-term treatment, which is a significant limitation; further investigation will have to evaluate its role relative to other agents that may also be of benefit in progressive forms of MS, such as interferon beta-1b\(^{[43]}\) and mitoxantrone.\(^{[44]}\)

TPE results in improvement in patients with acute, devastating attacks of demyelinating disease who fail to respond to high-dose corticosteroids as demonstrated in a double-masked, randomized, sham-controlled, cross-over study supported by the US National Institutes of Health. Based on this study, the American Society for Apheresis has reclassified TPE for acute, severe attacks of inflammatory demyelinating disease as a category II indication.\(^{[45]}\) An analysis of the subsequent experience at Mayo Clinic suggests that patients with a variety of demyelinating syndromes respond to this treatment, but patients with neuromyelitis optica may have a superior response. Significantly better response rates were found in men than in women, with early treatment (<20 days from onset of attack) than with later treatment, and in patients with preserved reflexes than in patients with flaccid areflexia.

Further studies are required to define better the patient groups most likely to respond, the optimum use of TPE, and its mechanism of action. Whether intravenous immunoglobulin will have efficacy similar to that of TPE for acute attacks of disability, as has been found with peripheral nervous system demyelinating disease, remains to be studied.

**ACKNOWLEDGMENTS**

This work was supported by grant support from the National Institutes of Health (Grant NS32774 and Grant RR00585 to the Mayo Clinic General Clinical Research Center). Ms Mary Bennett assisted with the manuscript preparation.

**REFERENCES**


Treatment of multiple sclerosis with methylprednisolone
Robert J Fox and R Philip Kinkel

INTRODUCTION

Treatment of multiple sclerosis (MS) with pulses of high-dose methylprednisolone (MP) has gained increased acceptance over the past two decades, supplanting adrenocorticotrophic hormone (ACTH) as the treatment of choice for MS relapses. More recent evidence suggests that high-dose MP not only hastens recovery from MS relapses but may modify the course of relapsing-remitting MS as well as secondary progressive MS. In this chapter the evidence supporting the high-dose use of MP for these indications will be reviewed. For a comprehensive review of MS clinical trials pertaining to the use of ACTH or preparations of corticosteroids other than MP, the reader is referred to Myers’s review.\[1\]

BACKGROUND

Pharmacology

MP is a synthetic glucocorticoid that differs from hydrocortisone (cortisol) by the addition of a double bond at the 1,2 position and a methyl group at the 6 position.\[2\] These structural differences increase the relative glucocorticoid effect, decrease the mineralocorticoid effect, and increase the duration of action (Table 27.1). The biologically active sterol is highly insoluble in aqueous solution and must be given as a sodium hemisuccinate ester when administered intravenously. Following intravenous administration, 10–15% of the ester is excreted unchanged in the urine and the rest is converted into MP and eventually into one of several metabolites.\[3\] At normal or low concentrations, 80–90% of corticosteroids are bound to corticosteroid-binding globulin, a protein with high affinity but low capacity for binding glucocorticostereoids. A smaller percentage of corticosteroids binds to albumin, which displays a higher binding capacity but lower binding affinity. At the high concentrations achieved with high-dose MP, the protein binding capacity in serum is exceeded and a greater proportion of serum corticosteroid exists in a free state. An increased proportion of unbound corticosteroids allows corticosteroids to enter cells and interact with specific receptors, and also allows effective penetration of the central nervous system (CNS), since the blood-brain barrier is
relatively impermeable to bound corticosteroids.\textsuperscript{[4]} Accordingly, peak cerebrospinal fluid (CSF) levels are delayed for over 6 hours following a 1500 mg bolus of high-dose MP, whereas peak plasma levels occur within 2 hours.\textsuperscript{[5]} Similarly, high CSF concentrations persist at a time when serum concentrations are much reduced.\textsuperscript{[6,7]}

In addition to intravenous formulations, oral preparations of MP as the parent sterol compound are available up to a maximum strength of 32 mg. While well absorbed, the relatively small size of the tablet formulation renders oral administration of high doses (500–2000 mg/day) impractical. As an alternative, for oral megadose administration, recent studies suggest that the intravenous solution may be taken orally; up to 1000 mg/day are well absorbed and well tolerated.\textsuperscript{[6]} Concerns regarding a potential increase in gastrointestinal side effects with oral high-dose MP appear to be unfounded, since oral administration does not increase gastrointestinal permeability or the incidence of endoscopically identified lesions in the gastric mucosa compared with intravenous administration.\textsuperscript{[8–10]} Further studies regarding the tolerability, efficacy, and pharmacokinetics of high-dose MP pulses administered orally are required before this route is established as an alternative to intravenous administration.

**Molecular biology and mechanism of action**

Unbound MP freely diffuses across plasma membranes and exerts its effects through interaction with both intracellular and membrane-associated glucocorticoid receptors. The glucocorticoid receptor consists of a DNA-binding domain, a steroid-binding domain, and an immunogenic domain.\textsuperscript{[11]} In the steroid-free state, the intracellular receptor exists as an oligomer complexed to immunophilins and heat-shock protein 90 (HSP), which facilitates its interaction with glucocorticoids.\textsuperscript{[12]} Binding of the sterol to the receptor complex causes dissociation from HSP and immunophilins and allows the steroid-receptor complex to translocate into the nucleus, where it binds in conjunction with other activating proteins to glucocorticoid responsive elements on the 5′-flanking region of various genes.\textsuperscript{[13–16]} This may lead to an enhancement of transcription in certain instances (i.e. glucose metabolism) or, in the case of many anti-inflammatory effects, inhibition of transcription. Corticosteroids also regulate RNA processing, RNA transport, RNA translation, and protein secretion.
Corticosteroids also act through a more immediate, non-genomic pathway, involving membrane glucocorticoid receptor interaction with protein kinase C, G proteins, and adenylyl cyclase, thereby inducing changes in calcium and potassium currents that lead to alterations in neuronal firing and cell activity. An important non-genomic effect on inflammation is mediated through direct interaction of the steroid-receptor complex with activator protein-1 (AP-1) complex molecules such as c-jun and c-fos. The AP-1 complex is activated by proinflammatory stimuli and alters the transcription of many genes involved in the inflammatory response. The steroid-receptor complex modulates expression of target genes through AP-1, which in turn inhibits transcription of proinflammatory growth factors and cytokines.

Corticosteroids have many biological effects of potential therapeutic benefit in MS. These effects include restoration of the blood-brain barrier, reduction of tissue edema, suppression of inflammation, and immunomodulation. Animal models of neural tissue injury have provided evidence in support of the efficacy of corticosteroids. Corticosteroids reduce cytokine expression in injured neural tissue in animal models of spinal cord injury. Furthermore, they regulate expression of adhesion molecules at the blood-brain barrier, and in so doing inhibit lymphocyte recruitment into injured tissue and reduce further injury. In a rat model of spinal cord injury, corticosteroids reduced the infiltration of microglia and macrophage cells by 66–82% over a 2-month period following injury. This reduced cellular infiltration was accompanied by a reduction in tissue loss, increased axons near and in the injury site, reduced Wallerian degeneration of axonal fibers, and, perhaps most importantly, increased sprouting of fibers near the lesion. Other potential mechanisms of corticosteroid-induced neural protection include a decrease in after-hyperpolarization, increased synthesis and release of neurotrophic factors and lipocortin feedback regulation of Ca(2+) currents, and induction of antioxidant enzymes. In very high doses, MP suppresses lipid peroxidation associated with progressive neuronal degeneration following spinal cord injury. Corticosteroids induce apoptosis in lymphocytes, which may help to curtail the inflammatory response. The mechanism by which apoptosis is induced is unknown, but it may involve interactions with AP-1, calmodulin, β-galactoside-binding protein, and NFκB and IκBα. Many studies of blood and CSF from MS patients treated with corticosteroids support these potential mechanisms of action (Table 27.2).

All of these effects are complex, inter-related, and dose-dependent in ways that are only partly understood. No particular biological activity of the corticosteroids has been causally linked to the clinical benefits observed in MS patients, in part owing to the pleiotropic effects of corticosteroids on cell function and survival.

**CLINICAL TRIALS OF HIGH-DOSE MP IN RELAPSING MS**

The use of corticosteroids as treatment for MS was first reported in 1951. Seven subsequent clinical trials between 1954 and 1979 failed to show a convincing benefit of low to intermediate doses of daily or alternate-day oral corticosteroids, as reviewed by Myers. Although the design of these studies would be considered suboptimal compared with current standards, a consensus developed that chronic corticosteroid administration
in low doses does not prevent disease progression. In 1970, an influential clinical trial provided convincing clinical evidence that ACTH improves recovery from MS.

Table 27.2 Corticosteroids: potential mechanisms of action in MS

<table>
<thead>
<tr>
<th>Effects on cellular immune system function and inflammation</th>
</tr>
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<tbody>
<tr>
<td>Redistribution of T cells with transient alterations in T cell counts (CD4&gt;CD8)(^{[57,88,89]})</td>
</tr>
<tr>
<td>Decreased T cell responses to antigen and mitogen(^{[33]})</td>
</tr>
<tr>
<td>Decreased synthesis and release of pro-inflammatory cytokines and growth factors (IL-1, IL-2, IL-6, IFN-(\gamma), IFN-(\alpha), IL-8, TNF-(\alpha))(^{[90–93]})</td>
</tr>
<tr>
<td>Decrease in constitutive HLA-DR expression(^{[88,94,95]})</td>
</tr>
<tr>
<td>Upregulation of TGF-(\beta) and IL-10 expression(^{[90,92,96,97]})</td>
</tr>
<tr>
<td>Increased numbers of monocytes, neutrophils, and T and B lymphocytes(^{[93]})</td>
</tr>
<tr>
<td>Increased leukocyte apoptosis (predominantly CD4 cells)(^{[98]})</td>
</tr>
<tr>
<td>Inhibition of IFN-gamma-induced upregulation of class II expression by macrophages and microglia(^{[99]})</td>
</tr>
<tr>
<td>Decreased eicosanoid production by monocytes(^{[100]})</td>
</tr>
<tr>
<td>Decreased Fc receptor expression by macrophages(^{[101]})</td>
</tr>
<tr>
<td>Decreased immunoglobulin levels 2–4 weeks after treatment(^{[102]})</td>
</tr>
<tr>
<td>Increased synthesis of lipocortin 1 and reduced transcription of cyclooxygenase II gene(^{[103,104]})</td>
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</table>

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<tr>
<th>Effects on endothelial cell function and permeability</th>
</tr>
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<tbody>
<tr>
<td>Decreased peripheral blood mononuclear cell adhesion to endothelium(^{[105]})</td>
</tr>
<tr>
<td>Downregulation of expression of cell adhesion molecules (ELAM-1, ICAM-1, VLA-4, VCAM-1, LFA-1)(^{[106,107]})</td>
</tr>
<tr>
<td>Increase in CD11a, CD18, and sVCAM(^{[105]})</td>
</tr>
<tr>
<td>Reduced activity of matrix metalloproteinase (gelatinase B) and increased activity of tissue inhibitors of metalloproteinases in CSF(^{[108]})</td>
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<tr>
<th>Effects on cerebrospinal fluid immune compartment</th>
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</thead>
<tbody>
<tr>
<td>Transient, dose-dependent decrease in cell count (CD3, CD4, CD8)(^{[109,110]})</td>
</tr>
<tr>
<td>Transient, dose-dependent decrease in IgG and IgM synthesis(^{[33,40,109,111–115]})</td>
</tr>
<tr>
<td>Decreased myelin basic protein and antibodies against myelin basic protein(^{[113,115,116]})</td>
</tr>
<tr>
<td>Decreased soluble adhesion molecule sICAM(^{[117,118]})</td>
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<tr>
<td>Decreased TNF-(\alpha)(^{[119]})</td>
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<tr>
<td>Decreased nitric oxide metabolism (nitrite and nitrate)(^{[120]})</td>
</tr>
<tr>
<td>Decrease in the lipid peroxidation marker malondialdehyde(^{[121]})</td>
</tr>
<tr>
<td>Increase in TGF-(\beta)1 and soluble TNF-(\alpha) receptor Rp55(^{[115,117]})</td>
</tr>
</tbody>
</table>

IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TGF, transforming growth-factor; ELAM, endothelial leukocyte adhesion molecule; ICAM, intercellular adhesion molecule; VLA, very late activation; VCAM, vascular cell adhesion molecule; LFA, leukocyte function antigen; sICAM, soluble ICAM; sVCAM, serum VCAM.
relapses.\[^{[25]}\] Despite the 2-week course of administration and side effects, ACTH became widely used for treating MS relapses.

During the 1970s, high-dose MP pulses were reported to be beneficial in acute allograft rejection,\[^{[26]}\] and shortly thereafter therapeutic benefits of pulsed high-dose MP were reported in lupus nephritis,\[^{[27]}\] Goodpasture’s syndrome,\[^{[28]}\] crescentic glomerulonephritis,\[^{[29]}\] polyarteritis nodosa,\[^{[30]}\] and rheumatoid arthritis.\[^{[31]}\] These reports were followed by several uncontrolled, short, open trials of intravenous high-dose MP for MS relapses. Rapid improvement was reported in the majority of patients, with few adverse effects.\[^{[32–36]}\]

### High-dose MP for MS relapses

After ACTH became the standard of treatment for MS relapses, there followed a series of three randomized trials (Table 27.3) to assess the relative benefit of intravenous high-dose MP versus ACTH.\[^{[37–39]}\] In these trials, a small number of patients were treated with a single course of high-dose MP or ACTH and followed for a brief period of time. The studies lacked statistical power to detect small but significant differences between treatments, and the trial durations were too short to assess the effects on long-term disease course. The most influential of these trials was a randomized, placebo-controlled, double-blind comparison of intravenous high-dose MP for 3 days versus intramuscular ACTH for 14 days.\[^{[39]}\] Both treatment groups improved significantly but there were no significant differences between the groups at 3, 7, 14, 28, and 90 days after treatment. The investigators concluded that intravenous high-dose MP was an effective alternative to ACTH, required shorter treatment durations, and was better tolerated. This led many clinicians to abandon ACTH treatment for

#### Table 27.3 Clinical trials of high-dose MP versus ACTH for MS relapses

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment regimens</th>
<th>n</th>
<th>Study design</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Abbruzzese et al.[^{[37]}]</td>
<td>Intravenous MP 20 mg/kg per day for 3 days, 10 mg/kg per day for 4 days, 5 mg/kg per day for 3 days, 1 mg/kg per day for 5 days</td>
<td>30</td>
<td>Open, randomized</td>
<td>No difference at any time point between treatments</td>
</tr>
<tr>
<td>Barnes et al.[^{[38]}]</td>
<td>Intravenous ACTH 0.5 twice daily for 15 days</td>
<td>30</td>
<td></td>
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<tr>
<td></td>
<td>Intravenous MP 1000 mg/day for 7 days</td>
<td>14</td>
<td>Single-blind, randomized</td>
<td>MP better at 3, 7, and 28 days but not 3 months after treatment</td>
</tr>
<tr>
<td></td>
<td>Intramuscular ACTH 60 U/day for 7 days, 40 U/day for 7 days, 20 U/day for 7 days</td>
<td>11</td>
<td></td>
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</tr>
<tr>
<td>Thompson et al.[^{[39]}]</td>
<td>Intravenous MP 1000 mg/day for 3 days</td>
<td>29</td>
<td>Double-blind,</td>
<td>No difference at 3, 7, 14, 28, and</td>
</tr>
</tbody>
</table>
Intramuscular ACTH 40 U twice daily for 7 days, 20 U twice daily for 4 days, 20 U/day for 3 days.

Clinical relapses in favor of intravenous high-dose MP.

Ongoing questions about the clinical efficacy of high-dose MP led to three randomized, double-blind, placebo-controlled trials of intravenous or oral high-dose MP for relapses in MS (Table 27.4). These studies randomized a small number of patients and were of short duration (2–8 weeks), all three studies found a significant benefit of high-dose MP compared with placebo. Interestingly, in the studies by Durelli et al. and Milligan et al., patients who entered into the trial up to 8 weeks after the onset of their relapse still experienced a significant impact on their clinical recovery when compared with placebo. A meta-analysis and a Cochrane review found convincing evidence to support the use of high-dose MP to treat acute relapses.

Several randomized studies of corticosteroids have focused on the relative benefit of different preparations, doses, and routes of administration (Table 27.5). In a randomized, placebo-controlled trial by Alam et al., oral versus intravenous high-dose MP were compared. Mean change in disability status score (DSS) between the two groups were compared 28 days after the start of treatment. There were neither significant differences in clinical outcome nor increased gastrointestinal side effects in the patients who received oral high-dose MP. Barnes et al. reported a double-blind, placebo-controlled, randomized trial comparing intravenous high-dose MP for 3 days with low-dose oral MP for 3 weeks. The authors found no significant difference in median change in expanded disability status score (EDSS) at 1, 4, 12, and 24 weeks after treatment. In a study by Oliveri et al., low doses (500 mg/day for 5 days) and high doses (2000 mg/day for 5 days) of intravenous MP were compared in a double-blind, randomized fashion. All patients improved their EDSS, but

<table>
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<th>Study</th>
<th>Treatment regimen</th>
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<th>Study design</th>
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<tbody>
<tr>
<td>Durelli et al.</td>
<td>Intravenous MP 15</td>
<td>12</td>
<td>Double-blind,</td>
<td>MP better than placebo at the end of</td>
</tr>
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<td></td>
<td>mg/kg per day</td>
<td></td>
<td>randomized</td>
<td>treatment. No further follow-up</td>
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<td></td>
<td>for 3 days, 10</td>
<td></td>
<td></td>
<td>comparison</td>
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<td></td>
<td>mg/kg per day</td>
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<td>for 3 days, 5</td>
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<td>mg/kg per day</td>
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<td>for 3 days, 2.5</td>
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<td></td>
<td>mg/kg per day</td>
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<td>for 3 days, 1</td>
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<td></td>
<td>mg/kg per day</td>
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<td></td>
<td>for 3 days</td>
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<tr>
<td>Placebo</td>
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<td>8</td>
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<tr>
<td>Milligan et al.</td>
<td>Intravenous MP 500</td>
<td>13</td>
<td>Double-blind,</td>
<td>MP better than placebo at 1 and 4</td>
</tr>
<tr>
<td></td>
<td>mg/day for 5 days</td>
<td></td>
<td>randomized</td>
<td>weeks after treatment</td>
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<tr>
<td>Placebo</td>
<td></td>
<td>9</td>
<td></td>
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<tr>
<td>Sellebjerg et al.</td>
<td>Oral MP 500 mg/</td>
<td>26</td>
<td>Double-blind,</td>
<td>More MP treated patients improved</td>
</tr>
<tr>
<td></td>
<td>day for 5 days</td>
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there was no group difference in mean EDSS between the two doses of intravenous MP.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment regimens</th>
<th>n</th>
<th>Study design</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Bindoff et al.</td>
<td>Intravenous MP 1000 mg/day for 1 days</td>
<td>17</td>
<td>Unblinded, randomized</td>
<td>Improved EDSS in the 5-day-treated group</td>
</tr>
<tr>
<td></td>
<td>Intravenous MP 1000 mg/day for 5 days</td>
<td>15</td>
<td></td>
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<tr>
<td>Alam et al.</td>
<td>Intravenous MP 500 mg/day for 5 days</td>
<td>20</td>
<td>Double-blind, randomized</td>
<td>No difference at 5 and 28 days after treatment. Side effects minor and equally distributed</td>
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<tr>
<td></td>
<td>Oral MP 500 mg/day for 5 days</td>
<td>15</td>
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<tr>
<td>La Mantia et al.</td>
<td>Intravenous MP 1000 mg/day for 3 days, 500 mg/day for 3 days, 250 mg/day for 3 days, 125 mg/day for 3 days, 62.5 mg/day for 2 days</td>
<td>10</td>
<td>Double-blind, randomized</td>
<td>High rate of worsening in low-dose MP group during the month after treatment. Note: groups were of unequal disease duration</td>
</tr>
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<td></td>
<td>Intravenous MP 40 mg/day for 7 days, 20 mg/day for 4 days, 10 mg/day for 3 days</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous dexamethasone 8 mg/day for 7 days, 4 mg/day for 4 days, 2 mg/day for 3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnes et al.</td>
<td>Intravenous MP 1000 mg/day for 3 days</td>
<td>38</td>
<td>Double-blind, randomized</td>
<td>No significant difference in median EDSS change at 1, 4, 12, and 24 weeks after treatment</td>
</tr>
<tr>
<td></td>
<td>Oral MP 48 mg/day for 7 days, 24 mg/day for 7 days, 12 mg/day for 7 days</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliveri et al.</td>
<td>Intravenous MP 2000 mg/day for 5 days</td>
<td>15</td>
<td>Double-blind, randomized</td>
<td>No significant difference in mean EDSS score at 7, 15, 30, and 60 days. Lower MRI activity in high-dose group</td>
</tr>
<tr>
<td></td>
<td>Intravenous MP 500 mg/day for 5 days</td>
<td>14</td>
<td>with MRI</td>
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</table>
These three studies are limited by their reliance on group mean changes in EDSS, thus reducing the power to detect a significant difference in treatments. More importantly, EDSS is a nominal scale, with unequal differences between each step, rendering mean changes in EDSS statistically inappropriate in measuring differences between groups. The study by Oliveri et al. found significant differences in magnetic resonance imaging (MRI) activity between the two doses of intravenous MP (see below), despite no evidence of clinical difference. These MRI findings highlight the insensitivity of mean EDSS measures in clinical studies. The duration of high-dose MP therapy required to produce clinical benefits was assessed in a trial comparing a single injection of 1000 mg MP versus a 5-day course of therapy. The superior results of a 5-day course of therapy in this trial suggest that a 3–5-day course of high-dose MP may be necessary to treat MS relapses effectively.

**High-dose MP for relapsing MS disease course**

The benefits of corticosteroid treatment on subsequent disease activity have only recently been addressed by clinical trials. The largest and perhaps most influential of these trials was the Optic Neuritis Treatment Trial (ONTT). A total of 457 patients with acute monocular optic neuritis of less than 8 days’ duration (mean 5 days) were randomized to treatment with oral prednisone (1 mg/kg per day for 14 days), intravenous high-dose MP (250 mg four times/day for 3 days followed by oral prednisone 1 mg/kg per day for 11 days), or oral placebo. The two groups receiving oral treatment alone were masked to treatment, but patients receiving high-dose MP were not. Baseline characteristics, including the severity of baseline MRI abnormalities, were well matched in all three groups. In a series of publications based on pre-planned analyses, the investigators systematically reported the effects of treatment on the speed of recovery, the extent of recovery, and the subsequent disease course. Compared with placebo, intravenous high-dose MP resulted in more rapid recovery of vision, most evident during the first 2 weeks. The extent of improvement in visual field deficits, contrast sensitivity, and color vision were significantly better in the high-dose MP group at 6 months but not at 12 months, indicating little difference in final visual outcome. The intravenous high-dose MP group had a rate of recurrent optic neuritis in either eye over the subsequent 2 years of 14%, compared with 16% in the placebo group and 30% in the oral prednisone group. This surprising result suggested that oral prednisone is associated with an increased rate of recurrent optic neuritis.

In subsequent reports from the ONTT, the rate of conversion to clinically definite MS was evaluated in a cohort of 389 patients without definite or probable MS at study onset. The intravenous high-dose MP group had a lower rate of conversion to clinically definite MS (7.5%) during the subsequent 2 years compared with the placebo group (16.7%) or the oral prednisone group (14.7%). As might be expected, most of this benefit occurred in patients with abnormal MRI scans at study entry, since this group of patients was at highest risk of a recurrent demyelinating event. Among those patients with grade 3 or 4 MRI scans (i.e. two or more typical white matter lesions), clinically definite MS developed in 35.9% of the placebo patients, 32.4% of the prednisone patients, and 16.2% of intravenous high-dose MP patients. This benefit on conversion to clinically definite MS was no longer evident 3–5 years after treatment.
One major question is whether the results of the ONTT also apply to patients with established relapsing-remitting MS. Several lines of evidence indicate that patients with a single clinical demyelinating episode and typical MRI lesions of MS probably already have MS but that their MS lesions have not involved eloquent areas of the CNS. In fact, new criteria for MS allow for a formal diagnosis of MS if a follow-up MRI shows new lesions despite no further clinical episodes. Since the ONTT did not perform on-study MRI scans to study the effect of a single treatment on subsequent MRI activity, we are limited to only the clinical data from this trial.

Several small prospective studies offer further evidence in support of the prolonged benefits of a single course of high-dose MP. In the trial by Sellebjerg et al., 1-year follow-up evaluations found that the patients treated with high-dose MP had a higher median improvement in EDSS and were more likely to maintain an improved EDSS compared with the placebo patients, \( p=0.04 \) and \( p=0.03 \), respectively. La Mantia et al. reported a randomized, double-blind comparison of intravenous dexamethasone versus intravenous MP in equivalent low dose versus intravenous high-dose MP. Intravenous administration was used to simplify the blinding procedure, but the lower dose preparations could have been administered orally. The authors reported a high rate of symptomatic worsening in the low-dose MP group during the first month after treatment with fewer low-dose MP patients achieving a 1.0 or more step improvement in EDSS. Furthermore, there was a lower relapse rate in the high-dose MP group than in the low-dose MP group during the year after treatment: 66% of the high-dose MP group were relapse-free, while only 13% of the low-dose MP group were relapse-free. There was a trend \( p=0.08 \) of lower relapses rate in the high-dose MP group compared with the dexamethasone group.

Accumulating evidence suggests that high-dose MP administered in pulses may have more profound biological effects favorable to the course of MS with fewer adverse reactions. Zivadinov et al. studied 88 patients, who were randomly assigned to received either regular pulses of intravenous MP (1000 mg/day for 5 days with an oral prednisone taper), or intravenous MP in the same fashion, but administered only for relapses. Pulsed intravenous MP was given every 4 months for 3 years, then every 6 months for the subsequent 2 years. No patients were treated with long-term immunomodulating therapies other than corticosteroids. They found that the onset of sustained EDSS worsening was significantly delayed in the pulsed intravenous MP group compared with the relapse-only intravenous MP group \( p<0.0001 \), but there was no significant dose-dependent effect on relapse rates between the two groups. Both patients and examining neurologists were unblinded regarding treatment assignments, so clinical assessments should be interpreted with caution. However, the beneficial effects of pulsed therapy with intravenous MP on MRI measures of disease (described below) suggest a potential neuroprotective effect of therapy as an explanation for the lessened development of disability after 5 years.

**High-dose MP for secondary progressive MS**

A significant proportion of patients with relapsing-remitting MS eventually experience gradual progression of disability occurring between attacks or in the absence of attacks—the secondary progressive stage of MS. Until recently, it has been unclear whether...
chronic corticosteroid administration alters the disease course in secondary progressive MS. Two studies published in the last few years have addressed this issue (Table 27.6).

In a short study, a single course of high-dose MP was studied in a double-blind, placebo-controlled trial of 35 patients with a primarily chronic progressive form of MS.[60] High-dose MP was found to improve EDSS better than placebo, with improvements primarily in pyramidal, cerebellar, and sensory systems. The improvement was evident after 10 days, and persisted through the end of the study, which lasted for 3 months.

Goodkin et al. conducted a double-blind, dose-comparison study of bimonthly MP ‘pulses’ in patients with early secondary progressive MS.[61] A total of 109 patients with secondary progressive MS were randomized to pulses of intravenous high-dose MP (500 mg/day for 3 days followed by oral MP taper starting at 64 mg/day) or intravenous low-dose MP (10 mg/day for 3 days followed by oral MP starting at 10 mg/day) every 8 weeks for 2 years. The low-dose regimen was used to improve the success of blinding, since it was anticipated that high-dose MP pulses would produce side effects that would unmask the patients.

The primary outcome measure was the proportion of sustained treatment failures in each treatment arm at the end of the 2-year study. Confirmed treatment failure was identified using criteria from a composite outcome involving EDSS, ambulatory index, nine-hole peg test, box and block test, and relapses. Treatment failure was defined as sustained (5 months or longer) worsening on any component of the composite outcome measure or three relapses over a 12-month period. Survival analysis using Kaplan-Meier curves to estimate treatment failure rates over the course of the study was a pre-planned secondary analysis. Of the 108 patients who initiated therapy, 29 of 54 (53.7%) patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment regimens</th>
<th>n</th>
<th>Study design</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzato et al.</td>
<td>Intravenous MP 1000 mg/day for 5 days, prednisone taper for 5 days Placebo</td>
<td>35Cazzato et al.[60]</td>
<td>Double-blind, randomized cross-over</td>
<td>EDSS improved in MP-treated patients more than placebo</td>
</tr>
<tr>
<td>Goodkin et al.</td>
<td>Intravenous high dose MP 500 mg/day for 3 days, oral MP taper for 11 days starting at 64 mg/day Intravenous low dose MP: 10 mg/day for 3 days, oral MP taper for 11 days starting at 10 mg/day</td>
<td>54Goodkin et al.[61]</td>
<td>Double-blind, randomized</td>
<td>No difference in proportion of patients with progression (primary outcome), but high-dose better than low-dose in analysis of time to disease progression (secondary outcome)</td>
</tr>
</tbody>
</table>
receiving low-dose MP and 21 of 54 (38.9%) patients receiving high-dose MP met the criteria for sustained treatment failure, a 28% reduction in the proportion of treatment failures ($p=0.18$). The pre-planned secondary analysis, a log rank comparison of survival curves by treatment group, showed significant differences between groups in estimates of overall sustained treatment failure ($p=0.04$) (Fig. 27.1).

Methodological differences probably account for the slight differences in statistical significance using the primary and secondary outcome results.

![Graph showing Kaplan-Meier analysis of treatment failure rates in bimonthly high-dose MP study. Reprinted with permission from Goodkin et al.][61]

The primary outcome analysis (the proportion of treatment failures in either arm), utilizes only the entry and exit examination data, while the secondary outcome analysis using survival techniques takes into account the distribution of time when treatment failures occurred, as well as available data on patients who dropped out of the study before 2 years. Although the difference in the proportion of treatment failures at 24 months was not statistically significant, the distribution of sustained treatment failures throughout the 24-month course of the study significantly favored the high-dose MP group. There was a disparity in the number of males in the two groups (52% of the high-dose group was male, but only 28% of low-dose group). However, Cox regression analysis did not find an interactive effect of sex.
EFFECTS OF HIGH-DOSE MP ON DISEASE ACTIVITY MEASURED BY COMPUTED TOMOGRAPHY SCANNING AND MRI

Shortly after development of computed tomography (CT) imaging, it became clear that corticosteroids produce a rapid, dose-dependent reduction in contrast enhancement in MS. This effect is evident within 8 hours, presumably represents an effect on the blood-brain barrier, and is associated with rapid clinical improvement. Resolution of contrast enhancement raised the possibility that the rapid benefits of corticosteroids therapy could be attributable to abrupt resolution of edema, followed later by reduction of inflammation. Consistent with this interpretation, intravenous mannitol was found to reduce edema rapidly but improvement in MS symptoms was only transient. In contrast, corticosteroids reduced CT contrast enhancement and clinical symptoms for up to 4 months.

Studies over the past decade found that high-dose MP produces a rapid reduction in gadolinium enhancement on MRI. In early studies focused on the periods immediately before and after high-dose MP treatment, there was an 84–96% reduction in gadolinium-enhancement within 1–4 days after treatment. Other studies found that this effect correlated with clinical improvement. Monthly gadolinium-enhanced MRI scans following high-dose MP treatment for acute relapses demonstrated that many lesions re-enhanced within days and that new lesions frequently appear within 1 month despite continued clinical improvement. In an uncontrolled study, the effect of high-dose MP on gadolinium enhancement persisted for an average of 9.7 weeks, but other studies reported that high-dose MP does not prevent acute lesions from progressing into permanent lesions, and does not reduce the overall lesion burden.

The above studies suggested that high-dose MP has only transient effects on gadolinium enhancement and inflammation. However, this interpretation may be incorrect. First, the studies did not include sufficient serial observation of MRI lesion activity before treatment with high-dose MP to determine the effect of treatment on subsequent MRI activity. Second, the studies did not include randomized, placebo, or dose-response control groups for comparison.

Several studies in the past decade address these methodological concerns. A study by Smith et al. followed nine patients with relapsing-remitting MS using monthly gadolinium-enhanced MRI scans in a natural history study. The investigators found an increased total number of enhancing lesions, increased new enhancing lesions, and increased total area of enhancement in the month that preceded clinical worsening. High-dose MP treatment for clinical worsening resulted in a 33% reduction in new lesions over the subsequent 6 months. A second study by Oliveri et al. was a double-blind, randomized comparison of two doses of intravenous MP (500 mg for 5 days versus 2000 mg for 5 days) using gadolinium-enhanced MRI obtained at baseline and at 7, 15, 30, and 60 days after the beginning of treatment as the main outcome measure. Both doses of intravenous MP resulted in early dramatic reduction in the number of enhancing lesions followed by a rebound of enhancing lesions at day 15. However, there was a significant dose-dependent reduction in the total number of enhancing lesions over the course of the study, and this difference was evident at each time point from day 15 to day 60. These
two studies suggest that high-dose MP has an impact on subsequent MRI disease activity, and that this impact is dose-dependent.

The study by Zivadinov et al. [58] (see above) was the first to provide information on the long-term effects of repeated intravenous MP pulses on MRI measures of the disease in relapsing-remitting MS. They found that patients treated with routine high-dose MP had no progression of brain atrophy, while the control group (which received high-dose MP only for relapses) had significant progression of atrophy. Although the increase in T2 lesion volume was not affected by routine high-dose MP, the increase in T1 lesion volume was significantly reduced in the routine high-dose MP group. Changes in MRI measures (T1 and T2 lesion volume change, brain atrophy change) showed significant correlation with change in EDSS. Of further interest, the total amount of high-dose MP received by each patient was inversely correlated with the amount of brain atrophy in the routine high-dose MP group: the more high-dose MP received, the less brain atrophy was observed. This was the first study to provide MRI evidence that routine use of high-dose MP can slow the progression of brain atrophy as a result of neuroprotective effects, which may be independent of the effect of treatment on inflammatory activity (at least as measured by relapses and T2 lesion activity).

Further support for a neuroprotective effect of high-dose MP therapy comes from studies assessing tissue integrity utilizing magnetization transfer ratio (MTR) analysis. Architectural disruption from inflammation and axonal loss reduces the bound proton fraction, and thereby reduces the MTR as measured by MRI. Measurements of MTR can reflect the general tissue integrity, and such measurements have been used in MS studies to assess recovery of lesions as well as impact of the disease on normal-appearing white matter. Seventy-six contrast-enhancing lesions were studied in a group of MS patients receiving high-dose MP (1000 mg/day for 5 days) and compared with 109 untreated lesions. [72] Recovery of MTR was greater in the high-dose MP-treated lesions than in the untreated lesions, suggesting that high-dose MP reduces tissue damage and promotes lesion recovery.

The above studies suggest a rationale for pulsed high-dose MP treatment as a form of disease-modifying therapy in selected cases of relapsing-remitting MS. It remains unclear whether pulse high-dose MP will provide synergistic benefits when combined with currently available disease-modifying therapy. One recent study suggests that high-dose MP may have additive benefit when combined with interferon therapy. In a 1-year crossover design utilizing monthly MRI scans as an outcome measure, 68 patients with relapsing-remitting MS were followed for 6 months before therapy and then for 6 months after starting interferon beta-1a. [73] Relapses were treated with high-dose MP (1000 mg/day for 6 days). When high-dose MP was administered during the 6-month baseline period, there was a brief decline in gadolinium-enhancing lesions during the first month after intravenous MP treatment, but then an increase in the second and third months. When high-dose MP was given during interferon treatment, there was a similar decline in gadolinium-enhancing lesions during the first month after intravenous MP, but this decline persisted over the next 2 months. In summary, this study [73] and the study by Zivadinov et al. [58] suggests a rationale for further studies to investigate combination therapy with pulsed high-dose MP and interferon therapy as disease-modifying therapy for relapsing forms of MS.
Side effects of intravenous high-dose MP are listed in Table 27.7. Corticosteroid toxicity is theoretically related to the daily dose, the cumulative dose, and the frequency of administration. In general, corticosteroid toxicity is reduced with short-term ‘pulsed’ administration of high-dose MP (1000 mg/day for 3–5 days).\cite{74-77} Osteoporosis, aseptic osteonecrosis, cushingoid features, infections, and suppression of the hypothalamus-pituitary axis are rare with 3–5-day pulses of high-dose MP. The function of the hypothalamus-pituitary-adrenal axis was studied in 10 MS patients during and after therapy with intravenous MP 1000 mg/day for 7 days, followed by abrupt cessation of therapy.\cite{76} ACTH response was normal, and cortisol response was suppressed only on the first day after ending therapy but recovered 2 days later.

Most of the common side effects are treatable or can be avoided with proper education. One of the most common side effects is a feeling of well-being or mild euphoria, which is usually welcomed by the patient and does not require treatment. Moderate to severe anxiety, especially in patients who are newly diagnosed with MS, is common and should be treated with reassurance and short-acting anxiolytic medication, if needed. Manic episodes or psychosis are rare and may be avoided in future treatment courses by pre-medication with antipsychotics or lithium carbonate.

### Table 27.7 Side effects associated with high-dose MP treatment

<table>
<thead>
<tr>
<th>Side effects occurring during therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia and mild euphoria</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Metallic taste during infusion</td>
</tr>
<tr>
<td>Increased appetite and weight gain</td>
</tr>
<tr>
<td>Flushing and increased sweating</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Easy bruising</td>
</tr>
<tr>
<td>Mania and/or psychosis*</td>
</tr>
<tr>
<td>Nausea or vomiting*</td>
</tr>
<tr>
<td>Intractable hiccups*</td>
</tr>
<tr>
<td>Pancreatitis*</td>
</tr>
<tr>
<td>Cardiac arrhythmias*</td>
</tr>
<tr>
<td>Glaucoma*</td>
</tr>
<tr>
<td>Gastrointestinal upset or pain*</td>
</tr>
<tr>
<td>Side effects occurring early in patients with underlying risk factors</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Side effects occurring with repeated use†</td>
</tr>
</tbody>
</table>
Depression is uncommon, but occurs more frequently than psychosis. This can be avoided with judicial coadministration of antidepressants in high-risk patients or patients with a history of depression during corticosteroid therapy. Insomnia is frequent, and many patients benefit from a short-acting sedative-hypnotic. Most other acute side effects require only education, symptomatic treatment if they occur, and dietary modifications for increased appetite. Anaphylactoid reactions are very rare but patients should receive their first treatment dose under medical supervision. Subsequent doses can be safely administered in the patient’s home unless there is a medical contraindication (e.g. cardiac condition, diabetes mellitus).

Side effects associated with repeated pulses of high-dose MP were assessed in the study by Goodkin et al. Adverse effects were significantly more frequent in the high-dose MP group than in the low-dose MP group ($\chi^2 p=0.009$). Nevertheless, cessation of study drug because of side effects occurred in only one patient. Dose-dependent side effects attributable to high-dose MP included weight gain (31.5% on high-dose MP; 13% on low-dose MP), insomnia (35.2% on high-dose MP; 5.6% on low-dose MP), depression (26% on high-dose MP; 5.6% on low-dose MP), infections (38.9% on high-dose MP; 20.4% on low-dose MP), and headache (26% on high-dose MP; 13% on low-dose MP). Most of the infections were of the lower urinary tract. Serious adverse effects were rare (Table 27.8). One high-dose MP recipient known to have dysphagia before treatment was initiated died of aspiration pneumonia. The pneumonia was not treated, at the request of the patient and family. One patient required cessation of high-dose MP after developing of psychosis.

The relative risk of osteoporosis in MS

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Relationship to treatment</th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses (n=3)</td>
<td>Unrelated</td>
<td>Low dose (n=2),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High (n=1)</td>
</tr>
<tr>
<td>Death: aspiration pneumonia* (n=1)</td>
<td>Unrelated</td>
<td>Low dose</td>
</tr>
<tr>
<td>Death: hepatic necrosis secondary to intravenous drug abuse (n=1)</td>
<td>Unrelated</td>
<td>High dose</td>
</tr>
</tbody>
</table>

Table 27.8 Serious adverse events in bimonthly high-dose MP study
<table>
<thead>
<tr>
<th>Cancers: cervical (n=1), prostate (n=1)</th>
<th>Unrelated</th>
<th>High dose (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis (n=1)</td>
<td>Drug-related</td>
<td>High dose</td>
</tr>
<tr>
<td>Compression fracture(^1) (n=1)</td>
<td>Drug-related</td>
<td>High dose</td>
</tr>
<tr>
<td>Aseptic meningitis (n=1)</td>
<td>Unlikely</td>
<td>High dose</td>
</tr>
</tbody>
</table>

*Patient and family elected not to treat this adverse event
\(^1\)No neurological sequelae
Data from Goodkin et al.[61]

patients treated with repeated pulses of high-dose MP compared with chronic daily or alternate-day corticosteroids is unknown. This is relevant since bone mineral density is decreased and the incidence of fractures is increased in MS patients.[80] Although only one patient experienced a fracture in the study by Goodkin et al., patients were not monitored for osteoporosis.[61] One recent study found no relationship between single or repeated pulses of high-dose MP and bone mineral density of the lumbar spine or femoral head in MS patients.[61] In fact, bone mineral density of the lumbar spine increased 6 months after a pulse of high-dose MP, presumably owing to improved mobility with treatment. This finding is consistent with a reported association between low bone mineral density and decreased mobility.[80] It is possible that improved mobility with pulses of high-dose MP, especially in premenopausal women with MS, may offset declines in bone mineral density related to corticosteroid use.

Although additional studies are needed, recommendations for preventing corticosteroid induced osteoporosis can be made at this time based on guidelines developed by the American College of Rheumatology.[82] Patients starting ‘pulsed’ therapy with high-dose MP should have measurements made of bone mineral density in the lumbar spine and femoral heads. Initial treatment should include regular exercise, calcium 1000–1500mg/day, and Vitamin D 400–800 IU/day supplements. Alendronate sodium (Fusamax) and calcitonin (Miacalcin) may also be considered. Patients should be advised to stop smoking and to limit alcohol intake. Regular stretching, strengthening, and aerobic exercise should be instituted to optimize mobility. Additional treatments should be determined by the degree of loss of bone mineral density. Options include thiazide diuretics in patients with high urine calcium levels, hormonal replacement in postmenopausal women, oral contraceptives in premenopausal women, testosterone in men with low testosterone levels, calcitonin, and biphosphonates.

**IMPLICATIONS FOR PRACTICE**

Altogether, these clinical and MRI studies suggest that high-dose MP not only has transient beneficial effects on clinical relapses and established areas of inflammation and demyelination, but may also have prolonged dose-dependent benefits involving early events in lesion formation, lesion propagation, and lesion recovery. The clinical effectiveness includes acute treatment of relapses, and long-term treatment in both relapsing-remitting MS and secondary progressive MS. The benefit from a single dose lasts for up to 6 months by MRI measures, and possibly even several years by clinical measures.[47,71] Repeated doses given at routine intervals (every 2–4 months) provide
benefits by clinical and MRI measures that may last for many years and in general are well tolerated. High-dose MP has also been found in a small series to be useful in uveitis associated with MS, so the use of high-dose MP in MS patients may broaden over time. These studies provide a strong rationale for further studies of pulsed high-dose MP as a treatment for relapsing-remitting MS and secondary progressive MS to assess further the effects of high-dose MP on the disease course.

The optimal dose, route, and frequency of administration for high-dose MP pulses are unknown. Doses ranging from 500 mg/day to 1000 mg/day (intravenous or oral) for 3–5 days have been found to hasten recovery from MS relapses, whereas a single day of high-dose MP treatment was found to be ineffective in an earlier study. One recent study reported that high-dose MP, 2000 mg/day for 5 days, significantly reduced new and total enhancing MRI lesion counts for 2 months. This raises the possibility that doses in excess of 1000 mg/day may be more effective in altering subsequent disease activity. Further studies are required to clarify this issue. In the interim, doses of 500 mg/day to 1000 mg/day (intravenous or oral) for 3–5 days are appropriate for the treatment of MS relapses associated with significant functional decline. Conventional doses of oral corticosteroids, such as the regimen studied by Barnes et al., cannot be currently recommended, although further studies of oral corticosteroid use would help clarify this issue.

It is likely that the results of the ONTT can be generalized to other isolated monosymptomatic demyelinating syndromes. There is little reason to believe that patients with MRI scans that are typical for MS who present with partial transverse myelitis or brainstem syndromes carry a risk of subsequent relapse that is different from that of patients presenting with optic neuritis and similar MRI abnormalities. Furthermore, a recent study suggests that all monosymptomatic groups with abnormal MRI scans at onset experience a frequency of enhancing lesion activity over the course of the subsequent year similar to that seen in relapsing-remitting MS patients. Therefore, such patients are likely to experience the same temporary disease-modifying benefit from high-dose MP as optic neuritis patients do. More importantly, monosymptomatic patients are not likely to receive significant benefit from conventional dose oral corticosteroids, which should be avoided in the absence of future controlled clinical trials. Therefore, it is recommended that all patients with a significant functional decline from a first clinical demyelinating event should be treated with a course of high-dose MP.

The role of pulsed high-dose MP treatment in relapsing-remitting MS is unknown, although the study by Zivadinov et al. suggests that this treatment is well tolerated, associated with favorable disease course, and decreases the development of brain atrophy and other MRI measures of disease. The role of pulsed high-dose MP as additive therapy for patients in whom conventional treatment with interferon beta or glatiramer acetate fails is unclear, and this is an area that is ripe for controlled clinical trials. The potential neuroprotective effect of high-dose MP pulsed therapy makes this an attractive combination therapy with currently available disease-modifying agents.

Lastly, the relative role for pulsed high-dose MP therapy for secondary progressive MS remains uncertain. The study by Goodkin et al. suggests that bimonthly pulses of high-dose MP, 500 mg/day for 3 days, delays development of disability progression, with few significant side effects in a population of patients with few treatment options. However, the optimal dose of pulsed high-dose MP therapy and its effect on MRI
parameters are unknown, and the efficacy relative to interferon beta (or possibly in combination with interferon beta) remains to be determined. As with relapsing-remitting MS, it is likely that future studies will focus on pulsed high-dose MP treatment as additive therapy for patients who fail conventional treatment with interferon beta.

ACKNOWLEDGMENTS

Supported in part by a Physician Fellowship Award from the National Multiple Sclerosis Society and a Potiker Fellowship to RJF.

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Cyclophosphamide treatment of multiple sclerosis
Derek R Smith and Howard L Weiner

INTRODUCTION

Cyclophosphamide (CTX) is an alkylating agent widely used in the treatment of malignancies, notably hematologic malignancies, and immune-mediated non-malignant diseases. Treatment regimes range from marrow ablative to chronic low-dose oral therapy. The number of immune-mediated diseases for which CTX is considered effective continues to expand despite the fact that it has been available for many years. It has been studied as a treatment for multiple sclerosis (MS) for the past 30 years. Review of the recent literature suggests that it is efficacious in cases of worsening MS that have an active inflammatory component as evidenced by relapses or gadolinium-enhancing lesions on magnetic resonance imaging (MRI) or in patients in earlier stages of progression. There is no evidence of efficacy in primary progressive MS or later secondary progressive MS. Although usually considered a general immunosuppressive agent, immunologic studies indicate that CTX has more specific effects in MS. Side effects include nausea, alopecia, infertility, risk bladder toxicity, and a risk of malignancy. The most commonly used regimens involve outpatient intravenous pulsed therapy given every 4–8 weeks, with or without corticosteroids; such regimens are usually well tolerated by patients. CTX is currently used in MS patients whose disease is not controlled by first-line agents and those with a rapidly worsening course.

RATIONALE FOR CYCLOPHOSPHAMIDE TREATMENT OF MS

The rationale that led investigators to study CTX as a potential MS treatment rested on the hypothesis that MS is an inflammatory, cell-mediated autoimmune disease affecting the central nervous system (CNS).[1–3] The immunosuppressive effects of CTX have proved to be effective for the treatment of other putative autoimmune diseases.[4,5] More recently, it has become clear that a primary autoimmune hypothesis is not essential to the rationale for the use of immunosuppression, since inflammation is often the predominant cause of injury in viral infection. In this regard, Rodriguez and Lindsley investigated the effect of immunosuppression on CNS remyelination in a chronic virus-induced demyelinating disease.[6] They reported that treatment of animals with CTX or anti-T cell monoclonal antibodies enhanced new myelin synthesis by oligodendrocytes, suggesting...
that factors associated with immune T cells somehow impair remyelination and that interference with the function of immune T cells enhances CNS remyelination.

CTX was first tested in MS in 1966[7] and since then has been used in selected patients with MS. Its use has increased in recent years among clinicians who are confronted with evidence of persistently active inflammation in MS patients treated with the disease-modifying drugs, interferon beta and glatiramer acetate, that are approved by the Food and Drug Administration (FDA) in the USA. With FDA approval in 2000 of mitoxantrone for patients with worsening MS, the decision to treat such MS patients with more aggressive approaches has become common practice. According to a recent survey regarding the use of immunosuppressive drugs, CTX is being used by many neurologists for the treatment of MS.[8] There have been over 40 published reports on the clinical and immunologic effects of CTX in MS (Tables 28.1 and 28.2), including many that indicate CTX is efficacious in MS. Not all studies have shown positive effects, however, and this has created differing opinions about its utility, especially since two placebo-controlled trials did not show positive effects.[9,10] Furthermore, because CTX is not under patent, there is no expectation that pharmaceutical support for large-scale testing of CTX or FDA approval will be forthcoming. Thus, many questions remain unanswered about the role of CTX in the treatment of MS.

**Pharmacology and usage of CTX**

CTX is transformed in the liver to active alkylating metabolites, which then react with replicating DNA, killing susceptible rapidly proliferating malignant and non-malignant cells. It is widely used concurrently with other antineoplastic drugs for the treatment of leukemias, lymphomas, adenocarcinomas, and other malignancies. It is also used in marrow ablative regimens for both malignant and non-malignant diseases. CTX has been used in a number of regimens for the treatment of immune-mediated diseases.[4,5] Initially, out of concern for potential toxicities, its use was restricted to the most aggressive immune-mediated diseases such as Wegener’s granulomatosis, polyarteritis nodosa, refractory polymyositis, inflammatory neuropathies, and primary CNS vasculitis.[11,12] A landmark study by Gorley et al. demonstrated that pulse CTX therapy was much more effective than standard therapy in the treatment of lupus nephritis.[13] This study demonstrated that CTX could be well tolerated over time and highly effective in a chronic immune-mediated disease. It is now approved for the treatment of idiopathic nephrotic syndrome and is the recommended form of therapy for lupus nephritis, where it appears to have additive efficacy when given concomitantly with pulsed methylprednisolone (MP).[14] Pulsed CTX is now regularly used in the treatment of severe juvenile-onset systemic rheumatoid arthritis,[15] interstitial lung disease associated with collagen vascular diseases,[16] and idiopathic thrombocytic purpura. CTX has been adopted in the treatment of a number of immune-mediated disorders of the peripheral nervous system.[17]
Inflammation in the stages of MS

It has been proposed that later in the course of MS a separate process of neurodegeneration may proceed independent of active cell-mediated inflammation, which may not be amenable to

### Table 28.1 Studies and reports of CTX in MS

<table>
<thead>
<tr>
<th>Date</th>
<th>Study</th>
<th>n</th>
<th>Type of MS</th>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>Aimard et al. [7]</td>
<td>1</td>
<td>Progressive –</td>
<td>–</td>
<td>First reported use in MS. Disease stabilization in one patient</td>
</tr>
<tr>
<td>1967</td>
<td>Girard et al. [25]</td>
<td>30</td>
<td>Progressive</td>
<td>200 mg/day IV for 4–6 weeks up to 4–9 g total</td>
<td>50% stable or improved at 2 years. Open label</td>
</tr>
<tr>
<td>1969</td>
<td>Millac and Miller [26]</td>
<td>16</td>
<td>Progressive</td>
<td>75–100 mg/day PO</td>
<td>Toxicity associated with low white blood cell counts</td>
</tr>
<tr>
<td>1973</td>
<td>Cendrowski [29]</td>
<td>23</td>
<td>Relapsing or progressive</td>
<td>100–300 mg IV for 16–33 days plus 50 mg hydrocortisone</td>
<td>No difference in comparison with patients treated with ACTH or cortisol</td>
</tr>
<tr>
<td>1975</td>
<td>Drachman et al. [30]</td>
<td>6</td>
<td>Acute attacks</td>
<td>4–5 mg/kg IV for 10 successive days</td>
<td>No benefit on relapse recovery</td>
</tr>
<tr>
<td>1975</td>
<td>Hommes et al. [31]</td>
<td>32</td>
<td>Progressive</td>
<td>100 mg IV qid plus 50 mg prednisone twice daily; 8 g total over 20 days</td>
<td>Stabilization in 69% of patients. Open-label, uncontrolled</td>
</tr>
<tr>
<td>1977</td>
<td>Gonsette et al. [35]</td>
<td>110</td>
<td>Relapsing-remitting</td>
<td>IV over 2 weeks to achieve leukopenia of 2000/mm³ and lymphopenia of 1000/mm³; dose was 1–12 g; no corticosteroids</td>
<td>Stabilization in 62% of patients over 2–4 years. Decrease in relapse rate. Open label, uncontrolled</td>
</tr>
<tr>
<td>1980</td>
<td>Gonsette et al. [36]</td>
<td>134</td>
<td>Relapsing-remitting</td>
<td>Identical IV regime as in 1977 report, above</td>
<td>Stabilization in relapse rate in 76% of patients. Open-label, uncontrolled</td>
</tr>
<tr>
<td>1980</td>
<td>Hommes et al. [33]</td>
<td>39</td>
<td>Chronic progressive</td>
<td>400 mg IV plus 100 mg</td>
<td>Stabilization in 69% of patients.</td>
</tr>
</tbody>
</table>
prednisone (8 g total) | Open-label, uncontrolled. Factors associated with response: disease onset before 28 years of age, short duration of disease before treatment, rapid progression of disease, low initial disability, and HLA-DRw2 positivity

1981 Theys et al.\[34\] | 21 Progressive 6–8 g IV given over | No benefit in patients with moderately advanced MS over 2 years

1983 Hauser et al.\[37\] | 20 Progressive 400–500 mg/day IV for 10–14 days plus ACTH | 16 of 20 patients stabilized at 1 year versus of four of 20 treated with ACTH and nine of 18 treated with plasma exchange. Randomized ACTH control. No blinding or placebo control

1987 Goodkin et al.\[40\] | 27 Chronic progressive | In-patient induction for 10–14 days with IV CTX/ACTH or out-patient induction with 700 mg/m² weekly for 6 weeks plus prednisone. Maintenance therapy of 700 mg/m² every 2 months for 24 months | Stabilization in 59% of patients induced at 12 months versus 17% in non-randomized controls. Trend favoring maintenance therapy versus randomized controls. Nausea and vomiting a limiting side effect of maintenance therapy

<table>
<thead>
<tr>
<th>Date</th>
<th>Study</th>
<th>n</th>
<th>Type of MS</th>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Theys et al.[34]</td>
<td>21</td>
<td>Progressive</td>
<td>6–8 g IV given over</td>
<td>No benefit in patients with moderately advanced MS over 2 years</td>
</tr>
<tr>
<td>1983</td>
<td>Hauser et al.[37]</td>
<td>20</td>
<td>Progressive</td>
<td>400–500 mg/day IV for 10–14 days plus ACTH</td>
<td>16 of 20 patients stabilized at 1 year versus of four of 20 treated with ACTH and nine of 18 treated with plasma exchange. Randomized ACTH control. No blinding or placebo control</td>
</tr>
<tr>
<td>1987</td>
<td>Goodkin et al.[40]</td>
<td>27</td>
<td>Chronic progressive</td>
<td>In-patient induction for 10–14 days with IV CTX/ACTH or out-patient induction with 700 mg/m² weekly for 6 weeks plus prednisone. Maintenance therapy of 700 mg/m² every 2 months for 24 months</td>
<td>Stabilization in 59% of patients induced at 12 months versus 17% in non-randomized controls. Trend favoring maintenance therapy versus randomized controls. Nausea and vomiting a limiting side effect of maintenance therapy</td>
</tr>
<tr>
<td>Year</td>
<td>Study, Authors</td>
<td>Study Design</td>
<td>Treatment Details</td>
<td>Outcome/Comment</td>
<td></td>
</tr>
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</tr>
<tr>
<td>1987 Myers et al. [63]</td>
<td>14 Chronic progressive</td>
<td>400–800 mg/m² IV or PO escalating to 1200–2000 mg/m² monthly. With or without corticosteroids. Five to 13 doses given over 5–14 months to reduce B cell and CD4⁺ cell counts</td>
<td>Three improved, nine unchanged, two worse. Open-label, uncontrolled. Regimen found too toxic for long-term use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987 Siracusa et al. [48]</td>
<td>14 Chronic progressive</td>
<td>Short course of intensive CTX until white blood count reached 3000/mm³</td>
<td>Five patients discontinued because of side effects. Patients stable, though not improved. Regimen felt to be too toxic without marked clinical benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 Carter et al. [38]</td>
<td>164 Progressive 2 week IV CTX/ACTH regimen</td>
<td>81 % stable or improved at 1 year. Regression in 69% of patients at mean of 17.6 months. Improvement in younger patients with shorter disease duration.</td>
<td>Open-label, uncontrolled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 Killian et al. [50]</td>
<td>14 Relapsing-remitting</td>
<td>750 mg/m² IV monthly for 1 year</td>
<td>A trend showing fewer relapses in six treated patients versus eight placebo patients ($p=0.06$). Positive response in placebo patients treated in open-label continuation study. Pilot randomized, double-blind, placebo-controlled trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989 Mauch et al. [46]</td>
<td>21 Chronic progressive day intervals until 8 mg/kg IV</td>
<td>20 of 21 patients stable at 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
lymphocyte count was half the initial value. Average total dose 1.9 g versus seven of 24 patients receiving ACTH. Open label, non-randomized controls

1989 Trouillas et al.[47] 10 Progressive IV (450 mg/day) for 3 weeks plus MP Six of 10 stabilized at 3 years versus nine of 10 in plasma exchange regimen versus 0 of 10 in untreated or azathioprine controls. Open-label, non-randomized controls

1990 Millefiorini et al.[52] 15 Remitting-progressive IV CTX followed by booster every 2 months for 2 years 50% clinically stable at 2 years. No major side effects

1990 D’Andrea et al.[51] 7 Relapsing-remitting IV induction (11 doses of 300 mg/m²) then every 6 months for 3 years Decreased relapse rate in all patients at 1 year. In subsequent 2 years, two patients worse, others clinically stable

1991 Canadian Cooperative Multiple Sclerosis Study Group[10] 55 Progressive 1 g IV on alternate days up to 9 g plus PO prednisone No difference versus placebo or plasma exchange regimen. Randomized, double-blind, placebo-controlled

Date Study n Type of MS Regimen Comments

1991 Likosky et al.[9] 22 Chronic progressive 400–500 mg IV 5 days/week until white count was below 4000/mm³ No difference versus placebo at 12, 18, or 24 months. Randomized, single-blind, placebo controlled

1993 Weiner et al.[39] 256 Progressive Published IV CTX/ACTH induction versus modified IV CTX/ACTH No difference between published and modified induction (56% stable at 12)
induction (600 mg/m² on days 1, 2, 4, 6, and 8) followed by 700 mg/m² IV pulses every 2 months for 2 years

1997 Weinstock-Guttman et al. [54]
17 Fulminant 500 mg/m² plus MP IV for 5 days followed by maintenance therapy with methotrexate, MP, or interferon beta-1b

1998 La Mantia et al. [53]
30 Chronic progressive 600 mg/m² IV every 2 months for 12 months with or without induction (300 mg/m² IV for 9 days)

1999 Gobbini et al. [55]
5 Refractory relapsing-remitting Monthly IV pulses for 12 months

1999 Hohol et al. [41]
95 Progressive Induction with 1 g IV MP for 5 days followed by IV pulse CTX/MP every month for 1 year, every 6 weeks for 1 year, and every 2 months for 1 year

2001 Perini et al. [59]
26 Secondary progressive 800–1250 mg/m² with MP IV monthly for 1 year then every 2

months); benefit of booster versus no boosters at 24 and 30 months. Better response in patients 40 years of age or younger. Randomized, single-blinded, non-treatment control for boosters

13 of 17 (75%) patients stable or improved at 12 months, nine of 13 (69%) at 24 months. Open-label, uncontrolled, consecutive patients

At 12 months, 75% stable with induction, 35% stable without induction. Increased response to treatment in relapsing-progressive patients

MRI outcome: decreased gadolinium-enhancing lesions in all patients

Response to therapy linked to duration of progressive disease; a trend favoring responses in secondary versus primary progressive disease

Clinical improvement at 2 years, reduction in gadolinium-
months for 1 year enhancing lesions and T2 lesion volume

2001 Khan et al.\[56\]
14 Rapidly deteriorating refractory 1000 000 mg/m² with 20 mg dexamethasone IV monthly 14 of 14 patients clinically stable or improved at 6 months, sustained at 18 months

2001 Patti et al.\[57\]
10 Rapidly progressive 500–1500 500 mg/m² IV monthly for 18 months Reduction in relapses, disability, and T2 lesion burden

2002 Zephir et al.\[60\]
111 Progressive 700 mg/m² with MP IV monthly for 1 year Response in patients with a relapse in 2 years before therapy

IV, intravenous, PO, by mouth.

### Table 28.2 Studies of immunologic effects of CTX in MS

<table>
<thead>
<tr>
<th>Date</th>
<th>Study</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Bahr et al.[70]</td>
<td>CTX detected in the cerebrospinal fluid following 3 weeks’ treatment with 400 mg/day</td>
</tr>
<tr>
<td>1982</td>
<td>Ten Berge et al.[73]</td>
<td>Lymphopenia involving T and B cells; serum levels of immunoglobulin and primary and secondary antibody responses depressed</td>
</tr>
<tr>
<td>1983</td>
<td>Brinkman et al.[74]</td>
<td>Alteration in lymphocyte populations in peripheral blood and cerebrospinal fluid</td>
</tr>
<tr>
<td>1983</td>
<td>Hommes et al.[69]</td>
<td>CTX present at same levels in serum and cerebrospinal fluid</td>
</tr>
<tr>
<td>1986</td>
<td>Wender et al.[71]</td>
<td>Decreased intrathecal synthesis of immunoglobulin G, though not as pronounced as with high doses of prednisone</td>
</tr>
<tr>
<td>1987</td>
<td>Moody et al.[75]</td>
<td>47% reduction in CD4⁺ cells, 22% reduction in CD8⁺ cells; magnitude of reduction of CD4⁺ cells correlated with total dose received. B cells reduced by 50% and phytohemaglutinin responses reduced. No reduction in natural killer cells. Recovery of immune function after 4 months</td>
</tr>
<tr>
<td>1988</td>
<td>Lamers et al.[72]</td>
<td>Reduced cerebrospinal myelin basic protein and intrathecal production of immunoglobulin G following treatment with CTX and prednisone</td>
</tr>
<tr>
<td>1989</td>
<td>Uitdehaag et al.[77]</td>
<td>Decreased CD4⁺ cells following short-term therapy (8 g in 20 days) lasting up to 13.5 years after treatment</td>
</tr>
<tr>
<td>1997</td>
<td>Smith et al.[78]</td>
<td>Immune deviation following pulse CTX/MP treatment of MS. Increased interleukin-4 production and associated eosinophilia</td>
</tr>
<tr>
<td>1998</td>
<td>Comabella</td>
<td>Elevated interleukin-12 in progressive MS correlates</td>
</tr>
</tbody>
</table>
anti-inflammatory therapies. With time, MS becomes less inflammatory as measured by gadolinium-enhancing lesions on MRI.\cite{18,19} It has been suggested that primary progressive MS may represent an entirely different pathologic process and, thus, respond differently to therapy.\cite{20} As a result, primary progressive MS is tested separately in clinical trials. There currently are no approved drugs for primary progressive MS. Mitoxantrone, an anti-inflammatory anti-cancer drug which is effective in active secondary progressive MS,\cite{21} has been specifically labeled as not having demonstrated efficacy in primary progressive MS. There is an ongoing trial in this category of patients.\cite{22} Immunomodulatory drugs with proven efficacy in MS may not show efficacy in all clinical trials depending on the patient populations being studied. This is best illustrated in studies of interferon beta-1b. The European trial of interferon beta-1b in secondary progressive MS\cite{23} demonstrated benefit on expanded disability status score (EDSS) progression, the primary endpoint, whereas the North American trial of the same agent\cite{24} failed to show benefit. Analyses of patient demographics showed that those in the European trial were at an earlier stage of the disease. Thus, a strong anti-inflammatory drug such as CTX should be evaluated according to the stage of MS and the degree to which inflammation plays a role in the pathology of the patients being treated. As discussed below, one of the major reasons for conflicting reports about the efficacy of CTX in MS may be that the patient populations treated were at different stages of the disease.

### CLINICAL STUDIES OF CTX IN MS

Clinical trials of CTX in MS are summarized in Table 28.1.

#### Initial European studies

In 1966, Aimard et al. described the successful treatment of a patient with progressive MS using CTX.\cite{7} This led to an open-label, uncontrolled clinical trial in which 30 MS patients were treated with intravenous CTX 200 mg/day for 4–6 weeks up to a total of 4–9 g. At the end of 2 years of follow-up, 50% of the patients were stable or improved.\cite{25} In 1969 Millac and Miller described their experience in treating 16 patients with oral CTX.\cite{26} Initially, patients were given sufficient CTX to reduce their white blood cell count to 2000/mm³. The rate of complications was considered too high, so the dose was reduced to maintain the leukocyte count at 3000/mm³. The daily dose varied from 75 mg to 150 mg. Seven patients dropped out of the study because of adverse effects. In 1971 Wieczorek et al. reported that CTX combined with azathioprine appeared to be efficacious in an open uncontrolled trial.\cite{27} Gopel et al. reported a similar experience.\cite{28} However, Cendrowski reported that CTX was no better than corticosteroids or adrenocorticotropic hormone (ACTH) alone.\cite{29} In addition, Drachman et al. found no
effect of intravenous CTX 4–5 mg/kg given for 10 successive days for the treatment of acute relapses.\cite{30}

Following these initial studies, groups led by Gonsette and Hommes reported positive effects with CTX in both relapsing-remitting MS and progressive MS, laying the groundwork for later controlled studies. Hommes and colleagues published three reports on their experience with CTX in pilot studies of chronic progressive MS.\cite{31–33} A total of 86 patients were treated with a short course of CTX (400 mg/day) plus prednisone (100 mg/day) given to induce a leukopenia below 2000/mm$^3$. Patients received a total dose of 8 g of CTX and were treated in an uncontrolled, open-label fashion. Hommes and colleagues reported on groups of 32 and 39 patients with varying times of follow-up and analysed the factors associated with a response to therapy. They reported stabilization of the disease for 1–5 years in 69% of the patients. The factors that predicted a good response to therapy included disease onset before 28 years of age, short duration of disease before treatment, rapid progression of disease, low disability, and HLA-DRw2 positivity (Table 28.3). Those factors were consistent with a report by Theys et al., who found no benefit of 6–8 g of CTX given over 3–4 weeks in patients with moderately advanced MS.\cite{34}

Gonsette et al. treated 201 patients with relapsing-remitting MS with CTX and reported on groups of 110 patients with follow-up for 2–6 years\cite{35} and 134 patients with follow-up for 2–10 years.\cite{36} Patients were treated with intravenous CTX without corticosteroids over a 1–2-week period and received between 1 g and 2 g to maintain a leukopenia of 2000/mm$^3$ and a lymphopenia of 1000/mm$^3$ for 2–3 weeks. In summarizing their experience, Gonsette et al. reported a 75% decrease in the annual relapse rate in 70% of patients treated compared with the relapse rate 1–2 years before treatment, with the most pronounced effects in those with shortest duration of disease. There was no effect in patients who were already severely disabled. Thirty per cent of patients failed to respond to CTX. Stabilization as measured by time to next relapse was approximately 2.5 years. In addition, 60% of patients experienced improvement in neurologic signs and disability. The study was open label and uncontrolled. The authors discussed the known decrease in relapse rate that occurs in patients without treatment and stated that the decrease that they observed was more than expected. They also reported that the effect of a short 2–3-week treatment was of limited duration, lasting 2–3 years, and discussed the need for strategies to prolong the remission.

In summary, European investigators first introduced the use of CTX for the treatment of MS. They identified two themes regarding treatment with CTX in MS: first, treatment

Table 28.3 Factors associated with a response to therapy

<table>
<thead>
<tr>
<th>Younger age</th>
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</thead>
<tbody>
<tr>
<td>Rapidly progressive course</td>
</tr>
<tr>
<td>Relapses in the year before therapy</td>
</tr>
<tr>
<td>Less than 2 years in progressive phase</td>
</tr>
<tr>
<td>Absence of primary progressive course</td>
</tr>
<tr>
<td>Gadolinium-enhancing lesions on MRI</td>
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</table>
at an earlier stage in the disease is more effective, and second, the benefit of a short course of treatment lasted for a finite period, after which additional therapy was required.

**Early North American trials**

As with other immune-mediated diseases, early studies of CTX in MS focused on more severely affected patients and shorter courses of treatment. A randomized, controlled study of the use of CTX was reported in 1983 by Hauser et al.\[37\] based on the previous studies of Gonsette et al.\[35,36\] and Hommes and colleagues.\[31–33\] Patients with progressive MS were treated with a 2–3-week course of intravenous CTX (400–500 mg/day) plus ACTH given in hospital to achieve leukopenia of 2000/mm\(^3\); this group of patients was compared with a group that received ACTH alone and with a group that received plasma exchange, ACTH, and oral CTX. All patients treated with CTX developed alopecia. Although the study was randomized and controlled, it was neither blinded nor placebo-controlled. Eighty per cent (16 of 20) of the intravenous CTX-treated patients were stable or improved at 1 year, compared with only 20% (four of 20) in the group treated with ACTH alone. The plasma exchange group showed an intermediate (50%) response. Benefit also was demonstrated by change in EDSS and in the proportion of patients classified as treatment failures. Analysis of the patient profiles demonstrated that the patients were relatively young (35 years) with disease duration before treatment of 2–3 years. It was reported that 11 of the 16 patients who were stable or improved at 1 year experienced disease progression in the second or third year after treatment. Carter et al.\[38\] reported follow-up of 164 patients treated with CTX plus ACTH induction. Almost all patients exhibited return of progression, on average 18 months after CTX treatment, some as soon as 6 months after treatment.

As it became clear that a single treatment was not sufficient, the Northeast Cooperative Treatment Group tested two questions.\[39\] First, was a modified induction regimen with a fixed dose of CTX equivalent to a published regimen in which dose was adjusted according to leukocyte count? Second, would a maintenance regimen of CTX pulses (700 mg/m\(^2\)) every 2 months prevent or delay return of progression? Patients were randomized into four groups, all received the published or modified induction followed by outpatient pulsed therapy or no pulsed therapy. There was no placebo group. Patients were evaluated in a single-blind fashion. There was no difference between the published and modified induction regimens either in terms of initial stabilization (56%) or subsequent progression in those not receiving boosters. A statistically significant (though modest) effect of boosters in delaying re-progression was observed at 24 months and at 30 months (\(p=0.04\)). Differences between the booster and non-booster groups may have been blunted by the fact that both groups received an initial induction. Post hoc subgroup analyses showed an age effect, with boosters delaying time to treatment failure in patients aged 18–40 years (\(p=0.003\)) but not in patients aged 41–55 years (\(p=0.97\)). In addition, patients with primary progressive MS had a poorer response than patients with secondary progressive disease (\(p=0.04\)). Patients with recent-onset progression responded better to boosters (\(p=0.02\)) than patients with progressive disease for longer than 7 years (\(p=0.58\)).

Goodkin et al. carried out a similar study.\[40\] Twenty-seven patients with progressive MS were treated with bimonthly boosters of CTX 700 mg/m\(^2\) after induction and
compared to non-randomized controls receiving induction therapy only. A trend favoring boosters was observed.[40]

An outpatient protocol was subsequently developed involving induction with five consecutive days of intravenous MP (1 g/day) with a single dose of intravenous CTX (800 mg/m²) given on day 4 or 5. This induction was followed by monthly pulses of intravenous CTX/MP with increasing CTX doses until a dose was reached that produced a mid-month white blood cell nadir of 1500–2000/mm³, up to a maximum dose of 1600 mg/m². Pulses were given monthly for the first year, every 6 weeks during the second year, and every 3 months during the third year. This protocol was established to reduce alopecia and to produce a consistent level of leukopenia. Boosters were given more frequently than in the Northeast Cooperative Treatment Group and over a longer period of time. A retrospective study of 95 consecutive patients treated by this protocol examined factors associated with clinical response and found that length of time in the progressive stage was linked to a positive response.[41] Patients with primary progressive MS appeared not to respond.

In summary, randomized trials appeared to confirm reports by European investigators that CTX was of benefit in MS and that its efficacy was more prominent in certain patient categories. The studies also highlighted the need for periodic retreatment.

**Placebo-controlled trials**

Two studies have been reported in which a placebo control group was used and no positive clinical effects were observed with a 2-week induction regimen.[9,10] In the Canadian study,[10] 55 patients with progressive MS received 1 g of CTX on alternate days until the leukocyte count fell below 4500/mm³ or until a total of 9 g had been administered, plus 40 mg prednisone orally for 10 days. The study was placebo-controlled and single-masked, and it included a third treatment group that received plasma exchange. In the study by Likosky et al.,[9] 22 patients with progressive MS received intravenous CTX 400–500 mg on 5 days per week until the leukocyte count fell below 4000/mm³; this group was compared to a group receiving folic acid in a randomized, single-blind study. No benefit of intravenous CTX was demonstrated in either study.

The differences in design and results of these two studies as compared to the studies of Hauser et al.[37] and the Northeast Cooperative Treatment Group[39] have been debated extensively in the literature.[42–44] The Canadian study[10] and the study by Likosky et al.[9] have the advantage of being placebo-controlled and blinded. It has been argued that the negative results in these studies demonstrated that CTX is not effective in patients with progressive MS. Conversely, these results may have been subject to type 2 errors (false-negative results), similar to what occurred in a pilot study of mitoxantrone in progressive MS.[45] Analysis of the results of the Canadian study[10] and the study by Likosky et al.[9] suggests that these investigators indeed identified patient groups that are not responsive to CTX, though these were different from patient groups reported by others to be responsive. Differences in treatment regimens also are notable. What is most dramatic in the negative studies was the lack of progression in the placebo group. For example, in the study by Likosky et al., 70% of the placebo patients were stable at 1 year and 53% were stable at 2 years.[9] The Canadian study reported that 67% of the placebo group were
stable at 2 years and 36.7% were stable when the data were re-analysed using less stringent criteria at higher EDSS levels.\textsuperscript{[10]} In the Canadian study, 60% of the CTX-treated patients were classified as having chronic progressive MS whereas 40% had relapsing progressive MS.\textsuperscript{[10]} Patients had longer disease duration than those reported in the study by Hauser et al.\textsuperscript{[37]} Thus, it appears that the conflicting findings may be due to reasons similar to the conflicting results of the European and North American interferon beta-1b studies of secondary progressive MS, in which patient populations at different stages of disease were treated.

The conclusion here is that the study by Hauser et al. correctly identified CTX as being effective in early, aggressive, inflammatory MS.\textsuperscript{[37]} The Canadian study\textsuperscript{[10]} and the study by Likosky et al.\textsuperscript{[9]} confirmed that, in later stages of progressive MS, CTX is not effective.

### Studies using pulse therapy and MRI

Although there have been other reports of short 2–3-week courses of CTX for the treatment of MS with both positive\textsuperscript{[46,47]} and negative results,\textsuperscript{[48]} most physicians currently use intermittent pulse therapy for the treatment of MS. Meyers et al. treated 14 patients with escalating monthly doses up to 2000 mg/m\textsuperscript{2}, a regimen that was found to be too toxic for long-term use.\textsuperscript{[49]} Killian et al. treated 14 patients with relapsing-remitting MS with monthly pulses of 750 mg/m\textsuperscript{2} for 1 year in a pilot randomized, double-blind, placebo-controlled trial that showed a positive trend ($p=0.06$) in six treated versus eight placebo patients.\textsuperscript{[50]} D’Andrea et al. treated seven patients with relapsing-remitting MS with pulses every 6 months after induction,\textsuperscript{[51]} and Millefiorini et al. treated 15 patients with remitting progressive MS with boosters every 2 months for 2 years after intravenous induction.\textsuperscript{[52]} Both reported positive effects in open-label trials. La Mantia et al. reported a better response in 30 patients with relapsing progressive MS and in those receiving induction plus boosters (600 mg/m\textsuperscript{2}) every 2 months for 12 months.\textsuperscript{[53]}

With the widespread use of interferon beta and glatiramer acetate, physicians have been confronted with refractory patients. Several groups have reported positive results following treatment of such patients with CTX in open-label studies.\textsuperscript{[53–57]} These patients have been described as having ‘fulminant’, ‘refractory relapsing-remitting’, and ‘rapidly deteriorating refractory’ disease. Weinstock-Guttman et al. reported that 75% of patients were stable or improved 12 months after receiving intravenous CTX for 5 days followed by maintenance therapy.\textsuperscript{[54]} Khan et al. reported clinical stability or improvement in 14 consecutive patients given monthly CTX pulses (1000 mg/m\textsuperscript{2}).\textsuperscript{[56]}

In the first MRI-based study of CTX, Gobbini et al. at the National Institutes of Health (NIH) in the USA treated patients with relapsing-remitting MS that was not responsive to other immunomodulatory drugs with monthly pulses of CTX (1000 mg/m\textsuperscript{2}).\textsuperscript{[55]} Patients were followed with monthly MRI scans and clinical evaluation for a mean of 28 months. All patients showed a rapid reduction in gadolinium-enhancing lesion frequency, and three patients had a decrease in T2 lesion load within the first 5 months of starting CTX treatment. CTX treatment was well tolerated. MRI studies in patients receiving CTX before bone marrow transplant demonstrated a marked decrease in gadolinium-enhancing lesions.\textsuperscript{[58]} Perini et al. reported significant reduction of T2 lesions and gadolinium enhancement on MRI in 26 secondary progressive patients given monthly intravenous
CTX pulses at 800–1250 mg/m^2 for 1 year and then doses every 8 weeks during the second year.\textsuperscript{59} Significant clinical improvement was also observed, and the treatment was safe and well tolerated. Zephir et al. reported 111 consecutive patients with progressive disease (21 with primary progressive MS and 90 with secondary progressive MS) who were treated with pulsed CTX for 12 months.\textsuperscript{60} They found that the response to CTX was linked to whether patients with secondary progressive disease had superimposed relapses during the year before treatment. Patti et al. recently reported on the effectiveness of a combination of CTX and interferon beta in patients with rapidly progressive or ‘transitional’ MS, characterized by frequent and severe attacks plus worsening on the EDSS.\textsuperscript{57} They treated 10 such patients with monthly pulses of intravenous CTX (500–1500 mg/m^2) to obtain a lymphopenia of between 600 and 900/mm^3 for 12 consecutive months and then at 2-month intervals for a further 6 months. They found significant reductions in the number of relapses, in disability and T2 MRI burden of disease. They found that the treatment was safe and well tolerated.

In summary, the use of CTX in MS has evolved towards the use of intermittent pulse therapy given over a 1–3-year period. Positive MRI and clinical effects have been observed in patients with active MS refractory to the approved immunomodulatory drugs.

**Controlled combination therapy trial of CTX and interferon beta**

A multicenter, randomized, single-blind trial of combination therapy with CTX and interferon beta-1a that uses MRI parameters is in progress.\textsuperscript{61} Fifty-nine patients with active relapsing disease while on interferon beta therapy were randomized to either intravenous CTX and MP or MP monthly for 6 months in addition to weekly interferon beta-1a. Patients are to be followed for a further 18 months. MRI results from the initial 6 months indicated a significant reduction in gadolinium-enhancing lesions in the CTX group versus both baseline and MP control group (Fig. 28.1). The proportion of CTX-treated patients with gadolinium-enhancing lesions was reduced by 62% at 3 months and 6 months versus MP (eight of 60 versus 21 of 54). Preliminary analyses also suggested that the time to treatment failure was prolonged by CTX. Final results of this trial should be available in 2003.

**TREATMENT REGIMENS**

As described above, a large number of treatment regimens have been employed, including oral administration, induction regimens given over a
**Fig. 28.1** CTX-MP in active MS resistant to interferon beta. Mean number of gadolinium-enhancing lesions in patients with active MS despite interferon beta therapy, randomized to either 6 months of monthly intravenous CTX-MP or MP alone. Cohort sizes are given over the baseline data, which was 1 month after an initial 3-day course of intravenous MP. MRI scans were obtained 1 month after infusion treatments. CTX-treated patients showed significantly fewer gadolinium-enhancing lesions at both 3 months and 6 months compared with patients treated with intravenous MP alone. Percentage reduction and p-values are given.

2–3-week period, and maintenance pulse therapy given at varying doses and intervals (Tables 28.1 and 28.4). Most physicians using CTX have adopted a pulse therapy regimen in which CTX is given for 6–36 months depending on clinical response and MRI findings. In some instances of fulminant MS, induction therapy may be administered. In some studies, including the NIH MRI study by Gobbini et al., pulse CTX was given without corticosteroids with beneficial effect, whereas most groups, including the Boston group, have administered them together. Studies from the lupus literature suggest that the combination of CTX and corticosteroids may be more effective than CTX alone, with
decreased side effects. Long-term oral CTX is limited by the increased risk of bladder toxicity.

**TOXICITY**

The adverse effects of CTX are well known, since the drug has been used for over 30 years (Table 28.5). Some investigators have reported that CTX is too toxic to administer because of its side effects and because of patient discomfort. In contrast, most groups have reported that CTX is generally well tolerated and easy to administer with attention to dosing schedules, concomitant use of corticosteroids, and the use of appropriate antiemetics.

Apart from alopecia, infertility, and nausea, the most frequently seen complication is hemorrhagic cystitis. This has been also seen in lupus nephritis protocols and has been the major reason for the avoidance of long-term oral CTX in MS. In addition, cases of bladder cancer have been observed in patients treated with long-term CTX. At the authors’ center, patients are hydrated with 3 liters of fluid on the day of treatment and on the day after treatment. In addition, urine cytology is obtained routinely at yearly intervals in patients treated with CTX, and yearly cystoscopy is recommended after 2 years of therapy.

Gonadal failure occurs in both men and women receiving alkylating agents such as CTX. Most of the available data concern the rate of ovarian failure in cancer survivors in whom alkylating agents were used as part of a multidrug regimen and at different doses than those used for immunologic diseases. In a controlled trial in lupus nephritis, a
setting more relevant to MS, 23 of 46 women (50%) developed amenorrhea after receiving monthly CTX for 6 months then every 3 months for at least 2 more years, beginning with a dose of 750 mg/m² then adjusting the dose on the basis of the white cell nadir. Risk factors for persistent amenorrhea and premature menopause included age over 30 years and cumulative dose over 300 mg/kg. A number of approaches have been considered to attempt to preserve ovarian function. The rate of amenorrhea in women with MS treated with CTX (approximately 40–80% in large series) appeared similar to that reported for rheumatic diseases. There are very few data concerning the frequency of infertility in men with immune-mediated diseases treated with CTX.

An increased incidence of secondary hematologic malignancies with CTX has been reported both in patients with cancer. In patients with rheumatic diseases, bladder cancer may occur after cessation of therapy. The risk appears to increase as a function of total dose. Care must be taken when the cumulative lifetime dose exceeds 80–100 g. Based on this figure, we recommend patients receive no more than 50 doses of 1000 mg/m² over a lifetime.

**IMMUNOLOGIC EFFECTS**

MS is postulated to be an autoimmune disease mediated by T-helper type 1 cells, and although CTX was originally used as a general immunosuppressant, recent evidence suggests it may have more specific advantageous immunologic effects in MS (see Table 28.2). It can be detected in the cerebrospinal fluid (CSF), and it reduces CSF myelin basic protein and intrathecal production of immunoglobulin G. Early studies demonstrated lymphopenia involving T and B cells, with a more pronounced effect on CD4⁺ cells. These changes reversed after 4 months, although others reported changes lasting as long as 13.5 years. Recent studies showed that the drug may also have selective effects on the immune system. MS patients treated with pulsed CTX demonstrated increased interleukin (IL)-4 production and eosinophilia. It has a pronounced effect on IL-12, which may be linked to response to therapy. Takashima et al. found CTX preferentially deviates myelin-reactive cells to those secreting IL-4. They reported an increased frequency of IL-4 secretion from both myelin basic protein-reactive cells and proteolipid protein-reactive cells in patients treated with CTX. No such increase was observed in patients treated with MP. Thus, CTX therapy appears to induce myelin-antigen specific T-helper type 2 cell responses.

**CONCLUSIONS AND FUTURE INVESTIGATION**

Based on the body of literature on the treatment of MS with CTX, it is concluded here that CTX is of benefit for MS patients with an active inflammatory component to their illness. This inflammatory component is not prominent in later stages of secondary progressive disease or in patients with primary progressive MS. Thus, like other immunomodulators, CTX is ineffective in these settings. Given that early inflammatory events appear to correlate with later disability, strong anti-inflammatory drugs such as
CTX or mitoxantrone may have an impact on later degenerative changes if given early in the disease to halt inflammation.

However, drugs such as CTX and mitoxantrone are limited by their toxicity for widespread use in early stages of MS. These drugs should be tested at early stages in patients who are felt to have poor prognosis on the basis of MRI and clinical parameters. With a better understanding of the immune mechanisms in the disease, MRI parameters and other criteria could be established to decide when drugs such as CTX should be used. For example, patients with elevated levels of IL-12 may not respond as well to interferons. Such patients may be candidates for early aggressive therapy. Similarly, other immune abnormalities may be identified that predict response to CTX.

With the approval of mitoxantrone for worsening forms of MS, the question remains of the place of CTX in this patient group. There have been no formal comparisons between mitoxantrone and CTX. As there are not any reported studies of mitoxantrone in later stages of MS, one might expect that, like CTX, mitoxantrone may be less effective in advanced MS. Mitoxantrone is easier to administer than CTX. However, because of cardiac toxicity, mitoxantrone can be given only for 2–3 years and cannot be given again if patients begin to progress. CTX can be administered for longer periods of time, although it too is limited by cumulative dose considerations. Sequential use of these agents has been carried out by some investigators, but toxicity profiles are unknown at this time.

In summary, 30 years of experience with CTX suggests that it is efficacious in MS at earlier stages of the disease, when there is rapid progression, or when there is active gadolinium enhancement on MRI. These attributes suggest the presence of ongoing inflammation. The conflicting data in the literature concerning the benefit of CTX probably reflect limitations in study designs and differences in MS patient populations. It is concluded here that CTX given as pulse therapy or as an acute induction regimen has an ameliorating effect on the disease process in selected MS patient groups, but that it must be used judiciously with regard to toxicity, patient selection, and duration of use.

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Treatment of multiple sclerosis by hematopoietic stem cell transplantation
Richard K Burt, Bruce Cohen, Lorri Lobeck, William H Burns and Christopher Bredeson

BACKGROUND

Hematopoietic stem cells

Cells capable of both differentiation and perpetual self-renewal are termed stem cells. Some adult tissues have relatively rapid tissue turnover that mandates a dynamic stem cell compartment. Circulating blood cells have a limited half-life and are continually regenerated from pluripotent hematopoietic stem cells (HSCs). While the exact phenotype of HSCs is unknown, subpopulations expressing the surface membrane antigen CD34 are pluripotent stem cells capable of reconstituting life-long hematopoiesis following marrow ablative lethal irradiation.\[1\]

Although HSCs are primarily located in the axial bone marrow, low numbers of HSCs are found in the peripheral vascular circulation during steady state. The numbers of HSCs in the circulation can be increased after recovery from moderate-intensity chemotherapy or with the administration of hematopoietic growth factors (HGFs) such as granulocyte-colony stimulating factor (G-CSF). These mobilized HSCs and partially committed progenitor cells may be easily collected from the circulation by apheresis and cryopreserved for later use. Hundreds of millions of CD34\(^+\) cells may be easily and repetitively collected from a patient. Currently, so other adult stem cells (e.g. neural stem cells) are so readily accessible and available in such large numbers.

HSCs differentiate not only into red blood cells, platelets, and neutrophils but also into immune cells such as T and B lymphocytes, dendritic cells, and tissue macrophages. The ability of HSCs to generate an immune system was recognized as early as the 1960s when the first successful human allogeneic HSC transplants (HSCT) were successfully performed to correct genetic immune deficiency diseases.\[2\] In fact, the immune system arising from HSCs not only determines immunity but also tolerance to self. In animal models, depending on circumstances, HSCs can cause, prevent, or cure an autoimmune disease.

Some animal autoimmune-like diseases are hematopoietic stem cell defects that arise spontaneously. For example, diabetes in non-obese diabetic mice is a genetic stem cell defect that arises spontaneously. Spontaneous-onset autoimmune diseases require an allogeneic HSCT from a normal murine strain to be cured\[3,4\]. Alternatively, engraftment of non-obese diabetic mice HSCs into a non-insulin prone strain causes diabetes.\[5\] Other animal autoimmune diseases require immune stimuli such as immunization or infection
to break tolerance. Environmentally induced autoimmune diseases may be cured by syngeneic or pseudoautologous HSCT. Cure of environmental autoimmune diseases has been demonstrated for models of arthritis (adjuvant arthritis, collagen-induced arthritis), myasthenia gravis (experimental autoimmune myasthenia gravis), and multiple sclerosis (experimental autoimmune encephalomyelitis, EAE).[6–12]

Clinical tolerance is defined as inability to reject an antigen or tissue without immune suppressive medications but with normal rejection of pathogens and third party antigens. The ability of HSCs to introduce tolerance is best demonstrated by combining solid organ transplants and HSCTs from the same donor. Transplantation of solid organs such as heart, lung, liver, or kidney, whether in animals or humans, is complicated by rejection despite life-long immunosuppression as well as potentially lethal immune suppression-related opportunistic infections. Co-transplantation of purified HSCs and solid organs from the same animal donor has been demonstrated to result in clinical tolerance to both donor and recipient tissues/organs.[13,14] Immune competence is demonstrated by the ability of the transplant recipient to reject third party tissues. An animal transplanted with HSCs resulting in hematopoietic chimerism or mixed chimerism will not reject tissues or organs from the stem cell donor even in the absence of immune suppression. This ability of stem cells to introduce tolerance has led to numerous clinical trials of HSCT for autoimmune or presumed autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Crohn’s disease, and multiple sclerosis (MS).

**HSCT in animal models of multiple sclerosis**

EAE is an autoimmune demyelinating disease that can be induced either by immunization with peptides of myelin proteins such as proteolipid protein or myelin basic protein or produced by adoptive transfer of T cells from animals immunized with myelin peptides. EAE can be induced in rodents and primates. Disease manifestations vary by strain. In the Lewis rat, EAE is a monophasic disease with complete recovery following the initial attack, while in Swiss Jackson Lab/Jackson (SJL/J) mice, EAE is a relapsing-remitting disease.

Multiple therapeutic interventions have been successfully tried in EAE before development of clinical trials for the treatment of MS. Several investigators have reported amelioration or cure of EAE following syngeneic or pseudoautologous HSCT.[10–12,15] Syngeneic HSCs are from genetically identical animals that do not have EAE. Pseudoautologous transplants utilize marrow from a syngeneic animal with EAE in the same stage as the recipient. Although successful in ameliorating or curing disease, pseudoautologous HSCTs have a higher relapse rate than syngeneic transplants from a normal donor, suggesting that T cells or other immune cells contaminating the graft may contribute to relapse.[15]

Most treatments for EAE, including HSCT, have been performed before onset or early after onset of the disease. Therefore, it is difficult to extrapolate results of experiments in early relapsing-remitting EAE to patients who have had MS for several years, may have significant lesion burden, and have clinically progressive rather than early relapsing-remitting disease. In fact, if HSCT is performed in chronic EAE that no longer manifests acute relapses, neurologic disability does not improve.[16] Histologic analysis of chronic EAE reveals glial scarring that would be unlikely to improve with either conventional
immune suppression or HSCT. As with other immune-based therapies, HSCT needs to be performed early after disease onset to be effective in EAE. Early intervention with immune suppressive therapy, while the disease is still immune-mediated, may also be applicable to MS.

Theiler’s murine encephalomyelitis virus (TMEV)-induced demyelination is another animal model relevant to MS. TMEV is a neurotrophic picornavirus (small RNA virus) that infects neurons within gray matter. Neurons infected during ex vivo culture are killed and immune deficient mice infected in vivo die within days or weeks of infection. Murine strains that are resistant to TMEV-induced demyelination clear viral infection within 2 weeks. In susceptible strains, the virus persists indefinitely at low level within the central nervous system (CNS). The initial viral-related neuronal injury resolves and is replaced by a demyelinating white matter disease with a clinical course similar to primary progressive MS.[17] Demyelination appears to be a consequence of bystander activation of the immune system against myelin epitopes.[18] HSCT in mice with TMEV-induced demyelination results in high mortality from immune suppression-related viral hyperinfection of the CNS.[19] This suggests that if MS is related to a persistent neurotrophic viral infection, HSCT in humans might be expected to result in disease exacerbation and/or lethal complications. To date no such indication of a persistent viral or other infectious cause for MS has been suggested in patients undergoing HSCT for MS.

**Mechanism of HSCT-induced remission**

The rationale for autologous HSCT is to increase immune suppression to the point of immune ablation and then rescue the patient from marrow failure and prolonged cytopenia by infusion of HSCs. A new immune system, generated from the stem cells, should be similar to that of the patient’s pre-MS condition and tolerant to myelin and other self-epitopes. Whether this ‘reset’ of the immune system actually occurs is currently unproven.

Mechanisms of HSCT-induced remissions have been investigated in EAE by two laboratories with different results.[10,16] In normal SJL/J mice, lymphocyte repertoires capable of recognizing self-epitopes of myelin are represented but are functionally inactive (anergic) and unable to produce demyelination. After immunization, lymphocytes proliferate and release cytokines in response to stimulation with myelin epitopes. These lymphocytes, after ex vivo repriming, are capable of adoptively transferring disease. One group reported that after syngeneic HSCT, post-transplant lymphocytes were unreactive to myelin epitopes, as in a normal animal.[10] A second group reported that, despite clinical remission, the proliferative responses and cytokine profiles of post-transplant lymphocytes were similar to mice with EAE.[16] The only immune parameter that correlated with transplant-induced clinical and histologic remission was normalization of delayed-type hypersensitivity responses.[16] This implied the existence of post-transplant regulatory or suppressor cells or the inability of disease-causing autoreactive lymphocytes to home into or accumulate within the CNS. Alternatively, residual autoreactive T cells may have been unable to induce demyelination because other immune effector cells that mediate demyelination, such as macrophages, were inhibited.
Even less is known about the mechanisms of HSCT-induced immune changes in patients with MS. Lack of post-transplant immune-mediated demyelination has been reported in an Italian study by Mancardi et al.\textsuperscript{[20]} Ten subjects undergoing HSCT followed with a frequent magnetic resonance imaging (MRI) protocol demonstrated no enhancing lesions or accumulation of T2 burden of disease over a post-transplant observation period of 4–30 months. However, the immune changes or mechanisms involved were unknown.

**TRANSPLANT CLINICAL TRIALS**

Currently published transplant trials were phase I studies designed to determine safety of the procedure. These trials were piloted to determine the safest stem cell mobilization and immune ablative regimen in patients with MS.

**Collection of HSCs**

**Bone marrow harvest**

The first two MS patients in the USA to have HSCT underwent harvest of HSCs from the bone marrow in the posterior superior iliac crest in the operating room under general anesthesia.\textsuperscript{[21,22]} Each patient had progressive disease and was confined to a wheelchair. The bone was unusually soft, perhaps owing to immobility-related demineralization, making harvest technically difficult with a resultant low HSC yield. General anesthesia did not result in a flare of MS in the two patients (from two separate institutions) who underwent marrow harvest. These institutions subsequently amended their protocols to collect HSCs from the peripheral blood.

**Peripheral blood cell mobilization**

As noted above, HSCs can be collected from the peripheral circulation following mobilization by chemotherapy or HGFs. While HGFs or chemotherapy alone result in a 7–10-fold increase above steady state in the number of circulating HSCs, the combination is synergistic in increasing the number of circulating HSCs. The combination of chemotherapy and HGFs is commonly used in patients with malignancies. Healthy donors are mobilized with HGFs alone. The most commonly used cytokine to mobilize peripheral blood stem cells (PBSCs) is subcutaneous G-CSF. If G-CSF (10 µg/kg per day) is used as the sole mobilizing agent, stem cells are collected by apheresis using either a peripheral vein or, if necessary, a central venous catheter beginning on either day 4 or 5 of G-CSF treatment. Apheresis methodology is well standardized for a variety of commercially available apheresis machines. After collection, peripheral blood cells can be processed and cryopreserved or manipulated to change the cellular content of the product before cryopreservation (see below).

In some patients with MS, the use of G-CSF alone has been associated with temporary disease exacerbation.\textsuperscript{[23,24]} One strategy to prevent this complication has been to add concomitant corticosteroids (prednisone 1 mg/kg per day) when mobilizing HSCs with
G-CSF. Since this modification to their mobilization strategy, they have been able to mobilize HSCs successfully without MS flares (Richard Nash, verbal communication).

An alternate method for mobilizing peripheral blood cells while avoiding potential flares of MS has been to administer intravenous cyclophosphamide (2.0 g/m²) followed 72 hours later by daily subcutaneous G-CSF (5–10 µg/kg per day).[24] Cyclophosphamide will cause a transient neutropenia that usually lasts no more than 1–2 days and, since it is an immune suppressive agent, it prevents flares of MS that could be induced by G-CSF. Leukapheresis is begun when white blood cells rebound over 1000 µl, approximately 10 days after the administration of cyclophosphamide.

The use of other cytokines for the mobilization of HSCs such as thrombopoietin or stem cell factor has not yet been investigated in patients with MS. To proceed to HSCT, a minimum of 2.0×10⁶ CD34⁺ cells/kg body weight is usually required. Most patients easily achieve this threshold with one or two aphereses.[24]

**Graft manipulation**

When collecting grafts for use in patients with MS or other autoimmune diseases, most but not all centers perform an ex vivo lymphocyte depletion on the collected product.[24] Graft depletion techniques may involve either positive selection for the HSCs (using the CD34 antigen) or negative selection to deplete lymphocytes. Individually, the approaches result in an approximate 2- to 4-log decrease in the number of T cells present in the graft. Double depletion (positive followed by negative selection) can result in profoundly depleted (>5-log) grafts. In MS trials, positive enrichment for CD34⁺ cells has been performed using CEPRATE (CellPro, Bothel, Washington, USA), Isolex (Nexel, Irvine, California, USA), or CliniMACS (Miltenyi, Bergish Gladbach, Germany) cell separation systems. Negative selection has been performed with T cell antibodies by e-rosetting or Nexel Isolex CD4⁺/CD8⁺ selection.

Insufficient clinical data are currently available to compare an unmanipulated versus a T-cell depleted graft in terms of disease response or relapse. As mentioned earlier, in animal models, lymphocyte depletion may help prevent disease recurrence by purging myelin reactive lymphocytes. Alternatively, aggressive lymphocyte depletion may adversely affect immune reconstitution against pathogens increasing the risk of serious post-transplant opportunistic infections such as cytomegalovirus, fungemia, *Pneumocystis carinii* pneumonia, or Epstein-Barr virus post-transplant lymphoproliferative disease (PTLD).[25] At present, the choice of mobilization regimen and graft manipulation strategy is based on the preference and experience of the investigator and, potentially, the MS population under study.

**Conditioning regimens and toxicity**

There are a number of considerations when transplant regimens are being developed. Depending on the disease being treated and the donor type (autologous or allogeneic), conditioning regimens are designed in varying degrees to kill neoplastic cells, result in myeloablation, and provide adequate immune suppression to allow for donor engraftment. When considering autologous transplantation regimens for the treatment of MS, the goal is to provide intense immunosuppression, with limited myelotoxicity.
Another consideration for MS is that we want the regimen to have good CNS penetration and limited regimen-related neurotoxicity. Lastly, the risk of the transplant strategy and conditioning regimen must be in keeping with the degree of risk (morbidity and mortality) of the disease being treated. With these considerations, a number of different regimens have been used in the initial HSCT trials in MS patients (Table 29.1).

The City of Hope (Duarte, California) used an

Table 29.1 Results of autologous, syngeneic hematopoietic stem cell transplantation in patients with MS

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths (n)/Patients (n)</th>
<th>Length of follow-up</th>
<th>Conditioning regimen</th>
<th>Cause and timing of death after transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Openshaw et al.[26]</td>
<td>2/5</td>
<td>Bu/Cy+ATG</td>
<td>One from influenza (day 22) and one from streptococcal infections (19 months)</td>
<td></td>
</tr>
<tr>
<td>Fassas et al.[29]</td>
<td>1/24</td>
<td>BEAM+ATG</td>
<td>One from aspergillosis (day 65)</td>
<td></td>
</tr>
<tr>
<td>Nash et al.[27]</td>
<td>1/20</td>
<td>Cy/TBI+ATG</td>
<td>One from Epstein-Barr virus PTLD (day 53)</td>
<td></td>
</tr>
<tr>
<td>Burt and colleagues[21,22,30]</td>
<td>0/27</td>
<td>Cy/TBI</td>
<td>No mortality</td>
<td></td>
</tr>
<tr>
<td>Mandalfino et al.[53]</td>
<td>0/1 (identical twin)</td>
<td>Cy/TBI</td>
<td>No mortality</td>
<td></td>
</tr>
<tr>
<td>Carreras et al.[54]</td>
<td>0/10</td>
<td>BEAM+ATG</td>
<td>No mortality</td>
<td></td>
</tr>
<tr>
<td>Kozak et al.[55]</td>
<td>0/8</td>
<td>BEAM+ATG</td>
<td>No mortality</td>
<td></td>
</tr>
</tbody>
</table>

Reports of MS conditioning regimens associated with deaths

Opening et al.[26] | 2/5 | Bu/Cy+ATG | One from influenza (day 22) and one from streptococcal infections (19 months) |

Reports of MS conditioning regimens not associated with mortality

Burt and colleagues[21,22,30] | 0/27 | Cy/TBI | No mortality |

Actual patient number may be more than reported in reference and are based on updated communication with author.

ATG, antithymocyte globulin; BEAM, carmustine, etoposide, cytarabine and melphalan; Bu/Cy, busulfan and cyclophosphamide; Cy/TBI,
intensive conditioning regimen of busulfan (16 mg/kg), cyclophosphamide (120 mg/kg), and antithymocyte globulin (ATG) (30 mg/kg) along with CD34+ selection to deplete lymphocytes from the graft.[26] Two out of five treated patients died from infections. One patient died 22 days after HSCT from influenza. The second died 19 months after HSCT from streptococcal pneumonia and sepsis. One of the major extramedullary toxicities of busulfan is pulmonary compromise that could exacerbate pulmonary infections such as influenza. Intense immune suppression combined with aggressive lymphocyte depletion of the graft could lead to prolonged hypogammaglobulinemia, which can predispose to lethal infections from encapsulated organisms such as streptococci.

The Fred Hutchinson Cancer Center Consortium treated 26 patients with progressive MS.[27] The conditioning regimen was total body irradiation (TBI) (800cGy given 200 cGy twice daily with lung shields to 650 cGy), cyclophosphamide (120 mg/kg divided into 60 mg/kg per day) and ATG, (either 90 mg/kg equine or 15 mg/kg rabbit) given for 6 days (days −5, −3, −1, 1, 3, 5). G-CSF-mobilized PBSCs were lymphocyte depleted by CD34 positive selection. The only patient in whom rabbit ATG had been given instead of equine ATG died from EBV-associated PTLD.[28] The patient who developed PTLD had received 6 days of rabbit ATG at 2.5 mg/kg per day (total dose 15 mg/kg). PTLD is a complication of prolonged and aggressive immune suppression occurring in both solid organ transplants and HSCT for malignancies when a lymphocyte or purged graft is infused. Therefore, PTLD is a complication not unique to rabbit ATG but rather secondary to the extent of immune suppression. It is possible that higher doses of equine ATG may also cause PTLD.

Fassas et al., of the Thessaloniki group in Greece, reported that BEAM which consists of carmustine (BCNU), etoposide, cytarabine (ara-c) and melphalar when combined with ATG and lymphocyte depletion of the graft was complicated by mortality from an opportunistic Aspergillosis infection.[29] As phase I studies, the results from three different centers suggest caution in combining lymphocyte-depleted grafts with aggressive immune-suppressive conditioning regimens. This may be accomplished by decreasing the dose intensity of conditioning agents, eliminating one of the conditioning agents, or infusing an unmanipulated graft that is not depleted of lymphocytes.

The only conditioning regimen not reported to be complicated by mortality or late opportunistic infections was a Northwestern and Milwaukee conditioning regimen of cyclophosphamide (120 mg/kg divided over 2 days) and TBI (1200 cGy divided into 150 cGy twice daily) with 50% lung, 20% right lobe of the liver, and 30% kidney radiation blocks.[30] PBSCs were lymphocyte-depleted via CD34 positive selection.

Phase I trials suggest that future transplant conditioning regimens should be less intense. Regimens being proposed in America are, first, the current Northwestern and Milwaukee regimen of cyclophosphamide (120 mg/kg) and TBI (1200 cGy) with vital organ shielding, second, a modified Seattle regimen using TBI (800cGy) with lung shields and cyclophosphamide (120mg/kg) with or without addition of dose-reduced equine ATG (30–60 mg/kg); or, third, an even less immunosuppressive transplant regimen of cyclophosphamide (200 mg/kg) and rabbit ATG (5–6 mg/kg) without T-cell depletion of the graft. For the non-transplant specialist, it is important to recognize that
the details of conditioning regimen intensity and graft manipulation determine toxicity, including risk of infection. In general, less intense immune suppressive regimens have less morbidity and lower mortality. Regimens used for HSCT in patients with MS should be designed to emphasize patient safety.

**Engraftment syndrome**

A unexpected triad of non-infectious fever, rash, and fatigue or lassitude that may also be associated with pruritus, pulmonary symptoms, and eosinophilia may occur around engraftment.\[^{31}\] In MS, fever (independent of its etiology) often causes transient worsening of neurologic symptoms (known as a pseudoexacerbation), owing to slowing of nerve conduction velocity and increased conduction blockade. Not surprisingly, engraftment syndrome is accompanied by fatigue and lassitude. The engraftment syndrome is usually self-limited but may require intervention with systemic corticosteroids. Phase II-III HSCT studies for MS are being designed to include a short course of post-transplant corticosteroids to prevent the engraftment syndrome.

**Outcome**

Fassas et al. have reported a 3-year progression free survival for primary progressive MS (39%), which appears to be significantly lower than for secondary progressive (92%).\[^{29}\] A second study, with a 5-year follow-up, noted potential discordant response between MRI and clinical results.\[^{30}\] Some patients had clinical progression of disability defined as an increase in the expanded disability status score (EDSS) by 1 or more points but no new attacks or change in MRI T2 disease burden. The patients whose EDSS increased despite lack of MRI changes had significant pre-transplant disabilities (EDSS of 7.0–8.5). Although longer follow-up is necessary, it appears that HSCT may limit acute attacks and slow further immune-mediated demyelination but not progressive disability, especially in disease of long duration or severe disability.

Initial phase I HSCT protocols were designed to determine safety. It is difficult to determine efficacy from these studies. Most of the patients had severe long-standing progressive disease. Such patients are not ideal candidates for any type of immune suppressive therapy. Phase II-III studies will need to focus on patients with more inflammatory disease and less disability.

**IMPLICATIONS**

These early observations on limited numbers of patients raise interesting questions about the pathophysiology and causes of disability in MS.
Pathophysiology of MS

A white matter demyelinating autoimmune disease

The view that MS is an autoimmune demyelinating disease comes from neuropathologic, epidemiologic, and experimental observations. First, the acute lesions are inflammatory ‘plaques’ that contain CD4+ and CD8+ lymphocytes, macrophages, and less impressively B cells and plasma cells. Second, genetic studies implicate the immunologically important major histocompatibility complex locus as an important predisposing factor to the disease. Third, the EAE model in which proteins or derived peptides of myelin are used to immunize rodents or subhuman primates to induce a disease that is clinically similar to the human disease is clearly based on an autoimmune response.

In accordance with the view that MS is an autoimmune disease, historically it has been treated with a variety of immune-suppressive medications such as intravenous pulsed corticosteroids, oral corticosteroids, cyclophosphamide, methotrexate, cladribine and azathioprine. More recently approved immune-modulating but not immune-suppressive agents for MS are interferon beta, inducing a Th2 shift in circulating lymphocytes that may limit T-cell migration into the CNS, and glatiramer acetate, a mixture of random peptide sequences containing L-glutamate, L-lysine, L-alanine, and L-tyrosine, which is thought to act as an altered peptide ligand blocking the binding site for myelin peptides on the T cell.

A neuronal disease

Results from neuropathologic studies indicate that axonal destruction in addition to demyelination occurs in MS lesions. Axonal injury or transection has been demonstrated in both acute and chronic CNS lesions. Natural history studies of MRI cohorts indicate that the majority of patients enter a phase of progressive neurologic impairment in concert with reduction or elimination of acute symptomatic attacks. There is a relatively weak correlation between active inflammation as evidenced by gadolinium enhancement or demyelination as monitored by non-specific T2 burden of disease and disability. Clinical disability appears to correlate better with indicators of axonal degeneration, such as increasing ventricular dimension, decreasing spinal cord diameter, and magnetic resonance spectroscopy of neuronal specific N-acetylaspartate (NAA). Recent studies of immunomodulating agents in secondary progressive MS demonstrated reduced relapses and inflammatory MRI activity with conflicting and, at best, modest benefit in delaying progressive neurologic impairments. These observations suggest that the pathogenesis of MS is more complex than simple immune-mediated injury to oligodendrocytes and myelin. One hypothesis generated by these data is that there is a limited period early in the course of the MS when immune-based therapies may be more effective in modifying or preventing subsequent disability.
What causes disability in patients with multiple sclerosis?

There are several possible explanations for neuronal injury resulting from immune-mediated destruction of myelin. ‘Death by injury’ may result from inflammatory cytokines released during demyelination. Myelin may insulate axons from blood or local metabolic oxidants. Therefore, demyelinated axons may be subjected to greater oxidant injury. There is likely a bilateral trophic interaction between axons and oligodendrocytes such that they may function as supporting or ‘nurse’ cells to each other.[44,45] Some axons extend from the brain to the distal end of the spinal cord. This is a huge distance for a microscopic cell, and the nucleus of a neuron may be unable to provide long-term support to a distant axon without other cells within the CNS having a nurturing role. Indeed, primary cultures of mouse neurons survive significantly longer ex vivo if layered over a mixture of non-neuronal CNS cells, including oligodendrocytes and astrocytes.[46,47] Long-standing demyelination may, therefore, lead to ‘death by neglect.’

The ultimate goal of treatment for MS is to prevent accumulative disability. It is likely that axonal degeneration or loss is responsible for irreversible cumulative disability. It is unknown whether therapy directed at suppressing or stopping immune-mediated demyelination has the potential to prevent accumulative disability over the long course of MS. This is unlikely if MS is primarily an axonal degenerative disease with secondary immune-mediated demyelination or if axonal degeneration occurs as a consequence of factors initiated by demyelination but not addressed by immune-based therapies. However, if MS begins as an immune-mediated demyelinating process that causes axonal injury, it is possible that early aggressive interventions may have a profound effect on mitigating subsequent disability. Early intervention in MS is supported by the Controlled High Risk Avonex Multiple Sclerosis Prevention Study (CHAMPS), in which, over a 3-year interval, treatment with interferon following the first clinical event significantly lowered the probability of developing clinically definite MS.[48]

FUTURE TRANSPLANT TRIALS

HSCT is a therapy designed to stop immunemediated demyelination. Phase II-III trial design must take into account that MS may be both an immune-mediated demyelinating disease and an axonal degenerative disease. Therefore, candidates for future studies should be selected early in the disease course to minimize the impact of already established irreversible and progressive axonal degeneration. Outcome measures would include clinical status by EDSS, Scripps Neurologic Rating Scale (NRS), and the Multiple Sclerosis Functional Composite measurement of accumulated atrophy on MRI of the brain and cervical spinal cord, and (potentially) measurements of whole brain NAA on magnetic resonance spectroscopy, which reflects neuronal and axonal integrity. Two possible randomized phase II trial designs are discussed below.
### Relapsing MS with progressive disability

Such a trial would be aimed at suppressing relapses in patients with progressive disability and continued relapses despite conventional therapy. Patients with accumulated baseline deficits but still early inflammatory disease could be considered candidates. This could include ambulatory patients with an EDSS of between 3.0 or 3.5 and 5.5 or 6.0 and continued relapses. Randomization could be between a TBI regimen and a cyclophosphamide regimen with CD34-selected HSC versus mitoxantrone every 3 months for 2 years. For patients with already gradually progressive disease without relapses, immune-based therapies may be insufficient to halt progressive neurologic impairment, particularly since the duration of disease and the level of disability increase.

### Relapsing-remitting MS

This protocol would be aimed at suppressing relapses in patients with minimal disability at entry but with characteristics associated with a high risk of subsequent disability. Weinshenker has reported that the number of relapses within the first 2 years correlates with late disability.\cite{49-51} Confavreux et al. reported that for patients with an EDSS of 4.0 or more (attained after a longer disease duration), the number of relapses does not correlate with progression of irreversible disability to an EDSS of 6.0.\cite{52} Thus, an EDSS of 4.0 or more may already be too late for therapy aimed at inflammatory demyelinating events to prevent progression of subsequent disability. Patients with an EDSS of less than 4.0 and continued relapses despite immunomodulating therapy could be randomized to cyclophosphamide (200 mg/kg) with low-dose ATG and HSCT versus either mitoxantrone or combination therapy with an immunomodulator and adjuvant immune-suppressive drug. Since patients in this study would be earlier in the disease course, a safer conditioning regimen that does not include TBI would be indicated. Cyclophosphamide at 200 mg/kg with ATG has been used safely in a variety of autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and aplastic anemia. If suppression of early demyelinating events is effective in preventing late disability, a safe but intense immune-suppressive regimen might be indicated in patients with early MS but worrisome prognostic factors.

### ACKNOWLEDGEMENT

We dedicate this chapter to the memory of Professor William H Burns. A gentleman, scholar and teacher who taught by example an empathy and compassion for patients and an unending thirst for knowledge.
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Emerging disease-modifying therapies for multiple sclerosis
Karim Makhlouf and Samia J Khoury

INTRODUCTION

The past decade has provided a rich interaction between the fields of neurology and immunology. This has given rise to improved understanding of the pathogenesis of multiple sclerosis (MS) and the development of new therapies that target specific immune pathways. The demyelinating process in MS involves T cells, immunoglobulins, and complement, but recent evidence shows that cytokines, chemokines, adhesion molecules, metalloproteinases, nitric oxide, and oxygen metabolites all participate in the effector stages of the disease and can therefore be potential therapeutic targets. This chapter focuses on some of the emerging therapies based on our new understanding of the immunopathogenesis of MS.

THERAPIES TARGETING T-CELL CO-STIMULATORY SIGNAL BLOCKADE

Background

CD4+ T cells play a critical role in initiating the immune response that ultimately leads to the effector mechanisms mediating autoimmune disease. For T cells to become activated, the T-cell receptor (TCR) must recognize the target antigen in the form of a processed peptide presented on MHC molecules expressed on the surface of antigen-presenting cells (APCs). In the case of autoimmunity, the antigenic peptide is derived from specific autoantigens after processing and presentation by self-APCs. TCR recognition of a peptide-MHC complex provides a signal (signal 1), which results in initial T-cell activation. Full activation, however, does not occur unless the T cell receives a co-stimulatory signal (signal 2) provided by the interaction of specific receptors on T cells with their ligands on APCs. The best-characterized co-stimulatory signal is that provided by CD28 on T cells interacting with the B7 (CD80 (B7–1) and CD86 (B7–2)) family of molecules on APCs. Blockade of this pathway induces a state of antigen-specific T-cell anergy in vitro, and it induces tolerance in experimental autoimmune and transplantation models in vivo.1,2 Another recently characterized T-cell co-stimulatory pathway is provided by interaction of CD40 on the surface of APCs and B cells with the CD40...
ligand (CD40L) on the surface of activated T cells. CD40 may provide a direct co-stimulatory signal for full T-cell activation. There also is evidence that engagement of CD40 and CD40L leads to upregulation of B7 expression on APCs. In addition, CD40-CD40L interaction is important in B cell and monocyte and macrophage activation. CD40-CD40L interaction is essential for B-cell survival and immunoglobulin (Ig) switching. Ligation of CD40 molecules triggers interleukin (IL)-12 production in monocytes and dendritic cells.

Experimental autoimmune encephalomyelitis (EAE) is an inflammatory disease of the central nervous system (CNS) that can be induced in a number of species by immunization with myelin basic protein or its major encephalotogenic peptide and adjuvant. It has been used as a model for the study of MS, and many treatments for MS were initially tested in the EAE model. The effects and mechanisms of inhibiting EAE by blockade of the CD28-B7 co-stimulatory pathway by the fusion protein CTLA4Ig or antiB7 monoclonal antibodies (mAbs) have been investigated by several laboratories. Similarly, blockade of CD40-CD154 interactions was shown to protect mice from clinical EAE. Furthermore, CD40 was identified in MS brain lesions, and expression of CD40 in the CNS of mice correlates with the bouts of clinical symptoms during the course of EAE. Blockade of CD28-B7 or CD40-CD154 pathways was successful in preventing disease or in ameliorating ongoing disease in numerous other autoimmune disease models. The approach of co-stimulatory signal blockade was also successful in preventing transplant rejection.

Clinical trials

Based on the success of this approach in animal models, clinical trials were initiated. A phase I clinical trial of CTLA4Ig (Bristol-Myers Squibb) treatment in psoriasis was completed and showed the treatment to be safe and demonstrated a hint of efficacy in controlling clinical and histologic disease. A phase I clinical trial of CTLA4Ig (RG2077 from Repligen) in MS is in the planning stages, and a phase II trial with the Bristol-Myers Squibb product also is being planned.

Anti-CD154 trials were initiated in several autoimmune diseases by Biogen, but the trials were halted after the occurrence of thrombotic events in lupus patients. A phase I study of antiCD154 (from IDEC) in MS was completed. It included 12 patients with relapsing-remitting disease; the primary outcome measure was safety. The study was designed as a dose escalation study and it showed this antibody to be safe as administered. A phase II study in MS is scheduled to start shortly with this material.

THERAPIES THAT TARGET CYTOKINES

Background

IL-12 is a heterodimeric cytokine produced mostly by phagocytic cells. It induces cytokine production, primarily of interferon (IFN)-γ, from T cells. Several studies in humans and in mice have assigned a role to IL-12 as the promoter of the generation of T-helper type 1 (Th1) cells, acting in antagonism with IL-4, the major
promoter of T-helper type 2 cell responses. Administration of IL-12 to mice after transfer of encephalitogenic cells resulted in increased severity and duration of EAE; treatment with anti-IL-12 antibodies substantially reduced the incidence and severity of adoptively transferred EAE. IL-12 message has been detected in MS brains, and increased anti-CD3-induced IL-12 secretion has been found in patients with progressive disease. Elevated serum levels of IL-12 have been reported in the chronic progressive form of MS. It has recently been reported that IL-12 production is elevated in monocytes from MS patients and that treatment with monthly cyclophosphamide and methylprednisolone boosters normalized IL-12 production. Furthermore, IL-12 production has been found to be linked to disease activity, with higher production in patients with active disease and in patients with gadolinium-enhancing lesions on magnetic resonance imaging (MRI). Because of its key role in MS and EAE, treatments targeting IL-12 are of potential interest in MS.

Clinical trials

Salbutamol (albuterol in the USA) is a β-2-adrenergic agonist that selectively inhibits the production of IL-12 by human monocytes in vitro and in vivo in healthy subjects, through increased intracellular cyclic adenosine monophosphate (cAMP). In animal models of autoimmune disease, β-2-agonists were shown to suppress chronic relapsing EAE in Lewis rats and to suppress collagen-induced arthritis, a murine model for rheumatoid arthritis. Furthermore, β-2-adrenergic receptor expression is increased on peripheral blood mononuclear cells of patients with MS and is correlated with clinical and MRI disease activity. It has been shown that oral administration of salbutamol decreases the percentage of IL-12-producing monocytes in patients with progressive MS. Its efficacy as an add-on therapy to glatiramer acetate is currently being tested in a phase II study.

Another class of drugs, the phosphodiesterase inhibitors, also target cAMP and increase its intracytoplasmic level by inhibiting its degradation by phosphodiesterase. Rolipram, a type IV phosphodiesterase inhibitor, is the most extensively studied. It was shown to suppress IL-12 in mice and to prevent EAE in rats and in non-human primates. An additional protective mechanism for rolipram in EAE in mice is its ability to reduce permeability of the blood-brain barrier. Although mostly known as an antidepressant in humans, rolipram has, like salbutamol, a therapeutic potential in autoimmune diseases mediated by Th1 cells and is now being tested in a clinical trial in MS patients.

THERAPIES THAT TARGET ADHESION MOLECULES

Background

Adhesion molecules promote cell-cell and cell-extracellular matrix interactions. As a result, they are involved in many steps of the immune response, in particular in the migration of inflammatory cells through the blood-brain barrier into the CNS. They are classified into three families according to their structure: Ig superfamily members,
integrins, and selectins. The expression of intercellular cell adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 is up-regulated on brain microvessel endothelial cells in active lesions of MS,[44] concomitant with up-regulation of the expression of their respective receptors on leukocytes (leukocyte function antigen (LFA)-1 for ICAM-1 and very large antigen (VLA)-4, also named α-4-integrin, for VCAM-1).

Anti-α-4 integrin mAb treatment reduced cellular infiltration in the CNS and inhibited development of EAE in rats and guinea pigs.[45,46] It also reversed the ongoing disease process in the guinea pig.[47] Anti ICAM-1 mAb inhibited EAE in rats,[48] although in another study, neither anti-ICAM-1 nor anti-LFA-1 could alter the course of EAE.[49] However, ICAM-1-deficient mice develop more severe EAE than controls,[50] suggesting that ICAM-1 plays an important role in down-regulating autoimmune inflammation in the CNS.

Circulating ICAM-1 is the most studied adhesion molecule in MS: its serum levels are elevated in active relapsing-remitting MS, and soluble ICAM-1 levels correlate with MRI disease activity.[51,52]

Clinical trials

In 1999, a randomized, double-blind, placebo-controlled trial of a humanized anti-α-4 integrin antibody was performed on 72 patients with relapsing-remitting or secondary progressive MS.[53] This study showed a significant reduction in the number of new active lesions on MRI. The drug was given intravenously and was well tolerated, but the study was not designed to look at the effect on the relapse rate. More recently, the results of a phase II clinical trial with a humanized anti-α-4 integrin antibody (natalizumab) were reported at the 2001 annual meeting for the European Committee on Treatment and Research in Multiple Sclerosis. A placebo-controlled trial of 213 patients with relapsing-remitting or secondary progressive MS was conducted at 26 sites in the USA, Canada, and the UK by Elan Pharmaceuticals. The study included two dose groups (3 mg/kg and 6 mg/kg) and a placebo group. Treatments were administered intravenously at 4-week intervals for 6 months. The primary analysis showed that patients treated with natalizumab for 6 months had fewer gadolinium-enhancing lesions than patients receiving placebo. Phase III clinical trials with natalizumab as a single agent or as an add-on to interferon beta-1a have been initiated.

THERAPIES THAT TARGET MATRIX METALLOPROTEINASES

Background

Matrix metalloproteinases (MMPs) are a family of zinc-containing endoproteinases that share structural domains but differ in substrate specificity, cellular sources, and inducibility. MMPs can degrade any protein component in the extracellular matrix, including but not limited to membrane-bound adhesion molecules, cytokine precursors and receptors, and proforms of MMP. Most MMPs are secreted by a wide range of cell types as proenzymes that need to be cleaved in order to get activated. Except for the...
membranetype MMP, all other MMPs are secreted into the extracellular space, including in the CNS, where their lytic activity has to be finely regulated to avoid potential tissue destruction.

In animal models, the injection of MMP-7, MMP-8 and MMP-9 in the brain parenchyma of rats is followed by breakdown of the blood-brain barrier and leukocyte recruitment into the CNS.\[54\] MMP-7 and MMP-9 mRNA expression is dramatically up-regulated at the peak of clinical disease in EAE.\[55\] Some MMP inhibitors can suppress the development of EAE in rats\[56\] or reverse ongoing clinical EAE in mice.\[57\]

There is evidence that MMPs are also involved in the breakdown of the blood-brain barrier in MS patients. MMP-9 was increased in the CSF of MS patients during clinical relapses.\[58\] High serum MMP-9 levels were significantly associated with more T1-weighted gadolinium-enhancing MRI lesions.\[59\] Treatment with high-dose methylprednisolone (which is known to down-regulate MMP) reduced both MRI gadolinium-enhancing lesions and CSF levels of MMP-9 in MS patients.\[60\]

Clinical trials

There are no ongoing trials with MMP inhibitors in MS, but such drugs are currently being tested in other autoimmune diseases and cancers.\[61\] Naturally occurring MMP inhibitors, called tissue inhibitors of metalloproteinases, are involved in the regulation of MMP expression, and it has been suggested that an abnormality in the inhibitory response to MMPs might play an etiological role in the chronicity of MS.\[59\]

THERAPIES THAT TARGET NEUROPROTECTION

Background

Axonal pathology appears early in the disease course of MS and may play a critical role in disease progression.\[62\] However, it is still unclear whether axonal pathology is the primary event or whether it is a consequence of neuronal toxicity. Neuronal toxicity may be mediated by components of the immune system or through excitotoxicity. L-glutamate (Glu) is the most widespread excitatory transmitter system in the vertebrate CNS. Glu mediates its effects through two general classes of receptors, those that form ion channels (‘ionotropic’ receptors), such as the kainate, AMPA, and N-methyl-D aspartate receptors, and those that are linked to G-proteins (‘metabotropic’ receptors). Glu is produced not only by neurons and glial cells, but also by cells of the immune system, such as macrophages and T cells, and Glu receptors are expressed both in neuronal and glial membranes. It was reported that activated immune cells release large amounts of Glu in the murine CNS.\[63\] and like neurons, oligodendrocytes are highly sensitive to AMPA and kainate receptor-mediated death.\[64\] Further-more, Glu degradation is down-regulated in astrocytes during EAE, owing to reduced expression of glutamine synthetase and glutamate dehydrogenase, thus leading to an increase of Glu in the CNS.\[65\] Recently, NBQX, an AMPA and kainate receptor antagonist, was shown to improve clinical EAE and to increase oligodendrocyte survival without reducing the lesion size or the degree of CNS inflammation in SJL mice\[66\] and in Lewis rats.\[67\] This finding suggests that Glu
excitotoxicity is an important mechanism in autoimmune demyelination. In humans the level of Glu was increased in the CSF of patients during acute attacks of MS.[68] Also, serum Glu is elevated during relapses.[69]

**Clinical trials**

AMPA antagonists are now being tested in stroke patients. There are no clinical trials of Glu receptors antagonists in MS patients.

**CONCLUSIONS**

Modern biotechnology and improved understanding of the immunopathology of MS have led to the development of new therapeutic targets for the disease. Most of the strategies outlined in this chapter are in the early phases of clinical investigation. Although it is not always straightforward to extrapolate from animal studies to humans, EAE and other animal models of MS have made it possible to bring to MS patients new effective treatments and new hopes for their disease.

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Combination therapies in multiple sclerosis

Christian Confavreux

BACKGROUND

Since 1993, the field of multiple sclerosis (MS) therapeutics has changed dramatically. Positive results of well-designed and well-conducted prospective multicenter, randomized, double-blind, placebo-controlled phase III trials have been published. This led to approval by North American and European regulatory agencies of interferon beta-1b, interferon beta-1a and glatiramer acetate for relapsing-remitting MS. The same process has led to approval in Europe of interferon beta-1b for secondary progressive MS.

Thousands of patients have already used one or more of these disease-modifying agents. The experience has not always been positive. This may not be surprising, considering that the level of efficacy of the interferons is limited to a one-third reduction in relapse rate and an approximately 10% absolute reduction of the proportion of patients with sustained worsening by at least 1 point on the Kurtzke expanded disability status score (EDSS). In daily practice, it appears that some patients respond well to current therapies, while others are much less responsive. Current therapies are also limited by the need for parenteral administration and by local and systemic adverse effects. Consequently, there is a clear and urgent need for more effective, more convenient, and better tolerated therapies.

Several approaches can be considered for future experimental therapeutics in MS. First, further studies could be performed of immunoactive drugs used as monotherapy, with the hope that a new agent will be superior to presently available agents in terms of efficacy, acceptability, tolerance, immediate and long-term safety, and cost. There are a number of drugs deserving to be tested in MS, some of which are already in phase I studies. There are no clear approaches to prioritizing these candidate agents, as our understanding of the pathogenesis of MS and the mechanisms of action of the drugs are not adequate to predict the results of clinical trials. This is a major problem, considering the limited number of patients available for clinical trials, and the finite resources for MS studies.

Second, trials based on new disease concepts could be performed. An outstanding example could come from the study of pregnancy in MS. The effect of pregnancy on MS measured by clinical and magnetic resonance imaging (MRI) activity is more marked than the effect of current disease-modifying agents. A better understanding of the biological mechanisms by which the fetal allograft is tolerated during pregnancy could lead to new and effective therapeutic strategies in MS.

Third, focused studies for optimizing the use of available agents could be performed. For instance, the use of current drugs at the first neurological episode compatible with...
MS may result in long-term benefits. Two prospective therapeutic trials using interferon beta-1a in this setting have showed that this strategy was able to delay the occurrence of the second neurological symptom,[13,14]

Finally, combinations of the currently available disease modifying agents could be used. This approach is the subject of this chapter.

RATIONAL FOR COMBINATION THERAPIES IN MS

Combination therapy has been used successfully for years in cancer and infectious diseases. A combination of various antibiotics is required for effecting cure in active tuberculosis and preventing the emergence of drug-resistant strains of Mycobacterium tuberculosis. More recently, the introduction of triple-drug combinations for human immunodeficiency virus infection reduced the viral load to undetectable serum levels and dramatically changed the clinical course and the prognosis in patients with AIDS. Similar progress has been observed in patients with chronic hepatitis C.[15] The addition of ribavirin (a synthetic guanosin analog with in vitro activity against several viruses) to interferon alfa-2b resulted in a sustained virological response with the disappearance of hepatitis C viremia in 31–43% of patients when used as initial therapy,[16,17] and in 49% when used for the treatment of a relapse after initial treatment with interferon.[18] Comparative rates achieved in these trials with interferon as a monotherapy ranged from 5% to 19%.

Combination therapy has also been explored in autoimmune diseases, notably rheumatoid arthritis.[19,20] Results show that not all combinations are equivalent in terms of efficacy and toxicity. For instance, the addition of gold[21] or azathioprine[22] to methotrexate was not more effective than monotherapy. The addition of hydroxychloroquine to gold was marginally more effective than gold alone, but also more toxic.[25] In contrast, the addition of cyclosporine to methotrexate,[24] of sulphasalazine and hydroxychloroquine to methotrexate,[25] of step-down prednisolone and methotrexate to sulphasalazine,[26] and of infliximab (a chimeric antitumor necrosis factor (TNF)-α monoclonal antibody) to methotrexate[27] were significantly more beneficial than monotherapy, without significant additional toxicity. Some combinations have led to dramatically improved results in comparison with monotherapy. For instance, when etanercept, a recombinant TNF receptor-Fc fusion protein was added to methotrexate,[28] the proportion of patients with a 20% improvement in clinical disease activity at 24 weeks increased from 27% for monotherapy to 71% with the combination; the proportion of patients with a 50% improvement increased from 3% with monotherapy to 27% for the combination.

Combination therapy in MS will probably be required, since it appears that multiple environmental and genetic factors play a role in the disease.[29] Viruses may trigger the disease, although no persistent viral infection has been clearly demonstrated during the clinically overt stage of MS. Chronic immune dysregulation ultimately targeting central nervous system (CNS) myelin is postulated to result in CNS injury. The mechanism is postulated to be cell-mediated autoimmunity, possibly due to defective T-cell suppressor function, brought about by altered immunological balance with a shift away from anti-inflammatory T-helper type 2 (Th2) cell responses towards pro-inflammatory T-helper
type 1 (Th1) cell responses. Owing in part to epitope spreading, there is not a single myelin antigen involved in MS pathogenesis. For these and other reasons, there are presumably different subtypes of MS.\textsuperscript{[30]} This may explain why patients respond to each effective monotherapy to a variable degree.\textsuperscript{[29]} Lastly, to cover the full scope of MS pathology, strategies for brain repair through protection and regeneration of axons and myelin will need to be implemented.\textsuperscript{[31]}

**GUIDELINES FOR COMBINATION THERAPIES IN MS**

The first question is which therapies to include in the combination. To improve the chances of additive or, even better, synergistic beneficial effects, a candidate drug for combination therapy should have a beneficial effect on the outcome criteria and should have a mechanism of action different from the other anticipated therapy. In the case of MS, drugs could be directed at different therapeutic domains such as tissue destruction and tissue repair. But the concept also holds within a given therapeutic domain. For example, presently available therapies act through modulating the immune system, but at different levels. Theoretically, in vitro or animal data could direct the choice among several candidate therapies. Unfortunately, results from such experiments do not necessarily predict results in MS patients. The most famous example is interferon gamma. It was shown to be effective in preventing experimental allergic encephalomyelitis (EAE), but it induced relapses when given to MS patients.\textsuperscript{[32]} Similarly, oral myelin administration is a potent method to induce myelin tolerance. This therapeutic strategy is highly effective in EAE.\textsuperscript{[33]} Despite the encouraging results of a small pilot trial,\textsuperscript{[34]} a large scale North American phase III trial failed to demonstrate significant clinical or MRI benefits over placebo.\textsuperscript{[35]} More recently, blocking the pro-inflammatory cytokine TNF-\(\alpha\) provided disappointing results.\textsuperscript{[36–38]}

Importantly, safety and tolerability also have to be taken into account. Each therapy in the combination must have an acceptable profile in this respect. Ideally, toxicity might be lessened with the combination by decreasing the dosage of each individual agent. This has been one of the rationales for combining azathioprine and corticosteroids in the treatment of myasthenia gravis.\textsuperscript{[39]} In practice, in a disease such as MS that afflicts relatively young subjects and does not significantly reduce life expectancy, drugs with a low level of side-effects and a good long-term safety profile should be selected preferentially.

The second question is how to test combination therapy in MS patients. Clearly, a preliminary evaluation of safety and tolerability of the combination is needed. The rationale for that is threefold: first, checking, by clinical and biological monitoring at regular intervals, that the combination is acceptably safe and well tolerated with respect to vital functions; second, assessing, by appropriate pharmacological assessments, the impact of the combination on the pharmacokinetics of each individual drug in the combination; and third, searching for hints of efficacy or, conversely, adverse interaction, by using relatively sensitive clinical criteria such as relapses or surrogate markers such as brain MRI activity on serial T2-weighted or gadolinium-enhanced T1 sequences.

The design of such phase II studies is simple when the combination consists of two drugs, A and B. It becomes more complex when the combination consists of more agents.
A tentative solution is illustrated in Fig. 31.1. The study begins with a run-in period of each single therapy followed by the addition of a second agent to each monotherapy, and with a third drug eventually added to each double combination of agents, and so on. Appropriate clinical and paraclinical monitoring must be done throughout the study. Such phase II studies should take place before a large phase III efficacy study, but this strategy may prove time-consuming and may delay a phase III study. This is a major problem in MS, where definitive phase III trials require years with presently available outcome criteria. In order to save time and money, an alternative could be to combine phase II and III studies with rigorous monitoring of safety and tolerability of the drug combination during the initial stages of the trial. Completion of the trial could be contingent on analysis of the initial part of the trial.

The third question is how to design the phase III efficacy trial. Ideally, a full factorial 2×2 design is recommended, with the use of a placebo for each single agent (Fig. 31.2). Combining two single agents (A and B) results in four cells, one with patients taking placebo A plus placebo B. In practice, such a design becomes unrealistic when combining three or more agents. Furthermore, this design is inappropriate on ethical grounds and may not be feasible when one drug is already approved for use as standard therapy in the population of patients to be enrolled. The study design, therefore, will be influenced by currently approved treatments. At the present time, combination therapy in relapsing-remitting MS must be compared with interferon-beta or glatiramer acetate as standard monotherapy. For secondary progressive MS, combination therapy must be...
compared with interferon beta-1b, at least in the European Union. In these clinical situations, a placebo arm is not acceptable, unless the study period is very short. By contrast, a placebo arm is acceptable and appropriate at the present time for studies in primary progressive MS, for which no approved disease-modifying drug is currently available.

These considerations concern combination therapies in which agents are used in parallel. For combination strategies of the sequential type (e.g. an induction phase followed by a maintenance phase), a conventional parallel design is appropriate.

**PRESENTLY AVAILABLE DATA ON COMBINATION THERAPIES IN MS**

**Experimental data**

From experimental models of MS, there are some indications that the therapeutic response is greater with drugs in combination than with either single drug. This has been shown with antagonists of the pro-inflammatory cytokines (TNF-α) and interleukin (IL)-1 in acute EAE in Lewis rats,[40] and with the anti-inflammatory cytokines IL-4 and IL-10 in Theiler’s virus-induced encephalomyelitis.[41] There are also in vitro studies demonstrating additive effects of glatiramer acetate and interferon beta-1b on inhibition of cellular immune reactivity to myelin basic protein.[42] However, the addition of glatiramer acetate to interferon beta proved to be of no benefit in acute murine EAE.[43,44]
Lastly, all-transretinoic acid was shown to potentiate the ability of interferon beta-1b to augment suppressor cell function in MS.\[45\]

**Progressive phase**

Results of relatively prolonged combination therapy in MS were first published for progressive MS. In a randomized, placebo-controlled, single-masked trial, 57 patients received low-dose oral cyclophosphamide and prednisone and weekly plasma exchanges for 22 weeks.\[46\] Patients were followed for a mean of 30 months. Comparison with 56 patients receiving placebo medication and sham plasma exchanges did not show any significant difference in terms of the proportion of patients with a confirmed worsening of 1.0 point or more on the EDSS.

More recently, in a pilot trial with a randomized, single-masked cross-over design involving 11 patients, brain MRI activity was assessed during a 24-week period of plasma exchange in combination with azathioprine and a control period of similar duration.\[47\] No significant difference was found between the two periods.

**Relapsing-remitting MS**

In relapsing-remitting MS, initiation of interferon beta therapy is associated with a flu-like syndrome and transient induction of TNF-\(\alpha\) and IFN-\(\gamma\). As recently shown in a pilot trial, clinical symptoms and cytokine changes can be significantly reduced by pentoxifylline, a phosphodiesterase inhibitor.\[48\] Furthermore, this combination enhances induction of the antiinflammatory cytokine IL-10 obtained with interferon beta-1b alone. The net result is normalization of the disturbed cytokine balance that is characteristic of MS, with a shift from a Th1 to a Th2 profile. However, long-term effects of this combination therapy on the course of MS are unknown.

In an open pilot trial involving 38 MS patients, monthly infusions of intravenous immunoglobulins were added to daily azathioprine for 3 years.\[49\] According to the authors, this combination resulted in a dramatic reduction in the number of relapses and a slight decrease in the EDSS score.

The combination of interferon beta-1b and azathioprine is being explored in relapsing-remit-ting MS within the ERAZIMUS project (EaRly AZathioprine and Interferon-\(\beta\) in MUltiple Scler osis).\[9\] These drugs in combination may have additive or synergistic efficacy in relation to their immunosuppressive, immunomodulatory, and anti-inflammatory effects, all of which have different mechanisms of action. Another potential mechanism of synergy could be the prevention of anti-interferon antibody production by azathioprine treatment, since neutralizing antibodies may cause waning therapeutic efficacy in interferon-treated patients.\[50,51\] A phase II study aimed at assessing the clinical and biological safety and tolerability of the combination has been completed. Thirty patients with relapsing-remitting MS already receiving azathioprine treatment for at least 6 months have been enrolled. Three different azathioprine dose groups of 10 subjects each have been studied consecutively: 50 mg, 100 mg or 150 mg daily. After enrollment, the patients received the first intramuscular injection of interferon beta-1a (6 MIU) followed by a weekly injection for 4 months. The safety profile of the combination was evaluated through hematology and biochemistry parameters and clinical assessment.
at specific time points throughout the study. Possible metabolic interaction of the two drugs was evaluated through serum neopterin and erythrocyte 6-thioguanine nucleotide assessments. This phase II trial has shown biological and clinical safety and tolerability of interferon beta-1a combined with azathioprine. A phase III trial aiming at assessing the efficacy of this combination was ready to be launched but eventually had to be abandoned for lack of sufficient funding.

A similar rationale has led to the assessment of the interferon-methotrexate combination. In an open trial involving 15 patients with relapsing-remitting MS, weekly oral methotrexate at a 20-mg dose was administered for 6 months as an add-on therapy to interferon beta-1a. To be eligible, patients were required to have been on interferon beta-1a for at least 1 year with at least one relapse. The most common side effect was nausea. In comparison with baseline, there was a significant (40%) reduction in the number of gadolinium-enhancing lesions on brain MRI \( (p=0.02) \), a trend towards fewer exacerbations, and no significant changes in the EDSS and the MS Functional composite scores. This combination, therefore, is another good candidate for a phase III trial of efficacy.

A trial to determine whether combined therapy with interferon beta-1a and glatiramer acetate is safe, as measured by MRI activity over a period of 6 months, has just been completed. A total of 33 patients with relapsing-remitting MS were enrolled. Preliminary results showed this combination to be safe and appropriate for a large-scale efficacy study.

MALIGNANT RELAPSING-REMITTING MS

Promising results of an open pilot trial were published. The trial involved a highly selected population of 10 patients suffering from ‘rapidly transitional’ MS with frequent relapses and rapid progression of disability, despite administration of interferon beta monotherapy for 12–16 months. Patients received intravenous infusions of cyclophosphamide (500–1500 mg/m\(^2\)) as an add-on therapy to produce a chronic lymphopenia (range, 600–900 mm\(^3\)). Infusions were administered monthly for the first 12 months, and then every 2 months. Assessment of this combination of interferon beta and cyclophosphamide was performed at 18 months. Relapses were suppressed in most patients. The mean EDSS was reduced by more than 50% by comparison with the previous period with interferon beta administered as a monotherapy. T2 lesion load on the brain MRI scans also was reduced. This trial confirmed the efficacy of immunosuppressants on the inflammatory component in MS. Its results require confirmation by better designed and more powerful trials. However, they already suggest therapeutic strategies for patients not responding to interferon beta.

THE PRESENT AND THE FUTURE

At present, anecdotal experience is accumulating in many centers about combination therapy in MS patients who do not respond to the currently approved disease-modifying drugs. To the author’s knowledge, no major adverse effect has been reported in
There is no direct relation to any combination of classic immunosuppressants, corticosteroids, interferon beta, or glatiramer acetate. It is impossible to draw any reliable conclusion about the efficacy of these combination strategies. As recently illustrated by the ERAZIMUS project, it is uncertain whether methodologically acceptable phase III trials that aim at assessing the efficacy of combination of classic immunomodulating drugs will be performed. They are indeed expensive, as for any phase III trial in MS, and they are not the top priority—whatever the reason—for the pharmaceutical industry. It is still to be demonstrated whether public health agencies are willing to promote and support such studies.

Despite these difficulties, structured efforts are developing. A French and Italian prospective, randomized controlled trial with blinded assessment at endpoint was launched in 1999 to assess the efficacy on clinical progression of an induction therapy with monthly infusions of mitoxantrone for a 6-month period followed by a maintenance therapy with interferon beta-1b. Comparison will be made with a control group treated with interferon beta-1b alone. Study treatment is for 36 months. Eligible patients have clinically active relapsing-remitting MS. To date (as of January 2002), 86 patients have been enrolled. A total of 124 patients is planned.

A prospective, randomized, double-blind, placebo-controlled trial of low-dose azathioprine and corticosteroids as an add-on therapy to intramuscular interferon beta-1a is in progress in the Czech Republic. A total of 105 patients with relapsing-remitting MS are to be enrolled. The study is for 2 years. Intermediate results showed a beneficial effect on the relapse rate of the combination therapy in comparison with interferon beta-1a monotherapy. No unacceptable side effect has been observed.

The first large-scale prospective multicenter, randomized, double-blind, placebo-controlled phase III trial of a combination therapy in MS started in January 2002. Its aim is to assess the efficacy, tolerance, and safety of natalizumab administered in intravenous infusions at monthly intervals, at a dose of 300 mg as an add-on therapy to weekly intramuscular injections of interferon beta-1a (30 µg). Natalizumab is a humanized monoclonal antibody directed against α4-β1 integrin that prevents adhesion and transmigration of lymphocytes through the vascular endothelium. A phase II trial involving 213 patients with relapsing-remitting MS showed a dramatic reduction in the number of new lesions on monthly MRI and a 50% reduction in the number of relapses in the treated groups in comparison with the placebo group during the 6-month period of treatment. No rebound effect was observed during the 6-month period following the cessation of natalizumab. Tolerance has been good with the exception of one instance of anaphylactoid reaction and two instances of serum sickness in the treated groups. These results and a mechanism of action clearly distinct from that of interferon beta render the combination of natalizumab and interferon beta attractive. The phase III combination trial is planned to enrol 1200 ambulatory patients with relapsing-remitting MS and continued activity despite treatment with interferon beta-1a for 12 months or longer. The treatment will last for 2 years. Results are expected at the end of 2004.
CONCLUSIONS

There are quite a number of drugs that deserve to be tested in combination therapy in MS.\(^{[60]}\) Realistically, protocols of combination therapy should include at least one drug already known to be beneficial and follow the add-on design, at least for relapsing-remitting MS and secondary progressive MS. Assessment of efficacy should be performed by comparison with the standard approved treatment. However, the sensitivity of conventional outcome measures, which is already low in untreated MS patients, is even lower in patients treated with the approved drugs. For instance, interferon beta reduces new MRI lesions in such a dramatic way that it may not be possible to measure additive effects on that parameter. In practice, this leads to an increased sample size and longer trial durations. One solution to this might lie in defining new outcome criteria with higher sensitivity, reliability, and predictive value. Great efforts are being put to that end, but their validity is still to be demonstrated. Alternatively, the efficacy of combined therapies could be assessed more quickly and convincingly by focusing on particular clinical situations, such as very active disease or individual cases for which approved treatments have proved to be unsatisfactory in monotherapy. Escalating doses of the add-on therapy depending on the clinical response could also be an appropriate strategy within pilot trials. Another difficulty lies in the collaboration of different drug companies that may be required for implementation of such trials, which is not an easy matter to deal with. However, discouraging these obstacles may be, combination therapy is undoubtedly an exciting emerging field in MS.

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Sex hormones and other pregnancy-related factors with therapeutic potential in multiple sclerosis
Rhonda R Voskuhl

INTRODUCTION

It has been appreciated for decades that the symptoms of patients with autoimmune diseases are affected by pregnancy and the postpartum period. The best characterized observations include those in multiple sclerosis (MS) and rheumatoid arthritis. Patients with these conditions experience clinical improvement during pregnancy with a temporary ‘rebound’ exacerbation postpartum.\[1–10\] This chapter focuses on mechanisms that may underlie this protection against disease during pregnancy in MS. This phenomenon of an improvement in disease during pregnancy is a unique opportunity to gain insight into MS disease pathogenesis and to capitalize on a naturally occurring situation in which the disease is down-regulated. Understanding disease-modifying mechanisms during pregnancy may lead to the identification of factors with therapeutic potential for MS. Furthermore, the therapeutic potential of an identified factor might be beneficial not only in MS but also in other autoimmune diseases characterized by significant improvement during pregnancy, such as rheumatoid arthritis.

THE EFFECT OF PREGNANCY ON MS

Most MS patients have either a relapsing-remitting course or a secondary progressive course. The relapsing-remitting phase is characterized by a higher incidence of gadolinium-enhancing lesions on cerebral magnetic resonance imaging (MRI) and by clinical relapses. In many patients with relapsing-remitting MS, the changes to secondary progressive MS, which is a less inflammatory disease with a much lower incidence of enhancing lesions on MRI and gradual neurological decline.\[11\] There are currently three available therapies with proven benefit in relapsing—remitting MS—interferon beta-1b, interferon beta-1a (available in two forms), and glatiramer acetate. All of these therapies are thought to act through anti-inflammatory mechanisms.\[12–15\] Therefore it is not surprising that all of these therapies have been shown to be more effective in relapsing-remitting MS than in secondary progressing MS. Indeed, they are all of demonstrated benefit in relapsing-remitting MS whereby a significant reduction in gadolinium-enhancing lesions and a reduction in relapse rates have been shown compared with
placebo control. On the other hand, they remain of questionable benefit in secondary progressive MS.\cite{16} This difference in therapeutic efficacy between the two phases of the disease is probably due to differences in immunopathogenesis. Two hypotheses, which are not mutually exclusive, are that inflammation is more important in the relapsing-remitting phase whereas axonal pathology is more important in secondary progressive phase,\cite{17,18} and that the nature of the immune dysregulation differs between the two phases.\cite{19–21}

What is the precise effect of pregnancy on MS? Although it has been observed for decades that MS improves in late pregnancy, early studies did not separate the MS patients into relapsing-remitting and secondary progressive groups.\cite{1–3} However, it was generally noted that there was a period of relative ‘safety’ with regard to relapses during pregnancy followed by a period of increased relapses postpartum. These clinical observations were supported by a small study of two patients who underwent serial cerebral MRI scans during pregnancy and postpartum. In both women, there was a decrease in MRI disease activity (T2 lesion number) during the second half of pregnancy and a return of MRI disease activity to pre-pregnancy levels in the first months postpartum.\cite{9} Other studies found that, in addition to there being a decrease in disease activity in patients with established MS, the risk of developing the first episode of MS was decreased during pregnancy compared with non-pregnant states.\cite{8} The most definitive study of the effect of pregnancy and the postpartum period was published in 1998 by Confavreux et al.\cite{4} Relapse rates were determined in 254 women with MS during 269 pregnancies and for up to 1 year after delivery. Relapse rates were significantly reduced from 0.7 per woman year in the year before pregnancy to 0.2 during the third trimester. Rates then increased to 1.2 during the first 3 months postpartum before returning to pre-pregnancy rates. No significant changes were observed between relapse rates in the first and second trimesters compared with the year before pregnancy. Together these data clearly demonstrated that the latter part of pregnancy is associated with a significant reduction in relapses, whereas there is a rebound increase in relapses postpartum.

Since the late part of pregnancy is associated with a reduction in relapses and the postpartum period with a transient increase in relapses, what is the net effect of pregnancy on the accumulation of disability? The net effect may be a positive one. Two studies have shown that the development of disability is reduced with pregnancy. A study by Damek and Shuster suggested that a full-term pregnancy increased the time interval to reach a common disability endpoint (walking with the aid of a cane or crutch).\cite{6} In essence, pregnancy increased the time interval to having a secondary progressive course. Run-marker and Andersen compared the risk of change from a relapsing-remitting course to a secondary progressive course in women who were pregnant after MS onset with that in women who were not pregnant after MS onset, with the two groups matched for neurological deficit, disease duration, and age.\cite{8} There was a significantly decreased risk of a progressive course in women who were pregnant after MS onset compared with those who were not pregnant. The fact that the patients were matched for neurological deficit, disease duration, and age is extremely important in this study, for one might predict that there might be a selection bias such that women with less disability would be more likely to get pregnant and a difference in baseline disability could explain the longer time interval to reach secondary progressive disease. Careful matching of the groups
made this explanation unlikely and, therefore, the study indeed provided support for a net beneficial effect of pregnancy on the accumulation of disability in MS.

While there is a clear short-term effect of pregnancy on decreasing relapse rates and possibly a long-term effect of pregnancy on increasing the time interval to reach a given level of disability, there appears to be no conclusive data supporting a long-term effect of pregnancy in healthy women and their subsequent risk of developing MS. One study reported that women of parity 0–2 developed MS twice as often as women of parity 3 or more, thereby implying a protective effect of multiple pregnancies, but the difference did not reach statistical significance.[22] Another study found no association between parity and the subsequent risk of developing MS.[23] Together, these data indicate that pregnancy in healthy women has no long-lasting effects with regard to reducing their risk of developing MS in the future, and hence that pregnancy does not have a permanent effect on the immunopathogenesis of MS. However, if women with MS get pregnant, it will indeed be associated with a temporary reduction in relapses during the pregnancy and it may ultimately take such women longer to reach a given stage of disability. The delay in the development of disability in MS patients with multiple pregnancies is probably due to the fact that these women have had several time periods in which they were protected from relapses. The effect of pregnancy appears to be similar to what is observed when patients take the approved anti-inflammatory therapies for MS: relapses are reduced temporarily when patients are on the treatments but when they are discontinued, relapses return. Theoretically, if patients were pregnant enough times or on the anti-inflammatory treatments for a long enough time, there would be some improvement in ultimate disability.

THE IMMUNOLOGY OF MS AND THE IMMUNOLOGY OF PREGNANCY

Since mechanisms of action of the approved injectable therapies for MS involve anti-inflammatory effects and since these treatments result primarily in a reduction in relapse rates, it is logical to hypothesize that mechanisms of action of the protective effect of pregnancy on MS involve anti-inflammatory effects. In order to understand why late pregnancy might exert an anti-inflammatory effect on MS, one must review both the immunopathogenesis of relapsing-remitting MS and the known changes that occur in the immune system during pregnancy.

MS is a demyelinating disease of the central nervous system (CNS) that is thought to be mediated by myelin protein-specific CD4⁺ T lymphocytes secreting T helper cell type 1 (Th1) cytokines such as interferon gamma (IFN-γ) (IFN-γ). T cells and macrophages infiltrate the CNS and secrete pro-inflammatory cytokines such as IFN-γ, interleukin (IL)-12 and tumor necrosis factor (TNF)-α, which then set off a cascade of events that ultimately lead to demyelination of axons. This acute demyelination leads to conduction block of neurons, and a clinical relapse results: a deficit in the function served by the affected neuronal pathway.[25] In contrast to the deleterious Th1 responses described above, T helper cell type 2 (Th2) responses, which include the production of cytokines such as IL-4, IL-5, IL-6, and IL-10, are thought to be beneficial in MS. In murine systems, Th1 and Th2 immune responses are counter-regulatory and, in states of health,
exist in a delicate balance.\textsuperscript{[26]} While there are clearly some differences in human and murine systems, therapies for MS have aimed at either reducing Th1 responses or at increasing Th2 responses, thereby causing a therapeutic immune deviation. Indeed, while the currently available therapies that have demonstrated benefit in relapsing-remitting MS (i.e. interferon beta-1b, interferon beta-1a, and glatiramer acetate) have numerous possible mechanisms of action, several reports indicate that they act, at least in part, through this therapeutic immune deviation.\textsuperscript{[12–15]}

Pregnancy is a challenge for the immune system. From the mother’s standpoint, the fetus is an allograft, since it harbors antigens inherited from the father. It is evolutionarily advantageous for there to be a transient suppression of cytotoxic, cell-mediated, Th1-type immune responses that would result in fetal rejection during pregnancy. However, not all immune responses should be suppressed, since humoral Th2-type immunity is needed for passive transfer of antibodies to the fetus. Thus, a shift in immune responses with a down-regulation of Th1-type responses and an up-regulation of Th2-type responses is thought to be necessary for fetal survival.\textsuperscript{[26–29]} It has been shown in both mice and humans that failure to shift immune responses in this manner results in an increase in spontaneous abortion.\textsuperscript{[28,30,31]} This shift in immune responses from Th1 to Th2 occurs both locally at the maternal-fetal interface,\textsuperscript{[26,32,33]} as well as systemically.\textsuperscript{[28,31,34–37]} The systemic shift away from Th1 and toward Th2 was initially shown in murine systems by a decrease in mixed lymphocyte reactions of splenocytes and an increase in antibody production during pregnancy.\textsuperscript{[36]} Antigen-stimulated splenocytes were then shown to produce fewer Th1 cytokines and more Th2 cytokines when derived from pregnant mice.\textsuperscript{[34,37]} In humans, peripheral blood mononuclear cells in women with successful pregnancies produced IL-10, but no IFN-\(\gamma\), upon stimulation with trophoblast antigens.\textsuperscript{[28]} In another study, antigen and mitogen-stimulated peripheral blood mononuclear cells derived from patients with normal pregnancies demonstrated a decrease in the production of IL-2 and IFN-\(\gamma\) and an increase in production of IL-4 and IL-10, with the lowest quantities of IL-2 and IFN-\(\gamma\) and the highest quantities of IL-4 and IL-10 present in the third trimester of pregnancy.\textsuperscript{[31]} Most recently, during the third trimester pregnancy, ex vivo monocytic IL-12 production was also found to be about three-fold lower and TNF-\(\alpha\) production was approximately 40% lower than postpartum values.\textsuperscript{[35]}

The physiological importance of this shift in the systemic immune response has been demonstrated by a significant alteration in the response to systemic infection in mice during pregnancy.\textsuperscript{[37]} A Th1 response in the host is required for clearance of cutaneous leishmaniasis in infected mice. During this infection, pregnant mice (compared with non-pregnant mice) demonstrated reduced IFN-\(\gamma\) and increased IL-4, IL-5, and IL-10 production by the spleen and the popliteal lymph node cells stimulated in vitro with Leishmania antigens. Furthermore, immunoglobulin (Ig)G1 (an antibody isotype that occurs during Th2 responses) was elevated in the serum of infected pregnant mice as opposed to an increase of IgG2a (an antibody isotype that occurs during Th1 responses) in infected but non-pregnant controls. Most importantly, this shift in immune response toward Th2 during pregnancy was associated with an increased severity of infection.

These observations demonstrated that the shift in the systemic immune response during pregnancy is not merely an interesting observation of the behavior of immune responses studied ex vivo or in vitro during pregnancy, but that the shift has a significant impact on systemic immunity. Thus, it became highly plausible that the systemic shift away from
Th1 and toward Th2 might underlie the improvement in Th1-mediated autoimmune diseases, such as MS and rheumatoid arthritis, during pregnancy.

CANDIDATE PREGNANCY FACTORS WITH THERAPEUTIC POTENTIAL

Sex hormones (estrogens and progesterone) in animal models of MS and rheumatoid arthritis

Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model to study immune mechanisms in MS. EAE models vary depending upon the species, the strain, and the method of disease induction, with some models being relapsing-remitting, others chronic progressive, and still others monophasic with full recovery. The most appropriate EAE model is generally selected to answer the question being examined. It was shown more than a decade ago that EAE in guinea pigs, rats, and rabbits improved during pregnancy. More recently, it was shown that relapsing-remitting EAE in SJL mice improved during late pregnancy. This model was then used to determine if an increase in levels of certain hormones during pregnancy might be responsible for disease improvement. Since estrogens and progesterone increase progressively during pregnancy to the highest levels in the third trimester, these hormones were candidates for mediating a protective effect. Also, it had been previously shown by Jansson et al. in the mid-1990s that treatment of B10.RIII mice with either estriol or estradiol delayed the onset of actively induced EAE. This group also demonstrated a beneficial effect of estrogens on collagen-induced arthritis. Importantly, a decreased incidence of disease occurred when estriol was used at doses to produce serum levels comparable to those found in pregnancy. On the other hand, estradiol needed to be used at doses that gave serum levels several times higher than would occur naturally during pregnancy in order to induce the same degree of disease protection as estriol. This was not surprising, since in mice estriol levels rise from undetectable in non-pregnant states to very high levels during the third trimester, while peak estradiol levels in the third trimester are relatively low, approximating peak levels during the menstrual cycle in non-pregnant states.

Owing to the above findings, studies in the relapsing-remitting model of EAE in SJL mice initially focused on investigations of estriol as the estrogen of pregnancy that might underlie disease protection. In agreement with the earlier findings of a decreased incidence of active EAE with estriol treatment in B10.RIII mice, it was found that SJL mice implanted with 90-day-release hormone pellets containing estriol had less severe disease compared with mice implanted with placebo pellets when identical myelin basic protein (MBP)-specific cells were adoptively transferred. Various doses of estriol were used. There tended to be greater disease protection with higher doses. However, a dose low enough to yield a serum level of estriol in the blood that approximated that observed during natural pregnancy was indeed capable of ameliorating disease. In contrast, there was no protection observed when various doses of progesterone were used, ranging from pregnancy doses to greater than pregnancy doses. The lack of a protective effect in EAE when progesterone alone was used had been previously observed in collagen-induced arthritis. Pathological studies of EAE mice treated with estriol revealed decreased
inflammation and demyelination in spinal cord sections compared with placebo-treated controls. It was then shown that treatment with estriol decreased disease severity even if it was administered after the onset of clinical signs of EAE.\textsuperscript{[43]}

As discussed above, a systemic shift in immune responses from Th1 to Th2 occurs during pregnancy.\textsuperscript{[10,26,37]} Therefore, it was next determined whether treatment of non-pregnant mice with estriol could recapitulate some of the immune changes of pregnancy.\textsuperscript{[43]} It was found that mice with EAE who had been treated with estriol had increased MBP-specific IgG1 antibodies in serum compared with mice with EAE who had been treated with placebo. It was also found that splenocytes from estriol-treated EAE mice had greater IL-10 production on stimulation with MBP than those from placebo-treated EAE mice. Finally, it was demonstrated that the cellular source of the IL-10 production in splenocytes of estriol-treated EAE mice was primarily the T-cell population.\textsuperscript{[43]} This increase in IL-10 production by T cells within the spleen with in vivo estriol treatment was consistent with the increase in IL-10 production that had been observed by others when human T cells were treated in vitro with pregnancy doses of estriol and estradiol.\textsuperscript{[45,46]} Thus, it appeared that estriol treatment recapitulated, at least in part, some of the immune changes of pregnancy.

More recent studies confirmed that not only estriol but also estradiol could ameliorate EAE if given in sustained doses which are sufficiently high.\textsuperscript{[39,47]} The severity of disease was significantly reduced in estradiol-treated animals compared with placebo-treated animals, and this disease amelioration was maintained regardless of whether 17-β-estradiol was used alone or in combination with various doses of progesterone.\textsuperscript{[39]} While it is clear that very high doses of estradiol are protective in EAE, it has not yet been clearly established whether low estradiol doses are protective. Some reports have found that ovariectomy of female mice worsens the severity of EAE,\textsuperscript{[48]} while others have found that ovariectomy does not have a significant effect on disease.\textsuperscript{[39]} Thus, it is uncertain whether low levels of endogenous estradiol have a significant influence on EAE. Levels of estrogens that are lower than those that occur during pregnancy, such as levels induced by doses used in oral contraceptives or hormone replacement therapy, may or may not be high enough to be protective in MS. It is not surprising that past use of oral contraceptives in healthy women would have no effect on subsequent risk to develop MS, since one would not anticipate that the effect of treatment on the immune system would be permanent.\textsuperscript{[23]} These data would not, of themselves, exclude the possibility that the use of oral contraceptives could have a temporary protective effect on disease in women with MS during use. However, in a very large study it was found that the incidence rates for MS in current oral contraceptive users were not decreased compared with the rates in ‘never users’.\textsuperscript{[49]} This latter observation would suggest that the estrogens in oral contraceptives are not of the type or of sufficient dose to ameliorate the immunopathogenesis of MS even temporarily during intercurrent use. This conclusion is supported by disappointing results in studies of hormone replacement therapy and effects on disease activity in rheumatoid arthritis.\textsuperscript{[50]} It is likely that a sustained level of a sufficient dose of an estrogen, creating an estrogen profile similar to that of late pregnancy, will be necessary to ameliorate disease activity in MS and rheumatoid arthritis.

Finally, evidence in animal models suggests that not only high levels of estrogens are protective in Th1-mediated autoimmune diseases during pregnancy, but that the
A precipitous drop in estrogens postpartum may lead to disease exacerbation. In type 2 collagen-induced arthritis in DBA/1 mice, a characteristic feature is the remission during gestation and the exacerbation of the disease during the postpartum period. Two possibilities were pursued with regard to hormonal changes underlying the postpartum flare—first, the precipitous fall in estrogens postpartum and, second, the surge of prolactin after delivery. It was shown that treatment with high-dose estrogens during a short period immediately after parturition protected mice from postpartum flares, whereas treatment with bromocriptine, a drug known to inhibit the endogenous prolactin release, had a less marked effect. Furthermore, studies of lactating arthritic mice (i.e. animals with physiological stimulation of endogenous prolactin release) and non-lactating arthritic mice revealed no clear-cut differences in flares, indicating that prolactin was of minor importance in the induction of postpartum flares. These data in arthritis in mice are consistent with data in MS in women. Confavreux et al. found that whether or not women were breastfeeding had no effect on the increase in relapse rates postpartum.

Since estriol is the predominant estrogen of pregnancy, with levels increasing progressively during pregnancy with highest levels in late pregnancy, and since estriol has been shown to be protective in both EAE and collagen-induced arthritis, these data together suggest that a precipitous drop in the protective hormone estriol after delivery may be responsible, at least in part, for postpartum exacerbations.

**Pregnancy doses of estriol used in a pilot clinical trial in MS**

Observations in animal models of Th1-mediated autoimmune diseases indicated that estriol was a strong candidate sex hormone for mediating disease protection during pregnancy. Thus, estriol was administered in a pilot clinical trial to women with MS in an attempt to recapitulate this protective effect on disease. A cross-over study was used whereby patients were followed for 6 months before treatment to establish baseline disease activity; they had cerebral MRI every month and a neurological examination every 3 months. The patients were then treated with oral estriol (8 mg/day) for 6 months with the same parameters being followed, then observed for 6 more months in the post-treatment period. There were six relapsing-remitting patients and four secondary progressive patients who finished the entire 18 month study period. The oral estriol dose resulted in serum estriol levels that approximated levels observed in untreated healthy control women who were 6 months pregnant. As had been previously observed when estriol was given for hormone replacement therapy, treatment was very well tolerated with only menstrual cycle abnormalities. Interestingly, a significant decrease in a prototypic in vivo Th1 response, the delayed-type hypersensitivity response to the recall antigen tetanus, was observed at the end of the 6-month treatment period compared with the pretreatment period. Furthermore, levels of the Th1 cytokine IFN-γ were measured by reverse transcriptase polymerase chain reaction in unstimulated peripheral blood lymphocytes and shown to be significantly lower at the end of the 6-month treatment period as compared to baseline pretreatment in the relapsing-remitting patients. On serial MRI, the patients with relapsing-remitting MS demonstrated a reduction in gadolinium-enhancing lesions during treatment compared with before treatment, whereas the patients with secondary progressive disease demonstrated no significant change. Specifically, within the first 3 months of treatment of relapsing-remitting patients, median total...
enhancing lesion volumes were decreased by 79% and numbers were decreased by 82%. They remained decreased during the next 3 months of treatment, with lesion volumes decreased by 82% and numbers decreased by 82%. Importantly, gadolinium-enhancing disease activity gradually returned to baseline in the post-treatment period. Median total enhancing lesion volumes and numbers became variable in the first 3 months of treatment, before they returned to near baseline levels at 6 months post-treatment. Finally, treatment with estriol was re-instituted in the patients with relapsing-remitting disease in an extension phase of the study. During the extension phase, progesterone (100 mg/day) was added to estriol to protect from endometrial hyperplasia, which accompanies unopposed estrogen use for extended periods. During the 4-month re-treatment extension phase, enhancing lesion volumes decreased again, by 88%, and numbers decreased again, this time by 48% compared with original baseline. Changes in median new enhancing lesion volumes and numbers followed similar patterns as median T2 lesion numbers and volumes. A stabilization of T2 lesion volume accumulation during treatment was also observed in relapsing-remitting patients, but not secondary progressive patients. As expected, relapse rates and disability were unaffected in this trial of very short duration. Based on the results of this pilot trial, a double-blind, placebo-controlled trial of oral estriol in relapsing-remitting MS is planned.

The observation that estriol treatment appeared to be promising in relapsing-remitting MS but not in secondary progressive MS is consistent with observations of the therapeutic efficacy of the approved anti-inflammatory injectable drugs for MS. They are of demonstrated benefit in relapsing-remitting MS, but of equivocal benefit in secondary progressive MS. This may suggest that the actions of estriol, at least when it is taken for short duration, involve anti-inflammatory mechanisms. The decrease in the delayed-type hypersensitivity response and in IFN-γ levels are consistent with this hypothesis but are not mutually exclusive of other mechanisms of action for estriol. These other mechanisms may include other immune mechanisms,[48] more direct actions on the blood-brain barrier,[55] or effects on cells in the target organ such as microglia[56] and neurons.[57–60]

If larger studies confirm a beneficial effect of estriol treatment on MRI, further studies of estriol treatment for longer periods of time will be needed to determine whether estriol treatment can result in a decrease in relapse rate and disability progression. This will require treatment for 3–5 years. If estriol is to be given for these long periods, it will need to be given in combination with progesterone to protect against uterine endometrial hyperplasia. Data from the pilot trial in which relapsing-remitting patients had treatment re-instated with estriol and progesterone demonstrated no evidence that progesterone antagonized the beneficial effect of estriol, at least in the short term.[52] The data are too preliminary to reveal whether progesterone might have a synergistic effect with estrogen treatment, as might be expected from data in mice with collagen-induced arthritis[44] and from data showing that progesterone caused a shift toward Th2 responses in cultures of human cells in vitro.[45,61]
OTHER PREGNANCY FACTORS WITH POSSIBLE THERAPEUTIC POTENTIAL

Numerous factors other than sex hormones have been identified in blood during pregnancy and have been shown to be immunosuppressive, either in cultures of immune cells in vitro or in EAE models. Hence, numerous factors have been proposed as possibly contributing to disease protection during pregnancy. The two key issues that should be considered when one weighs the possibility of whether a candidate factor is likely to be responsible for the decrease in disease relapse in MS include, first, whether the factor is increased early or late during pregnancy and, second, whether doses of the factors used in in vitro and in vivo models to demonstrate an immunosuppressive effect are associated with levels of the factor that are comparable to what occurs during natural pregnancy. Regarding the first issue, if a factor is increased only transiently very early during pregnancy, then it seems unlikely that it would be responsible for disease activity reduction in the third trimester followed by postpartum relapse. On the other hand, if a factor gradually increases in concentration to a peak in the last trimester followed by a precipitous drop postpartum, then it seems more likely that this factor might be responsible for alterations in the disease course. Regarding the second issue, if the factor is immunosuppressive only at doses that is much higher than that which occurs during pregnancy, then it would be unlikely that the factor is responsible for disease amelioration during pregnancy. On the other hand, if the factor is immunosuppressive at doses that are similar to those that occur during pregnancy, then it is plausible that the factor may be responsible, at least in part, for the immunosuppression and disease activity alteration during pregnancy. Unfortunately, for many of the proposed factors reviewed below (and listed in Table 32.1) these two key issues have not been addressed and, therefore it becomes difficult to ascertain what the contribution of each factor might be to the improvement in disease activity in MS during pregnancy.

Cortisol

The full protective effect of pregnancy on putative Th1-mediated diseases such as MS and rheumatoid arthritis may result from a synergistic effect of numerous factors that occur during pregnancy. Other factors, in addition to sex hormones, that may contribute to disease protection include cortisol or norepinephrine (noradrenaline). During late pregnancy urinary cortisol and norepinephrine excretion were found to be significantly higher than postpartum values. Cortisol is known to be immunosuppressive in both EAE and MS, and the third trimester of pregnancy is characterized by a mildly hyperactive hypothalamic-pituitary-adrenal axis, driven by

Table 32.1 Pregnancy-related factors with therapeutic potential in MS

<table>
<thead>
<tr>
<th>Sex hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen (estriol)</td>
</tr>
<tr>
<td>Progesterone</td>
</tr>
</tbody>
</table>
Cortisol
Vitamin D
Alpha-fetoprotein
Early pregnancy factor
Human chorionic gonadotrophin
Pregnancy-specific glycoproteins
Interferon-τ (ruminants)

Elevated circulating levels of corticotrophin releasing hormone of placental origin.

There is some evidence that norepinephrine may also be increased during pregnancy, and studies have attempted to link the expression of β-adrenergic receptors on peripheral blood mononuclear cells with the inflammatory process. However, mechanisms of immune effects mediated by the sympathetic nervous system remain unclear. Furthermore, it has been shown that the hypothalamic-pituitary-adrenal axis plays a more profound role than the sympathetic nervous system in the restraint of stress-induced suppression of EAE. Given the profound immunosuppressive effect of cortisol on MS and EAE, it seems likely that even the mild elevations of serum cortisol that occur during late pregnancy might contribute, at least in part, to the state of disease protection during this time.

**Vitamin D**

Vitamin D has been proposed, as a factor that is increased during pregnancy, as possibly contributing to disease protection during this time. In one study, 23 women with normal pregnancies were studied in the second and third trimesters and postpartum. 1,25-dihydroxyvitamin D levels were equivalent in the second and third trimesters but were two-fold higher than postpartum values. The increase in serum 1,25-dihydroxyvitamin D values during pregnancy is thought to be important in providing for the increase in maternal calcium requirements during pregnancy. Evidence that high levels of vitamin D are protective in MS come from epidemiological studies as well as work in the EAE model. Geographic studies demonstrating that areas with low supplies of vitamin D (e.g. Scandinavia) are regions with high incidence rates of MS and arthritis suggest that vitamin D may be protective in these diseases. However, numerous other factors, including genetic factors, may underlie the difference in disease incidence in various geographic regions. Interestingly, when EAE was induced by immunizing B10.PL mice with MBP, disease was completely prevented by the administration of 1,25-dihydroxyvitamin D3. Furthermore, vitamin D treatment also prevented the progression of EAE when administered at the appearance of the first disability symptoms. These data provide evidence that vitamin D can indeed be protective in EAE. However, it is not known if the levels of vitamin D needed to ameliorate EAE in mice are equivalent to, or much higher than, those that occur during normal pregnancy.

**α-Fetoprotein**

α-Fetoprotein is produced in high quantities during pregnancy. Daily administration of α-fetoprotein resulted in an amelioration and partial prevention of EAE induced in guinea pigs.
pigs by immunization with MBP or whole CNS homogenate.\cite{70} Levels of α-fetoprotein, α-2-pregnancy-associated glycoprotein, and pregnancy-associated plasma protein A (all immunosuppressive proteins associated with pregnancy) have not been found to be significantly different in pregnant patients with MS from levels in pregnant controls without MS, while an alteration in the number of CD8 ‘suppressor’ cells was found to be different in pregnancy in MS patients compared with pregnant controls. These data suggest that an equivalent amount of immunosuppressive proteins can be found in MS and healthy controls during pregnancy and that, if they influence disease in MS, it is mechanistically unlikely to be related to an alteration in the number of CD8 ‘suppressor’ cells.\cite{3}

**Early pregnancy factor**

Early pregnancy factor is a secreted protein with immunosuppressive and growth factor properties. During pregnancy, it appears in maternal serum within 6–24 hours of fertilization, is present for at least the first two-thirds of pregnancy, and disappears in the third trimester. It is essential for embryonic survival. It is a homolog of chaperonin 10, a heat shock protein, but, unlike other members of this family, early pregnancy factor has an extracellular role. It has the ability to modulate CD4+ T-cell-dependent immune responses, and it has been shown to suppress two models of EAE—acute EAE induced in Lewis rats by inoculation with MBP and chronic relapsing EAE induced in SJL/J mice by inoculation with myelin proteolipid protein peptide (residues 139–151).\cite{71,72}

**Human chorionic gonadotrophin**

Human chorionic gonadotrophin is increased during early pregnancy and has been associated with nausea and vomiting in the first trimester.\cite{73–75} It has been shown to inhibit the proliferative response of lymphocytes on stimulation with mitogens as well as in the mixed lymphocyte reaction when added in vitro to cultures of both human and murine cells.\cite{76,77} Furthermore, when given to mice in vivo, human chorionic gonadotrophin recapitulated the reduction in the mixed lymphocyte reaction of splenocytes observed during pregnancy.\cite{36}

**Pregnancy-specific glycoproteins**

Pregnancy-specific β-1-glycoprotein has been implicated with human chorionic gonadotrophin in contributing to nausea and vomiting during the sixth and 10th gestational weeks.\cite{73} Pregnancy-specific glycoproteins (PSGs) are increased in the first trimester and have also been shown to inhibit proliferative responses of lymphocytes to mitogens and the mixed lymphocyte reaction.\cite{76} Furthermore, when human monocytes and murine RAW 264.7 cells were treated with recombinant PSG-1, PSG-6, PSG-11, or a truncated PSG-6 consisting of only the N-terminal domain (PSG-6N), secretion of IL-10, IL-6 and TGF-β-1 was induced by both human and murine cells. In contrast, IL-1β, TNF-α, and IL-12 were not induced. These results suggested a role for PSGs in modulation of the innate immune system.\cite{78}
IFN-τ

The final factor of potential use as a therapeutic agent in MS is IFN-τ. IFN-τ is clearly not responsible for the decrease in disease activity in the last trimester of human pregnancy, since its expression is restricted to the embryonic trophoblast of ruminants during early pregnancy.[79] These trophoblast IFNs are expressed for a short period in high concentrations, and have antiluteolytic, antiviral, antiproliferative, and immunomodulatory effects through receptors on the endometrial epithelium.[80] Their use in MS was initially considered after the related molecule, IFN-β, was shown to be therapeutic in MS. IFN-τ was thought to be less toxic than IFN-β when used at high concentrations. Indeed, it was shown that IFN-τ was able to prevent development of EAE as effectively as IFN-β but without associated toxicity such as lymphocyte suppression and weight loss.[81] Oral feeding of IFN-τ was later shown to ameliorate EAE and was not associated with the development of neutralizing antibodies in mice.[82] The mechanisms through which IFN-τ ameliorates EAE are being pursued.[83,84]

CONCLUSION

The reduction in relapse rates in MS during the third trimester of pregnancy provides a unique opportunity to identify naturally occurring immunomodulatory factors. Knowledge in this area theoretically could be exploited to develop a novel therapy for relapsing-remitting MS. While numerous factors capable of immunosuppression in putative Th1-mediated autoimmune diseases may be present during pregnancy, it is important to discriminate between those factors that are increased during the third trimester and those that are not, as well as between those that are immunosuppressive when used at similar concentrations as occur in pregnancy and those that are not. The pregnancy estrogen, estriol, meets these criteria for a possible role in the decrease in relapse rates during late pregnancy. However, in light of the complex nature of events that occur during late pregnancy, it is very possible that the effects of estriol are synergistic with effects of other pregnancy factors to create the ultimately beneficial effect on MS that has been reported by patients and observed by clinicians for decades.

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Complementary and alternative treatments in multiple sclerosis
Vijayshree Yadav and Dennis N Bourdette

INTRODUCTION

Despite recent therapeutic advances, multiple sclerosis (MS) remains a chronic disabling disease with no cure. Recent national surveys have demonstrated the widespread use of complementary and alternative medicine (CAM) among the general population in the USA, and people with a variety of chronic illnesses are more likely to use CAM than the general population \(^{[1,2]}\). Therefore, it is not surprising that many MS patients explore CAM therapies. Neurologists have long recognized that many MS patients use alternative therapies but generally have taken little interest in these therapies. Patients and neurologists frequently adopt a ‘don’t ask, don’t tell’ policy about alternative therapies. Neurologists often are very negative about the use of alternative therapies, mainly for two reasons. First, they cite the lack of scientific evidence establishing efficacy for various CAM therapies. Second, they focus on highly publicized therapies that are expensive, seemingly bizarre, or even dangerous (such as replacement of amalgam dental fillings, magnet therapy, and bee stings) as being representative of CAM therapies and want to protect their patients from pointless expenses and risks.

However, this negative attitude is not well founded. Despite MS patients reporting benefit from some alternative therapies, there has been a paucity of scientifically valid research on CAM therapies for MS. The lack of scientific evidence on efficacy does not mean that there is no benefit; we simply do not have the data to allow us to determine what works and what does not. Moreover, most MS patients who use CAM therapies tend to use affordable and low-risk treatments, such as yoga, prayer, low-fat diets and dietary supplements. While there are certainly patients who make poor decisions regarding the use of CAM, MS patients who use CAM generally seem to be sensible in their approach. Rather than ignoring the issue or adopting a universally negative attitude about CAM, neurologists should be better informed about CAM use so that they can serve as a resource for their patients.

DEFINITION OF CAM

One of the challenges facing neurologists is the broad spectrum of therapies that fall under the rubric of CAM. CAM therapies are often defined as unconventional therapies
that are used in addition to (‘complementary’) or instead of (‘alternative’) conventional medicine. CAM therapies are not traditionally prescribed by conventional physicians and often are not covered by health insurance. The list of practices that are considered CAM is somewhat fluid since CAM therapies that are proven safe and effective become accepted as ‘mainstream’ health-care practices. The National Institutes of Health has provided a useful classification scheme of CAM (Table 33.1).[3]

**CAM USE AMONG MS PATIENTS**

Several surveys have documented the high prevalence of CAM use among MS populations. In these surveys, between 55% and 67% of respondents had tried various CAM therapies.[4–7] Similarly, in a survey of members of the Oregon Chapter of the National MS Society, 75% of respondents reported using CAM (unpublished results). MS patients who use CAM therapies are generally better educated, higher-income patients who report engaging in preventative health measures. It also appears that women are more likely to use CAM than men.[8] Level of disability does not seem to correlate with CAM use, since patients with all levels of disability use CAM at roughly similar frequencies. Importantly, most patients report using CAM in combination with conventional medicines for their MS. In the survey by Berkman et al., 53% of respondents used a combination of CAM and conventional treatments for MS, whereas only 6% of respondents used CAM as their only therapy for MS.[4]

MS patients who use CAM often report deriving benefit from these therapies—in the survey by Berkman et al., 59% of respondents reported using CAM and 91% of the CAM users reported deriving benefit from CAM therapy.[4] Most

**Table 33.1 National Institutes of Health classification system for alternative medicine**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative medical systems</td>
<td>Traditional Oriental medicine (acupuncture, t’ai chi, herbal medicine, oriental massage, qi gong) Ayurvedic medicine Homeopathy Naturopathic medicine</td>
</tr>
<tr>
<td>Biologically based therapies</td>
<td>Herbs</td>
</tr>
<tr>
<td></td>
<td>Diets (e.g. Dr Atkins diet)</td>
</tr>
<tr>
<td></td>
<td>Bee venom</td>
</tr>
<tr>
<td></td>
<td>Orthomolecular therapies</td>
</tr>
<tr>
<td>Mind-body interventions</td>
<td>Meditation</td>
</tr>
<tr>
<td></td>
<td>Prayer</td>
</tr>
<tr>
<td></td>
<td>Hypnosis</td>
</tr>
<tr>
<td>Manipulative and body-based methods</td>
<td>Chiropractic medicine</td>
</tr>
<tr>
<td></td>
<td>Massage</td>
</tr>
<tr>
<td>Energy therapies</td>
<td>Therapeutic touch</td>
</tr>
<tr>
<td></td>
<td>Magnets</td>
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</tbody>
</table>
patients indicated that CAM therapies improved various MS symptoms, such as fatigue, spasticity, or pain. Only 12% felt that CAM therapies had altered their disease course, and 9% reported that one or more CAM therapy had caused adverse side effects. In the Oregon survey of MS patients, 50% of respondents rated one or more CAM therapies as being ‘very beneficial’ compared with 42% who rated one or more conventional disease-modifying therapies as being ‘very beneficial.’ Interestingly, this survey found a wide range of perceived benefit among specific CAM therapies. Among 18 CAM therapies that at least 10% of the respondents had tried, respondents rating the individual therapies as being ‘very beneficial’ ranged between 10% and 49%, suggesting that patients perceive differences among various CAM approaches. These observations taken together suggest that MS patients who use CAM generally do so because they experience improvement in their quality of life and various MS symptoms, and they discern differential benefit among the various CAM therapies.

**CAM AND PLACEBO EFFECT**

It is worth asking why MS patients report deriving benefit from CAM use. The easiest answer is that they are simply experiencing a placebo effect. Placebos are generally regarded as inert substances or other interventions that presumably have no specific effect on a disease. Placebos in clinical trials are meant to mimic the medical interventions being studied and are used to control for non-specific benefits that patients experience as a result of taking a treatment for their condition rather than doing nothing. Placebo effects have been described in a large number of health problems, often resulting in 30–40% improvement. Certain conditions seem particularly susceptible to placebo effects, such as pain, fatigue, and autoimmune diseases. Physicians tend to think of the placebo effect as merely being a ‘psychologic’ phenomenon, but it may in fact have a physiologic basis. For instance, placebos may have the ability to alter neuronal function and neurotransmitters.

Placebo effects obviously occur in MS. Analysis of some of the recent trials of disease-modifying therapies yields some interesting results (Table 33.2). In the Phase III trials of all three forms of human recombinant interferon beta and of glatiramer acetate for relapsing-remitting MS, the relapse rate of the placebo group decreased during the trial compared with the 2 years preceding entry into the trial by between 13% and 47%. These effects are not limited to relapse rate. In one trial, the mean number of gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) in the placebo group fell from 2.3 to 1.7 at year 2, a reduction of 26%, compared with a 75% reduction in the active treatment group. While reduction in relapse rate and gadolinium enhancement in the placebo groups in these trials may represent a statistical phenomenon (‘regression towards the mean’), they may also represent a real physiological effect resulting from participating in a clinical trial and taking a treatment that patients feel might provide benefit.

It seems plausible that MS patients who report improvement with various CAM therapies are at least experiencing some placebo effect. Neurologists should keep in mind, however, that there is nothing wrong with a positive placebo effect, and that the
Table 33.2 Effect of placebo and disease-modifying therapies on relapse rate in MS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Placebo group</th>
<th>Active treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relapse rate before treatment (relapses per year)</td>
<td>Relapse rate during treatment (relapses per year)</td>
</tr>
<tr>
<td>Intramuscular Interferon beta-1a[^{15}]</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Interferon beta-1b[^{13}]</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Subcutaneous Interferon beta-1a[^{16}]</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Glatiramer acetate[^{14}]</td>
<td>1.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 33.2 Effect of placebo and disease-modifying therapies on relapse rate in MS

expense or subjecting themselves to potentially harmful therapies.

The beneficial effects that MS patients report with various CAM therapies might not be entirely the result of placebo effect. As discussed above, MS patients report a broad range of benefits with various specific CAM therapies, suggesting that some therapies may provide some beneficial effects above that of a placebo effect.

CAM THERAPIES USED COMMONLY BY MS PATIENTS

CAM approaches to exercise

MS patients are generally deconditioned. For a long time MS patients were advised against exercise partly because of motor and sensory impairment getting worse with the heat of exercise and partly because fatigue limited exercise tolerance. However, recent research has demonstrated the beneficial effects of exercise for MS patients. Regular exercise can increase strength, conditioning, improve quality of life and reduce stress among MS patients.\[^{17,18}\] A regular exercise program is now widely recommended for MS patients. Yoga and t’ai chi are two CAM approaches to exercise that combine a spectrum of systematic patterned physical activity along with meditation.

Yoga is an ancient, east Indian practice that has been gaining considerable popularity among MS patients. Some local Chapters of the National MS Society are now offering courses in yoga. An MS patient and yoga teacher, Eric Wall, who advocates the benefits of yoga for MS, has helped to increase the popularity of yoga. Before recommending
yogic exercises, physical activity patterns and limitations should be evaluated in individual patients. Yoga postures can be adapted for MS patients at varying levels of disability, and yoga appears to be safe, although MS patients should obviously avoid a new fad, ‘hot yoga’ or ‘Bikram yoga’, in which yoga is performed in a very warm, humid environment. In the Oregon survey of MS patients, about 22% reported having tried yoga, and about 49% of those who had tried yoga reported that it was ‘very beneficial’. There currently are no published research studies assessing the benefit of yoga compared with more traditional forms of exercise in MS patients.

T’ai chi is an ancient Chinese form of exercise that consists of slow, relaxed, continuous and patterned movements. The beneficial effects of this form of exercise have been studied and reported in elderly people and in several chronic pain syndromes.[19–21] T’ai chi appears to improve flexibility, range of motion, muscle strength, and balance, and thus it might be beneficial for MS patients. The potential benefits of t’ai chi in MS have been explored in a small pilot study. This non-randomized study found improvement in walking speed, hamstring flexibility, psychosocial well-being and quality of life among MS patients doing t’ai chi.[21] T’ai chi seems to be a promising alternative form of exercise in MS patients and warrants further research.

**Stress management and MS**

Many patients with MS report that stress worsens their MS symptoms, and there is a growing interest about the biological plausibility of this relationship. Under the auspices of the American Academy of Neurology, an expert panel reviewed the literature about the relationship of MS to psychological stress and concluded that there was a possible relationship between antecedent stress and either MS onset or MS exacerbations.[22] A subsequent prospective MRI study of MS patients found that conflicts and disruption in routine were related to subsequent MRI disease activity in MS but did not reliably predict clinical exacerbations.[23] There is thus evidence to support what most patients believe, namely that stress worsens MS. Regardless of the validity of this belief, many patients are interested in finding ways to manage stress and there are CAM therapies that appear to reduce stress.

CAM approaches to stress management include yoga, t’ai chi, prayer, meditation and massage therapy. There are several recent publications on the beneficial effects of meditation in patients with chronic illnesses that seem to be adversely affected by stress, such as rheumatic diseases,[24] irritable bowel disease,[25] and cancer.[26,27] For instance, in a randomized clinical trial in cancer patients, a ‘mindfulness meditation’-based stress reduction program seemed to reduce mood disturbance, fatigue, and a broad spectrum of stress related symptoms.[26,27] In other smaller studies, experienced meditators were shown to have not only psychologic benefits but also enhanced biochemical and physiologic functioning compared with non-meditators.[28–30] Programs combining CAM approaches such as t’ai chi and meditation with conventional medications appear to benefit patients with rheumatoid arthritis and osteoarthritis.[24] In the survey of the MS patients from Oregon, about 15% of the respondents were using meditation, and among these patients about 47% found it to be ‘very beneficial’. Apart from the small study on t’ai chi, CAM approaches to stress reduction among MS patients have not been studied.
Based on results in other chronic illnesses, meditation and other CAM approaches to stress reduction appear worthy of research for the treatment of MS patients.

**Low fat diet and MS**

Although low-fat diets are not recommended by most neurologists, many MS patients follow them, including the Swank diet, dietary recommendations of the American Heart Association, and vegetarian diets. About 44% of respondents in the Oregon survey followed a low-fat, low-cholesterol diet, compared with about 27% of respondents who used Swank diets and 11% who followed vegetarian diets. The Swank diet is named after a neurologist, Dr Roy Swank, who has advocated the use of a strict low-fat diet to treat MS for over 40 years and has contributed to the popularity of low-fat diet use among MS patients. This approach grew out of studies in the 1950s indicating a higher prevalence of MS among populations with a diet high in saturated fats and a lower prevalence among populations with a diet low in saturated fats. Swank published a book, now in its expanded edition, advocating the use of a diet containing only 10–15 g/day of saturated fat supplemented with cod liver oil. There is no convincing evidence that following the Swank low-fat diet, or any other diet, has a positive effect on reducing disease activity in MS. However, long-term follow-up of MS patients who had started the Swank diet suggested that those who followed the diet had a lower death rate and became less disabled than those who did not adhere to the diet. In support of the potential role of diet in MS, a case-control study performed in Canada found a positive association between animal food intake and the risk of MS, with a protective effect of plant-derived food.

Following a low fat-diet generally seems like a common sense approach for most MS patients given the general health benefits of a diet low in saturated fat. Whether there is any specific benefit with regard to controlling MS progression remains unknown but may deserve further research.

**Essential fatty acids and MS**

Many MS patients take essential fatty acids (EFAs) as supplements. The relationship of EFAs to MS was debated in 1970s and 1980s. Along with his low-fat diet, Swank recommended that MS patients take cod liver oil as a supplement. EFA supplements commonly used by MS patients include cod liver oil and other fish oils, evening primrose oil, and flaxseed oil. In our survey of MS patients, about 30% reported using one or more EFA.

There are two families of EFAs, the linoleic acid or omega-6 EFAs and the linolenic acid or omega-3 EFAs. Oils such as evening primrose oil, cod liver oil and other fish oils, and flaxseed oil contain both omega-3 and omega-6 EFAs, although they differ in their ratios. Evening primrose oil has higher content of omega-6 EFAs, whereas cod liver oil and other fish oils have higher content of omega-3 EFAs. Sunflower seed oil contains omega-6 EFAs predominantly.

Clinical trials of EFA supplementation or increased dietary EFA in MS patients have reported mixed results. Dworkin et al., who did a reanalysis of three double-blind trials of the omega-6 EFA, linoleic acid, found that there was a suggestion of modest
therapeutic benefit to supplementation. Among these three double-blind, controlled trials, two used sunflower seed oil as a source of linoleic acid and compared it with olive oil, which contains oleic acid; the third trial used a different preparation of linoleic acid. The first two trials studied only patients with relapsing-remitting MS, whereas the third trial also included some patients with progressive MS. The studies looked at changes in disability score, severity and duration of relapses, and annual relapse rate. Although for patients with moderate to severe disability the change in disability score was not significant, patients with minimal or no disability had a suggestion of stability of their disease with linoleic acid supplementation. The possible protective role of linoleic acid was more evident on relapse severity and duration, but there was no clear benefit on the annual relapse rate. These results were more consistent in the first two trials, whereas the third trial showed no benefit over placebo.

With regard to assessing the role of omega-3 EFA supplementation as MS treatment, there has been one large double-blind trial. In this trial of 312 MS patients with acute remitting disease, the ‘treatment’ group received omega-3 EFA supplementation and both the ‘control’ group and the ‘treatment’ group were advised to increase dietary omega-6 EFAs. Clinical analysis of duration, frequency, and severity of MS relapses, as well as the number of patients who had improved or remained unchanged, was performed. Despite a trend in the favor of the treated group, with 59% of patients in the treatment group remaining unchanged or improved over 2 years compared with 46% of the control patients, the results did not reach the level of statistical significance.

These trials suggest that there might be a rationale, at least, for using omega-6 EFA supplementation in MS. The data so far available for beneficial use of omega-3 EFA supplementation in MS are not as robust but further research on omega-3 EFA is worth pursuing further considering that many MS patients are still taking these supplements and find them ‘highly beneficial’ (unpublished data).

**Anti-oxidants and MS**

Another promising area of CAM research is the use of natural antioxidants to treat MS. Oxidative and nitrogen free radicals are believed to contribute to demyelination and axonal injury in MS. Macrophages are the most prominent inflammatory cell in active MS plaques and are active mediators of demyelination. Activated macrophages release a variety of reactive nitrogen and oxygen species, including nitric oxide, nitrite and nitrate, superoxide, and hydrogen peroxide, which may contribute to demyelination and axonal injury in MS. Natural antioxidants that prevent lipid peroxidation and are lipophilic may be particularly promising as therapeutic agents for MS since lipid peroxidation appears important in MS, and the antioxidants probably need to enter the central nervous system to be maximally effective. However, there is a long list of natural agents that have proven or postulated antioxidant effects, including vitamin C, vitamin E, Ginkgo biloba, grapeseed extracts, green tea, α-lipoic acid, and many others. While many MS patients take one or more of these agents, only Ginkgo biloba has been investigated as a treatment for MS; another antioxidant, α-lipoic acid, has been shown to be beneficial in an animal model of MS.
**Ginkgo biloba**

*Ginkgo biloba* is a herb that has been used to treat a variety of disorders in China for thousands of years. In the past two decades, *Ginkgo biloba* has gained considerable popularity in the Western world as a treatment for dementia and other neurologic conditions. Its biological and clinical effects are being studied extensively, and in Europe it is used to treat peripheral and cerebral vascular insufficiency, memory impairment, and senile macular degeneration. In 1998, a meta-analysis of published clinical trials suggested that *Ginkgo biloba* was effective in slowing progression of Alzheimer’s disease.[52]

The mechanisms of its therapeutic effects are probably multiple and are mediated by its varied constituents, including flavonoids, terpenoids, and organic acids. *Ginkgo biloba* has both antiplatelet and antioxidant activities. Several recent in vitro and animal studies have shown *Ginkgo biloba* to be an effective lipid-soluble antioxidant. Using a human low-density lipoprotein system, *Ginkgo biloba* was shown to scavenge peroxyl radicals, which are involved in the propagation step of lipid peroxidation.[53] Furthermore, in a red blood cell system, *Ginkgo biloba* was shown to be a more effective inhibitor of lipid peroxidation than vitamin C, uric acid, and reduced glutathione.[54] In rats with spinal cord injury, it significantly decreased malondialdehyde (a marker for oxidant stress), an effect similar to that seen with the administration of methylprednisolone.[55]

Gingkolide B, which is a terpenoid constituent of *Ginkgo biloba*, is an antagonist of platelet activating factor that has been studied in an animal model of MS, experimental autoimmune encephalomyelitis (EAE).[56] After it was found to have a beneficial effect on prevention and treatment of EAE, a placebo-controlled study looked at the effect of gingkolide B as a treatment of MS exacerbations.[50] This trial, involving 104 MS patients, failed to show any efficacy of gingkolide B over placebo on the exacerbations, although there was a trend, which did not reach statistical significance, favoring gingkolide B.

The effects of *Ginkgo biloba* on cognitive dysfunction in MS have not been studied, and this might be a fruitful area of research given its effects on Alzheimer’s disease.

**Vitamin C and vitamin E**

Both vitamin C and vitamin E are antioxidants and hence may have a potential to reduce the risk of MS. The literature available thus far, however, seems to be controversial about the efficacy of either vitamin in MS. One case-control study, involving 197 newly diagnosed MS patients and 202 healthy matched controls, reported a significant protective effect of vitamin C and vitamin E supplementation on the risk of MS development.[35] In contrast, another study, which looked at the occurrence of definite and probable MS within two large cohorts of women followed for 6–12 years, found no relationship between the use of vitamin C, vitamin E, and multivitamin supplements and the risk of developing MS.[57] To date there have been no clinical trials assessing the therapeutic benefit of vitamin C or vitamin E supplementation in MS.
Other CAM approaches and MS

Vitamin B12

It is well known that deficiency of vitamin B12 can mimic MS. Neurologic and psychiatric disturbances, including depression, dementia, and a demyelinating myelopathy, are known to occur secondary to vitamin B12 deficiency. In the past decade there have been several published articles about vitamin B12 and its relationship to MS, and an increased incidence of B12 deficiency among MS patients has been both claimed and refuted.\[58,59\] A small study by Kira et al.\[60\] showed that there was no decrease in vitamin B12 levels but a significant decrease in the unsaturated vitamin B12 binding capacity in MS patients. In this study, supplementation with a massive dose of vitamin B12 (60 mg every day for 6 months) in chronic progressive MS patients improved visual and brainstem evoked potential responses but not motor disability. Another small study suggested that lower vitamin B12 levels may predispose to earlier onset of MS.\[61\] A subsequent larger study showed that serum cobalamin deficiency is uncommon in MS.\[59\]

Despite the lack of objective data supporting its use in MS, some patients still use vitamin B12 supplementation. In the Oregon survey about 30% of respondents had tried vitamin B12 supplementation, but only 9% found it to be ‘very beneficial’. While it is plausible that vitamin B12 deficiency may aggravate MS or impair recovery, it remains controversial whether B12 supplementation in patients with MS without B12 deficiency has any merit.

St John’s wort

St John’s wort has been used for more than 2000 years for a variety of ‘nervous conditions’. Currently, it is one of the most popular herbs in the USA and in Germany for the treatment of depression, and the use of St John’s wort surpasses that of fluoxetine. One of the active ingredients of St John’s wort is thought to be hypericin, which has a high affinity for γ-amino butyric acid (GABA) receptors and may also mediate some of its effects through dopamine receptor activation. This may be responsible for the antidepressant activity of St John’s wort.

In a recently published review of newer antidepressants in depression, St John’s wort seemed to be more effective than placebo for short-term treatment of mild to moderately severe depressive disorders.\[62,63\] However, a subsequent randomized controlled trial in the USA failed to show efficacy of St John’s wort for treatment of major depression.\[64\] There are no studies assessing the efficacy of St John’s wort in treating depression among MS patients, although in the Oregon survey about 14% of MS patients had used St John’s wort. Because depression is common in MS, neurologists should be aware that some of their MS patients may be self-medicating with St John’s wort. While this may be a reasonable approach for patients with mild depression, MS patients with significant depression should be encouraged to take a non-CAM antidepressant of proven benefit.
Valerian

Valerian is another herb that is used by many MS patients apparently as an anxiolytic, hypnotic-sedative, and antispasmodic. Valerian root grows wild in temperate areas of North America, Europe, and Asia, and it has been a popular calming and sleep-promoting agent for centuries. The mechanism of action of valerian is not established, but it appears that, like benzodiazepines, it mediates its effects through the GABAergic system.

There have been several controlled clinical studies showing the efficacy of valerian in insomnia in general populations.\textsuperscript{[65–68]} In the Oregon survey, about 11\% of patients had used valerian and 62\% thought it had been beneficial. There are no reported studies in MS patients showing that valerian is more beneficial than conventional tranquilizers and sedatives.

Acupuncture

Acupuncture is a traditional form of therapy that has been used in China for at least 2500 years. According to the acupuncture theory, there are patterns of energy (Qi) that flow through the body along meridians, and disturbances of the flow of Qi results in ill health. Inserting acupuncture needles into specific points along these meridians supposedly corrects the imbalances of energy flow. Although the practice of acupuncture is based on a very different model of disease from that of Western medicine, scientific studies in animals as well as humans in the past two decades have shown that acupuncture can lead to multiple biological responses.

Acupuncture has been shown in several studies to be beneficial in controlling certain symptoms such as pain and nausea.\textsuperscript{[69,70]} In 1997 a panel of the National Institutes of Health concluded that acupuncture was effective as a treatment for some pain syndromes and for addictions, asthma, and nausea.\textsuperscript{[71]} Limited studies in MS also suggest that acupuncture might help a variety of MS symptoms, including pain, spasticity, insomnia, fatigue, and gait difficulties.\textsuperscript{[6]} In the Oregon survey of MS patients, about 17\% had tried acupuncture and, among these patients, about one-third thought that acupuncture was ‘very beneficial’, whereas one-third found it to be ‘not beneficial’. The differential benefit of acupuncture for various specific symptoms in MS thus needs further scientific exploration.

RECOMMENDATIONS FOR FUTURE RESEARCH

Despite the widespread use of CAM therapies among MS patients, most of these therapies have not been evaluated by well-designed, placebo-controlled clinical trials. The lack of randomized controlled trials assessing the efficacy of CAM therapies is the main reason why most neurologists do not incorporate CAM therapies into their management of MS patients. While it is not practical to study every CAM therapy, there are clearly some CAM therapies worthy of research into their efficacy in MS. There are significant differences in how MS patients rate the self-perceived benefit among specific CAM therapies, suggesting perhaps that some CAM therapies are more effective than
others. Clearly, certain therapies, such as antioxidants and essential fatty acids have a scientific rationale for use in MS and are also supported by preclinical or pilot clinical data. Other CAM therapies, such as yoga or meditation, which a high percentage of MS patients report as ‘very beneficial’, are also worth investigating further. Until placebo-controlled trials of CAM therapies are performed, however, we will not know what works and what does not.

RECOMMENDATIONS FOR PATIENTS

This chapter recommends that all MS patients follow a low-fat diet, exercise regularly, and learn to manage stress. Patients who are interested in incorporating CAM approaches into the management of their MS should consider using the Swank low-fat diet, yoga or t’ai chi for exercise, and meditation or regular prayer for stress management. Patients should be warned to avoid CAM therapies that are expensive or potentially dangerous. Patients can also be provided with sources of information about CAM therapies (Table 33.3), and encouraged to discuss with their physician any CAM therapies that they are considering trying or are already taking.

Table 33.3 Resources for information about CAM

<table>
<thead>
<tr>
<th>Type of resource</th>
<th>Societies</th>
<th>National MS Society (NMSS) and its local Chapters. Two useful NMSS pamphlets are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Web sites</td>
<td><a href="http://www.ms-cam.org/">http://www.ms-cam.org/</a></td>
<td><a href="http://www.ohsu.edu/orccamind">http://www.ohsu.edu/orccamind</a></td>
</tr>
</tbody>
</table>

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IV
Disease-modifying drug therapy in clinical practice
INTRODUCTION

The therapeutic paradigm for multiple sclerosis (MS) has changed dramatically since interferon beta-1b, the first treatment for relapsing-remitting MS was introduced. There are now four other approved agents for MS: two interferon beta-1a’s, glatiramer acetate, and mitoxantrone. Neurologists managing patients with MS now face the challenge of recommending which of these agents to use and when to initiate or modify treatment. This chapter attempts to outline practical approaches to disease-modifying therapy of MS.

GOALS OF DISEASE-MODIFYING THERAPY

MS is a chronic disease. The principle aims of immunomodulatory therapy in relapsing-remitting MS are to reduce relapses and to limit long-term disability. Natural history studies have demonstrated that over 50% of patients with relapsing-remitting MS will develop secondary progressive MS after 10 years.⁴ One-half of patients with relapsing-remitting MS will require an aid for ambulation 15–23 years after disease onset.⁴ Although MS has been thought to be primarily a disease of central nervous system myelin, recent neuropathological studies by Trapp et al. have demonstrated histologic evidence of axonal injury in both the early and late stages of illness.²

The therapeutic approach to patients with relapsing-remitting MS takes into account numerous variables, including clinical disease activity, magnetic resonance imaging (MRI) findings, and patient tolerance to the available MS agents. These factors must then be integrated with evidence-based data to devise rational treatment strategies.

RATIONALE FOR EARLY TREATMENT

There is growing consensus that disease-modifying therapy should commence early in patients with relapsing-remitting MS.³⁴ This has developed from the outcomes of a multitude of natural history studies, therapeutic trials, MRI data, and neuropathologic findings. Many MS experts now favor beginning disease-modifying therapy soon after a
diagnosis of relapsing-remitting MS has been established. Clinical trials with both interferon-beta and glatiramer acetate have demonstrated that delayed treatment adversely affects accumulation of disability in patients with relapsing-remitting MS. The presence of axonal transection, an irreversible neuronal injury, and inflammation in pathologic studies of patients with active MS of both short and long duration suggests that early control of the inflammatory, demyelinating phase of relapsing-remitting MS may reduce long-term neurologic disability.

Supporting this notion, Rudick et al. reported that treatment of patients with relapsing-remitting MS with weekly intramuscular interferon beta-1a reduced progression of MRI-detected whole brain atrophy, a putative marker of irreversible tissue loss in relapsing-remitting MS. In a 9-month double-blind, placebo-controlled serial MRI study, Filippi et al. reported that patients treated with glatiramer acetate had significantly less development of ‘black holes’, another measure of tissue disruption, at 7 and 8 months.

Taken together, these clinical, neuropathologic, and neuroimaging data offer a compelling argument for early intervention with disease-modifying therapy in relapsing-remitting MS.

CHOOSING A DISEASE-MODIFYING AGENT

There are no specific guidelines available to the physician selecting an immunodulatory drug for patients with relapsing-remitting MS. The interferon betas and glatiramer acetate are all reported to reduce relapse rate and influence accumulation of long-term disability. Because each of the agents approved by the Food and Drug Administration (FDA) in the USA for use in relapsing-remitting MS was studied differently, it is not possible to make direct comparisons across studies. Data from carefully designed clinical trials may eventually address this issue. On a practical basis today, the choice of a particular disease-modifying agent is arguably influenced most by the patient’s clinical status; MRI findings and patient preference also have important roles in drug selection.

Relapsing-remitting MS

There are now three formulations of interferon beta (interferon beta-1a for intramuscular use, interferon beta-1a for subcutaneous use, and interferon beta-1b) as well as glatiramer acetate approved for the treatment of relapsing-remitting MS (Table 34.1). None of these agents completely halts disease activity or progression; definitive superiority in long-term efficacy over the course of several years of therapy with any one of these medications in relapsing-remitting MS has not been established.

Interferon beta-1b

Interferon beta-1b, a non-glycosylated recombinant product derived from Escherichia coli, differs from natural interferon beta by a single amino acid substitution. A 2-year multicenter, double-blind, placebo-controlled study of 372 ambulatory patients (Kurtzke Expanded Disability Status Score [EDSS] 0–5.5) with relapsing-remitting MS, found that 8 million international units (MIU) of interferon beta-1b administered subcutaneously
every other day was found to decrease the annual exacerbation rate from 1.27 to 0.84 ($p=0.0001$), a reduction of 32%.\textsuperscript{[9]} A low dose of interferon beta-1b (1.6 MIU) was also significantly effective.

**Table 34.1 Current FDA-approved disease-modifying therapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type of MS</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b</td>
<td>Relapsing-remitting</td>
<td>8 MIU subcutaneously on alternate days</td>
<td>Flu-like syndrome, injection site reaction, depression (?), menstrual irregularity</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>Relapsing-remitting</td>
<td>30 µg intramuscularly once weekly</td>
<td>Flu-like syndrome</td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>Relapsing-remitting</td>
<td>22 µg or 44 µg subcutaneously three times weekly</td>
<td>Flu-like syndrome</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Relapsing-remitting</td>
<td>20 mg subcutaneously once daily</td>
<td>Post-injection syndrome*, injection site reaction</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Worsening relapsing-remitting, secondary progressive, progressive-relapsing</td>
<td>12 mg/m\textsuperscript{2} intravenously every 3 months for 2–3 years (maximum: 140 mg/m\textsuperscript{2})</td>
<td>Alopecia, nausea, leukopenia (rarely leukemia), cardiomyopathy (at cumulative dosages $\geq$100 mg/m\textsuperscript{2})</td>
</tr>
</tbody>
</table>

*Chest pain, palpitations, flushing, anxiety

compared with placebo, but less effective than the higher dosage. Patients in the high-dose arm of the study had less severe exacerbations and were more likely to be exacerbation-free during the investigation.

An accompanying study that analysed cranial MRI activity demonstrated a significant reduction both in disease burden and in disease activity in patients treated with 8 MIU interferon beta-1b compared with placebo at the end of 3 years.\textsuperscript{[13]} The placebo group had a mean increase in lesion load of 17.1% whereas the interferon beta-1b group had a mean reduction of 6.2% ($p=0.002$).

In a 5-year analysis of the original patient cohort, the benefits of interferon beta-1b on relapse rate were maintained.\textsuperscript{[14]} Although fewer patients on interferon beta-1b had confirmed disability progression after 5 years, this did not reach statistical significance.

**Interferon beta-1a**

Interferon beta-1a, a naturally sequenced glycosylated recombinant mammalian product, has also been approved for the treatment of relapsing-remitting MS. Both intramuscular and subcutaneous interferon beta-1a preparations are available in the USA, Canada, and Europe.
In a randomized, placebo-controlled, double-blinded study of 301 patients with relapsing-remitting MS (EDSS 1–3.5), weekly intramuscular interferon beta-1a at a dose of 30 µg was demonstrated to cause significantly slower accumulation of clinical disability over 104 weeks. In this study, the primary outcome variable, time to sustained worsening of disability, was defined as a 1.0 point increase on the EDSS persisting for at least 6 months. Disability progression occurred in 34.9% of the placebo group and in 21.9% of interferon beta-1a recipients ($p=0.02$), representing a 37% reduction in sustained disability accumulation. The annual exacerbation rate for all patients studied was 0.62 in the interferon beta-1a group and 0.82 in the placebo group (18% reduction, $p=0.04$). In the 170 patients who were followed for at least 104 weeks, weekly intramuscular interferon beta-1a reduced the 2-year exacerbation rate by 32% ($p=0.002$). Patients treated with interferon beta-1a had significantly reduced number and volume of gadolinium-enhancing MRI lesions at 12 months ($p=0.02$) and 24 months ($p=0.05$). Interferon beta-1a also reduced MRI-detected T2 lesion load after 2 years, but the difference compared with placebo was not statistically significant ($-13.2\%$ versus $-6.5\%$, $p=0.36$). Post hoc analysis of clinical data revealed that significantly fewer patients treated with interferon beta-1a progressed to EDSS levels of 4.0 and 6.0 at the end of 2 years. Post hoc MRI analysis of brain parenchymal fraction demonstrated that patients treated with interferon beta-1a had reduced progression of brain atrophy compared with placebo during the second year of the study ($p=0.03$).

In a 2-year multinational randomized trial of 560 patients with relapsing-remitting MS (EDSS 0–5.0), interferon beta-1a at doses of 22 µg subcutaneously and 44 µg subcutaneously three times a week reduced relapse rates over 1 year by 27% and over 2 years by 33%. Both doses prolonged time to first relapse, and patients in either treatment group were significantly more likely to be relapse-free than the placebo patients. Accumulation of sustained disability (confirmed 1-point EDSS progression) was less in both interferon beta-1a groups compared with placebo; however, in patients with high baseline EDSS (>3.5), a significant benefit in time to sustained progression was seen only in the 44 µg group. MRI activity and T2 burden of disease were also lower in both treatment arms. A modest dose effect favoring the 44 µg group was seen for most clinical parameters, including relapse rate and relapse severity, but the difference was greater for measures of MRI lesion load.

In a 2-year blinded extension study of the original cohort, patients initially given placebo were randomized to receive interferon beta-1a at 22 µg or 44 µg three times a week (cross-over groups), while patients on active treatment continued to be followed on their assigned dosages. Patients treated for 4 years with interferon beta-1a at 22 µg and 44 µg had relapse rates of 0.80 and 0.72, respectively; patients in the cross-over group (i.e. on interferon beta-1a for only 2 years) had a relapse rate of 1.02, a significant reduction from the prior placebo period. Moreover, there was a significant reduction ($p<0.001$) in exacerbation rate in patients treated with interferon beta-1a for 4 years compared with those treated for 2 years. Time to confirmed disability progression was significantly prolonged in patients in the 44 µg group (42.1 months) compared with the cross-over groups (24.2 months) ($p=0.047$). The difference in disability accumulation between the 44 µg and 22 µg group or the 22 µg group and the cross-over group did not reach statistical significance. There was, however, a significant diminution in MRI activity in patients treated for 4 years compared with those treated for 2 years, with a dose effect.
Thus, the results of this trial confirm ongoing efficacy of high-dose interferon beta-1a in reducing relapse rate, disability progression, and MRI activity in patients with relapsing-remitting MS. Furthermore, it appears that delaying treatment adversely affects these same parameters, since patients in the cross-over groups fared significantly worse on clinical and MRI measures of disease activity.[4]

**Glatiramer acetate**

Glatiramer acetate, formally known as copolymer-1, is a mixture of synthetic polypeptide chains consisting of four amino acids, L-glutamate, L-lysine, L-alanine, and L-tyrosine. Glatiramer acetate was originally developed as an analog to myelin basic protein and was found to modify or suppress experimental autoimmune encephalomyelitis, the animal model of MS.[12] Clinical studies of glatiramer acetate in the treatment of MS were based on these early findings.

Bornstein et al. first demonstrated that glatiramer acetate reduced exacerbations in relapsing-remitting MS in a pilot study of 50 patients.[16] Subsequently, Johnson et al. reported clinical benefits of glatiramer acetate in a randomized, multicenter, placebo-controlled trial of 251 patients with relapsing-remitting MS (EDSS 0–5).[12] Patients given 20 µg glatiramer acetate subcutaneously daily had a 2-year relapse reduction of 29% compared with those given placebo ($p=0.007$). Relapse rate reduction was more pronounced in patients with entry EDSS of 0–2. At the end of the study, significantly more patients in the glatiramer acetate arm had improved EDSS, while patients in the placebo arm were more likely to have worsened EDSS. Trends in percentage of relapse-free patients and median time to first relapse favored glatiramer acetate, although these parameters did not reach statistical significance. In a 12-month extension study,[17] glatiramer acetate continued to have a favorable impact on relapse rate and disability progression.

Finally, in a 7-year open-label extension study involving 208 patients from the original cohort, Johnson et al. reported a sustained relapse rate reduction of 0.23; 69.3% of patients who received glatiramer acetate for 5 or more years were neurologically stable by EDSS.[6] Patients who were treated with glatiramer acetate for the entire length of the study had trends towards less accumulated disability than those whose treatment was delayed for 35 months, suggesting that earlier initiation of treatment with glatiramer acetate resulted in better clinical outcomes.[6]

Beneficial effects of glatiramer acetate on disease activity determined by cranial MRI have subsequently been confirmed as well. Comi et al. randomized 239 patients with relapsing-remitting MS to receive either daily subcutaneous glatiramer (20 µg) or placebo, and each underwent monthly cranial MRI and clinical evaluation for 9 months.[18] Patients in the treatment arm had a mean reduction of 29% in gadolinium-enhancing lesions ($p=0.003$), which was the primary outcome measure. Glatiramer acetate was also associated with significant differences in development of new gadolinium-enhancing lesions, new T2-lesions, and total lesion volume during the study period. Filippi et al. have also reported that the percentage of new lesions evolving into ‘black holes,’ an in vivo marker of tissue loss, was also lowered by glatiramer acetate treatment.[8]
Comparing disease-modifying agents in relapsing-remitting MS

Interferon beta-1a, interferon beta-1b, and glatiramer acetate have each been demonstrated to have a favorable effect on relapse rate and MRI activity in relapsing-remitting MS. Methodological differences among the pivotal trials make comparisons difficult. Several studies comparing subcutaneous interferon beta-1a at weekly dosages ranging from 22 µg to 144 µg\(^{[5,10,19]}\) seem to demonstrate a dose response on both clinical and MRI measures, as was previously shown for interferon beta-1b.\(^{[9]}\) A 48-week, MRI-based, randomized, double-blind trial comparing once-weekly subcutaneous interferon beta-1a at 22 µg or 44 µg with placebo demonstrated a dose-dependent reduction in the median number of combined active lesions measured by MRI at 24 weeks (29% for 22 µg; 53% for 44 µg); however, treatment effect was statistically significant only for high-dose interferon beta-1a compared with placebo.\(^{[19]}\) T2 new lesion count at 48 weeks was significantly lower in both the 22 µg and the 44 µg arms; MRI burden of disease at 48 weeks was increased in the placebo group but decreased in both active treatment groups. Interestingly, there was no significant difference in secondary outcomes of relapse rate or percentage of patients who were relapse-free at 48 weeks, although there was a trend favoring high-dose interferon beta-1a compared with placebo and low-dose interferon beta-1a.

A double-blind, parallel-group, 34-center ‘European Interferon Beta-1a Dose-Comparison Study’ of 802 patients using interferon beta-1a in doses of 30 µg or 60 µg intramuscularly once weekly showed no significant differences in any of the clinical or MRI outcomes.\(^{[20,21]}\) An extension analysis, involving 491 patients who continued double-blind treatment for a total of 4 years has been completed. At the end of the 4-year treatment period, both doses yielded a similar percentage of progression-free subjects: 52% in the 30 µg group and 57% in the 60 µg group (\(p=0.32\)). Thirty percent in each group progressed to an EDSS of \(\geq 4.0\) (\(p=0.93\)), and 22% in each group progressed to an EDSS of \(\geq 6.0\) (\(p=0.46\)). Reduction in relapse rate from baseline was 43% in the 30 µg dose group and 42% in the 60 µg dose group. The proportion of patients with neutralizing antibody titers \(\geq 1:20\) at any time during the study were only 2.3% in the 30 µg group and 5.8% in the 60 µg group. In 386 of the patients followed for 3 years by annual MRI scans, the MRI outcomes corroborated the clinical results, showing similar benefit with both doses. Substantial reductions from baseline were seen in each group for all MRI measures at all time points. There were no statistically significant differences or trends observed between 30 µg and 60 µg dosed once weekly with regard to change in T2 and T1 lesion volume, number and volume of gadolinium-enhancing lesions, and number of new or enlarging T2 lesions. Thus, although no differences were found, sustained efficacy of both doses of interferon beta-1a intramuscularly once weekly was observed. To date, no studies have compared weekly versus more frequent doses given by intramuscular injection.

Panitch et al. recently reported the results of a 48-week prospective, randomized, single-blinded trial comparing therapy with interferon beta-1a at two different doses and methods of administration.\(^{[22]}\) The Evidence of Interferon Dose Response European-North American Comparative Efficacy (EVIDENCE) Study enrolled 677 patients with relapsing-remitting MS, who were randomized to treatment with either interferon beta-1a...
44 µg subcutaneously three times per week (339 patients) or interferon beta-1a 30 µg intramuscularly once weekly (338 patients). Clinical evaluations were performed every 12 weeks and all patients had screening brain MRI with and without gadolinium and then every 4 weeks through week 24, with a final unenhanced scan at 48 weeks. The primary endpoint was the proportion of patients who were relapse-free, with MRI active lesion count a secondary outcome. At the end of 48 weeks, the proportion of patients relapse-free were 62% in the 44 µg three times a week group and 52% in the 30 µg once weekly group ($p=0.009$). Similarly, the proportion of patients without active lesions on brain MRI was significantly lower in the 44 µg group than in the 30 µg weekly group (63% versus 45%, $p<0.001$). Adverse effects, including injection site reactions, elevated liver enzymes, and leukopenia, were more common in the high-dose group. Neutralizing antibodies were detected in titers of $>1:20$ in 25% of the high-dose subcutaneous group and in 3% in the once-weekly intramuscular group. Further analysis of data must await publication in peer-reviewed format.

Khan et al. conducted a prospective, non-randomized, open-label study comparing the effects of no treatment, interferon beta-1a (30 µg intramuscularly once weekly), interferon beta-1b (25 µg subcutaneously on alternate days), and glatiramer acetate (20 µg subcutaneously once daily) in patients with relapsing-remitting MS (EDSS<4.0) who had not been previously treated with immunomodulatory drugs.[23] Patients entering the trial were allowed to choose from among the three agents or to forego therapy; the primary endpoint was the relapse rate at 12 months. Relapse rates in the untreated group, the interferon beta-1a group, the interferon beta-1b group, and the glatiramer acetate group were 0.97, 0.85, 0.61 and 0.62, respectively. Compared with the untreated arm, only those receiving interferon beta-1b ($p=0.002$) and glatiramer acetate ($p=0.003$) had a significant reduction in relapse rate; there was no significant effect in the interferon beta-1a group ($p=0.309$). The study has been criticized for its open-label and non-randomized design, but the authors did suggest that their results support the concept of a dose response to interferon beta in relapsing-remitting MS, consistent with the observations of previous controlled trials.[9,10,19]

Finally, the first randomized study comparing interferon beta-1a (30 µg intramuscularly once weekly) with interferon beta-1b (25 µg subcutaneously on alternate days) was recently reported.[24] This trial was a 2-year prospective investigation conducted in multiple MS centers in Italy. In this open-label study, 188 consecutive patients with relapsing-remitting MS were randomly selected to receive either interferon beta1a or interferon beta-1b at the doses currently available in the USA. Both the clinical (unblinded) outcomes and the MRI (blinded) outcomes were evaluated after 6, 12, and 24 months. The primary clinical outcome was the percentage of patients who were relapse-free, a measure that may be more sensitive to disease activity, particularly since the clinical evaluations were unblinded.[24] At the end of 2 years, 51% of patients in the interferon beta-1b group were relapse-free, compared with 36% of patients receiving interferon beta-1a ($p=0.03$); the relative risk of relapse in the interferon beta-1b group was 0.76 compared with the interferon beta-1a group. Blinded evaluation of MRI parameters of active disease, determined by the absence of new proton density or T2 lesions after 24 months of therapy, favored treatment with interferon beta-1b over interferon beta-1a (55% versus 26%, $p<0.001$), which was consistent with the clinical
findings. Whether there is a persistent difference in efficacy between interferon beta-1a and interferon beta-1b beyond 2 years requires further study.

On the basis of the available evidence, it seems plausible that certain patients with more active relapsing-remitting MS, may respond more favorably to high-dose (more frequent administration) interferon beta-1a or interferon beta-1b than to low-dose (less frequent administration) interferon beta-1a. In practice, relapsing-remitting MS patients with a large amount of MRI-detected disease activity (gadolinium enhancement, new or enlarging lesions) may benefit more from interferon beta because of its rapid onset and superior effect in suppressing new active MRI lesions. Patients with relatively mild disease, more sensory symptoms, fewer relapses, and little or no residual deficits can probably be treated equally effectively with interferon beta-1a, interferon beta-1b, or glatiramer acetate. Convenience of dosing and tolerance or fear of side effects may help in determining which agent to use in these situations.

Isolated demyelinating syndromes

Patients with a first isolated demyelinating event (e.g. optic neuritis, partial transverse myelitis, or brainstem-cerebellar syndrome) are at high risk of developing clinically definite multiple sclerosis within 3–10 years. O’Riordan et al. found that 83% of patients who presented with a clinically isolated syndrome of the optic nerve, brainstem, or spinal cord and an abnormal T2-weighted MRI scan of the brain, developed clinically definite MS after 10 years. The number of MRI lesions on initial examination correlated with EDSS and disease severity at 10-year follow-up. At a mean follow-up of 14 years, 88% of patients with abnormal initial MRI had clinically definite MS.

In the Optic Neuritis Trial, the 5-year cumulative probability of clinically definite MS after a first episode of optic neuritis was 30%; patients with three or more MRI lesions at study entry had a 51% risk of clinically definite MS within 5 years. Interestingly, patients with acute optic neuritis treated with high-dose intravenous methylprednisolone (followed by oral prednisone) had a significantly lower 2-year risk of developing clinically definite MS than those receiving oral prednisone alone or placebo.

Two multicenter, randomized trials have addressed the question whether interferon beta1a initiated after a clinically isolated syndrome affects progression to clinically definite MS—that is, the occurrence of a second demyelinating event disseminated in time and space.

In one study, 383 patients with an acute isolated demyelinating event (e.g. unilateral optic neuritis, partial transverse myelitis, brainstem-cerebellar syndrome), no previous neurologic or visual symptoms, and two or more white matter lesions on cranial MRI, were assigned to receive treatment with interferon beta-1a 30 µg intramuscularly weekly or placebo. All patients were given a 14-day course of intravenous and oral steroids. The primary outcome was development of clinically definite MS; serial unenhanced T2 and gadolinium-enhanced T1 MRI findings were also analysed. The 3-year study was terminated after a preplanned interim analysis. The projected 3-year Kaplan-Meier cumulative probability of developing clinically definite MS was 35% in the interferon beta-1a group and 50% in the placebo group (relative risk 0.56, p=0.002); thus, patients treated with interferon beta-1a had a significantly lower risk (44%) of 3-year conversion to clinically definite MS. Patients in the interferon beta-1a group also had significant
reductions in MRI lesion load and fewer new, enlarging, or gadolinium-enhancing lesions at 18 months.

Another randomized, double-blind trial of interferon beta-1a in clinically isolated syndrome was conducted in Europe by Comi et al.\(^\text{[30]}\) In this study, 308 patients with a first demyelinating event, either unifocal or multifocal, and a brain MRI demonstrating three or more white matter lesions typical of MS, were administered 22 µg interferon beta-1a subcutaneously weekly or placebo for 2 years. Fewer patients in the interferon beta 1a arm compared with the placebo group (34% versus 45%, respectively;\( p=0.047\)) converted to clinically definite MS at the end of two years. The time at which 30% of patients developed clinically definite MS was 569 days in the interferon beta-1a group and 252 days in the placebo group (\( p=0.034\)). There was also a modest but significant reduction in relapse rate favoring treatment with interferon beta 1a (0.33, placebo 0.43; \( p=0.045\)). The number of new lesions and lesion load on MRI were significantly lower in the interferon beta-1a group.

The results of these two studies demonstrate that interferon beta-1a can delay the occurrence of a second clinical event in high-risk patients who present with an isolated neurologic syndrome compatible with MS.\(^\text{[29,30]}\) It is important to note, however, that treatment with interferon beta-1a did not completely suppress MRI disease activity in either study. In both studies, a sizeable number of patients in both the treated group and the control group had MRI evidence of disease dissemination in time and space at 6–18 months after randomization; although at a significantly lower rate in those on interferon beta-1a. Thus, according to recently updated diagnostic criteria for MS,\(^\text{[31]}\) a majority of patients converted to definite MS on the basis of MRI measures.

Since both studies were of relatively short duration, it is not possible to discern whether initiating treatment in this early phase of MS affects long-term accumulation of neurologic disability. Follow-up analysis of patients in these trials may help to clarify this issue. It does appear, however, that administration of weekly interferon beta-1a to patients in the earliest stage of MS has a short-term benefit. Although unproven, it is likely that therapy with interferon beta-1b or glatiramer acetate would be similarly effective.

Thus, the clinician confronting a patient with a clinically isolated syndrome that is typical of MS must decide whether and when to initiate disease-modifying therapy. Patients with normal brain MRI or with fewer than two lesions, who are at lower risk of developing MS,\(^\text{[25–27]}\) can probably be followed clinically and by serial MRI before immunomodulatory therapy is started. Those with abnormal MRI findings with two or more lesions consistent with MS\(^\text{[31]}\) can be considered candidates for treatment with immunomodulators. Patients with atypical clinical or neuroimaging findings require further diagnostic evaluation before therapeutic decisions are made.
ADVERSE EFFECTS ASSOCIATED WITH DISEASE-MODIFYING THERAPY

Interferon-beta

Common adverse reactions

Administration of interferon beta can be associated with a number of adverse effects. A ‘flu-like’ syndrome, which includes fever, chills, myalgia, fatigue, and headache occurs in up to 75% of patients. This reaction typically begins within 6 hours of injection and may last up to 24 hours. Its severity appears in part to correlate with body mass and its cause may be related to transient up-regulation of proinflammatory cytokines. These symptoms usually abate within the first 3 months of therapy and may be relieved by acetaminophen, ibuprofen (400 mg three times daily), or prednisone (10 mg/day). Pentoxifylline (800 mg twice daily) has also reported to be effective. Alternatively, to reduce side effects, interferon beta may be initiated at one-quarter to one-half the recommended dose and then gradually titrated to full dosage. Administration of interferon beta at bedtime may reduce daytime symptoms.

The association between interferon beta and depression has not been completely established, and depressive symptoms such as anhedonia, insomnia, and hopelessness are common in the MS population. Depression and suicide attempts have been shown to occur more frequently in treated patients, although the difference in attempted suicide rates was not statistically significant between the interferon beta-1b group and the placebo group. None of the studies of interferon beta-1a demonstrated an increased risk of suicide in treated patients. Most patients who develop depression while on interferon beta can be managed with antidepressant medication and psychotherapy; in rare instances, interferon beta may need to be discontinued.

Injection-site reactions are common in patients treated with subcutaneous interferon beta. With interferon beta-1b the possible skin disorders can include local erythema, bruising and pain, subcutaneous atrophy, cutaneous and subcutaneous infection, and, rarely, skin necrosis. In most cases, modification of injection technique and rotation of injection sites will ameliorate untoward skin effects. Occurrence of skin necrosis rarely warrants surgical consultation and withdrawal of interferon beta.

The most commonly reported laboratory abnormalities with interferon beta are leukopenia, lymphopenia, neutropenia, and elevated liver enzymes. These changes are reversible with temporary cessation of therapy. It is recommended that complete blood count and liver profile should be obtained before therapy with interferon beta is started and then monitored during the first 6 months of treatment and as required, with at least yearly assessment thereafter.

Neutralizing antibodies

The treatment of relapsing-remitting MS with interferon beta-1a and interferon beta-1b is associated with the formation of neutralizing antibodies directed against interferon. This
occurs in 14.3–38% of patients in the randomized clinical trials. On both clinical and MRI measures, the efficacy of interferon beta can be reduced in neutralizing antibody-positive patients treated with interferon beta-1a and interferon beta-1b.

In the pivotal interferon beta-1b trial, 38% of patients treated with 8 MIU subcutaneously on alternate days had detectable neutralizing antibodies by the third year of the study; neutralizing antibody positivity was defined as two consecutive serum samples (3 months apart) demonstrating the presence of neutralizing antibodies by an established bioassay. Exacerbation rates at 18 months in neutralizing antibody-positive patients were two-fold higher \( (p<0.001) \) than in neutralizing antibody-negative patients; MRI activity was also increased in the neutralizing antibody-positive group compared with the neutralizing antibody-negative group, although the difference was not statistically significant \( (p=0.067) \).

In the PRISMS trial, persistent neutralizing antibodies were found in 23.7% of patients treated with interferon beta-1a 22 µg subcutaneously three times a week for 4 years and in 14.3% of patients on a dose of 44 µg. Neutralizing antibody-positive patients in both dosage groups had higher exacerbation rates, which was significantly greater in years 3 and 4 of the study. MRI disease activity was also increased in neutralizing antibody-positive patients; median number of T2 active lesions in the 44 µg group was 0.3 for neutralizing antibody-negative patients and 1.4 for neutralizing antibody-positive patients.

In the controlled trial of interferon beta-1a 30 µg intramuscularly weekly, 22% of patients were neutralizing antibody-positive at week 104. Using a two-step assay, Rudick et al. subsequently analysed the incidence and significance of neutralizing antibodies in patients from the phase III trial and participants from an open-label study of interferon beta-1a. Neutralizing antibody status did not correlate with measures of clinical efficacy (disability progression, relapse rate) in the phase III group treated with interferon beta-1a for 2 years, although in vivo biologic activity of interferon was reduced in the neutralizing antibody-positive group. On cranial MRI at week 104, however, neutralizing antibody-positive patients \( (\text{titer} \geq 20) \) had more gadolinium-enhancing lesions than those who were neutralizing antibody-negative. The difference did not reach statistical significance (1.6 versus 0.6 lesions, \( p=0.062 \)). In the open-label study, 6% of interferon beta-naïve patients \( (n=84) \) treated with interferon beta-1a for 24 months developed neutralizing antibodies. In the majority of subjects, neutralizing antibodies were detected after 9 months of therapy. In patients who previously received interferon beta-1b \( (n=118) \), the percentage of neutralizing antibody-positivity to interferon beta-1a at study entry correlated with duration of prior treatment; approximately 25% of patients treated with interferon beta-1b for over 12 months had neutralizing antibodies directed against interferon beta-1a.

Finally, the relative immunogenicity of interferon beta-1a and interferon beta-1b was prospectively examined by Cook et al. In a cross-sectional analysis of interferon-naïve patients treated with conventional doses of intramuscular interferon beta-1a \( (n=98) \) or subcutaneous interferon beta-1b \( (n=64) \) uninterrupted for 12–21 months, elevated neutralizing antibody titers \( (2:60) \) were detected in significantly more patients receiving interferon beta-1b than interferon beta-1a \( (22\% \text{ versus } 7\%, \ p=0.008) \). Mean serum levels of neopterin, a biologic marker of interferon activity, did not differ significantly between the two groups; however, serum neopterin levels were decreased in patients with high
neutralizing antibody titers regardless of which interferon beta preparation was used. The clinical relevance of this remains unknown.

In clinical practice, the role of neutralizing antibodies against interferon beta remains controversial. Some neurologists consider relative immunogenicity an important factor in recommending a specific interferon beta product. There is evidence that elevated titers of neutralizing antibody to interferon beta can abrogate the therapeutic effects of interferon beta on both clinical and MRI measures in the short term, regardless of the type administered.[5,35–37] Nevertheless, neutralizing antibody titers may fluctuate in an individual patient and have been reported to fall spontaneously in patients on interferon beta.[37,38] Clinicians should consider determining the neutralizing antibody titers in patients whose disease activity seems to be accelerating after 6 months of interferon therapy if continuation of interferon is contemplated.

**Glatiramer acetate**

Glatiramer acetate is well tolerated. Unlike interferon beta, there have been no reports of skin necrosis or laboratory abnormalities in patients treated with glatiramer acetate for at least 6 years.[6] The most common adverse effect is an injection-site reaction, consisting of mild erythema and induration.[12] More infrequently, glatiramer acetate may be associated with a post-injection syndrome, characterized by a variable combination of chest tightness, flushing, dyspnea, palpitations, and anxiety.[12] This systemic reaction is sporadic and unpredictable, and is not associated with cardiac dysfunction. It was reported at least once in 15% of patients in the pivotal study and no more than seven recurrences in any one patient were described. It typically occurs within minutes of an injection and resolves spontaneously in 30 seconds to 30 minutes. Patients should be advised of this potential reaction before they start treatment with glatiramer acetate.

**OTHER DISEASE-MODIFYING AGENTS FOR RELAPSING-REMITTING MS**

**Corticosteroids**

The use of corticosteroids in MS is generally limited to the short-term treatment of acute exacerbations, although their role in maintenance therapy is under study. Corticosteroids generally hasten the time to recovery from a clinically significant relapse. There is no consensus on the optimal formulation, dosage, route of administration, or duration of treatment. One randomized study comparing the effects of oral methylprednisolone (48 mg daily for 1 week, followed by a 2-week taper) and intravenous methylprednisolone (1000 mg/day for 3 days) found no difference in neurologic recovery at 4 weeks.[39] Brusaferri and Candelise conducted a meta-analysis of clinical trials of corticosteroids of various preparations in the treatment of acute relapses of MS and optic neuritis.[40] They concluded that although corticosteroids produced significant improvement in disability at 30 days, there was no statistical difference compared with placebo at longer follow-up. The short-term benefits of corticosteroids were seen with either low or high doses.
Many neurologists favor a 3–7-day course of intravenous methylprednisolone (500–1000 mg/day) followed by an oral taper of prednisone for approximately 10–14 days.\[^1\] Because of the results of the Optic Neuritis Treatment Trial,\[^41\] patients with acute optic neuritis should receive intravenous methylprednisolone (1000 mg daily for 3 days), with or without an oral corticosteroid taper, rather than oral therapy alone.

Regularly scheduled pulsed treatment with intravenous methylprednisolone (often prescribed as monthly infusions of 1000 mg) can be given to patients either alone or in combination with any of the other disease-modifying therapies. This practice is supported by recent clinical trial data reported by Zivadinov et al.\[^42\] They conducted a randomized, controlled, single-blind, phase trial of intravenous methylprednisolone in 88 patients with relapsing-remitting MS. Patients were given either pulses of intravenous methylprednisolone (1 g/day for 5 days with an oral prednisone taper) or intravenous methylprednisolone at the same dose schedule only for relapses for 5 years. The scheduled pulses of intravenous methylprednisolone were given every 4 months for 3 years and then every 6 months for the subsequent 2 years. Compared with intravenous methylprednisolone as needed for relapses, treatment with regularly scheduled pulses of intravenous methylprednisolone resulted in significantly reduced development of T1 black holes ($p<0.0001$), whole-brain atrophy measured by brain parenchymal volume ($p=0.003$), and disability progression on EDSS by 32% ($p=0.0001$).

**BREAKTHROUGH DISEASE ACTIVITY**

Using the currently available disease-modifying therapies for relapsing-remitting MS, some patients have breakthrough relapses or appear to undergo a transition to a more gradually progressive (secondary progressive) course of worsening disability. There may be a variety of reasons for partial or suboptimal response or loss of response in each patient. The persistence of high titers of neutralizing antibodies to interferons may diminish efficacy, as discussed above. Another reason may be delayed initiation of therapy. Evidence accruing from extension studies of placebo-controlled clinical trials of interferon\[^4,5\] and glatiramer acetate\[^6,17\] suggests that delay in initiation of therapy decreases the likelihood of achieving maximal effect on disease activity. The severity of the inflammation and the size of individual lesions may be important in the response to therapy. In the European study of interferon beta-1b in secondary progressive MS, for example, Brex et al. found that interferon had a more pronounced effect in limiting the number of small (<5 mm) rather than large new enhancing T1 MRI lesions.\[^43\] Furthermore, the larger lesions had a greater tendency to evolve into permanent T1 hypointensities (‘black holes’). It is also likely that the tendency to form glial scar and permanent axonal damage is genetically determined and differs among patients.\[^44\]

There are no standard criteria that identify an unsatisfactory therapeutic response. Some of the proposed indicators include relapse rate and severity, change in EDSS, or change on serial MRI evaluation.\[^45\] Most authors agree that some combination of relapses greater than one (especially occurring after the first few months of immunomodulating therapy) or sustained progression of disability equivalent to a 1.0-point increase on the EDSS with or without relapse raises concern about the adequacy of an individual patient’s response to treatment.
No consensus has been reached about the best therapeutic approach in these situations. Many clinicians switch from interferon to glatiramer acetate or vice versa. Others continue to use one of the currently approved immunomodulators in combination with other available agents. Among the drugs being prescribed in combination are intravenous methylprednisolone (sometimes as monthly doses), azathioprine, methotrexate (weekly oral dosing), cyclophosphamide (monthly intravenous dosing), intravenous immunoglobulin, and mitoxantrone. In addition, some clinicians now prescribe one of the interferon formulations in combination with glatiramer acetate. With this combination, Lublin and colleagues have reported that there were no safety concerns observed in preliminary studies with particular attention paid to patterns of T1 enhancement in a series of MRI brain scans. The other various ‘add-on’ agents are discussed below. There are no definitive clinical trial data for any of these combinations. Mitoxantrone has been approved as a stand-alone agent for worsening relapsing-remitting MS and is discussed below.

Azathioprine

Azathioprine is a nucleoside analog of 6-mercaptopurine with immunosuppressive effects. It has been widely used for decades in a number of immune-mediated conditions, usually as a ‘steroid-sparing’ agent. Possible adverse effects include transaminitis, pancreatitis, leukopenia, and slightly increased potential risk of malignancy. A number of trials have reported mixed results of azathioprine used as a stand-alone agent. For example, a 3-year placebo-controlled European study of a 2.5 mg/kg oral daily dose showed a modest effect on EDSS but not on relapse rate, whereas a placebo-controlled study of 56 patients using a dose of 3.0 mg/kg showed benefit in prevention of attacks and time to defined clinical worsening. Combination trials with interferon are under way to test for both safety and efficacy. Preliminary results of a small National Institutes of Health study in the USA showed a significant effect in the reduction of T1 enhancing lesions when azathioprine was added to interferon beta-1b.

Methotrexate

Methotrexate is an inhibitor of dihydrofolate reductase and is often used as a chemotherapeutic agent, but it is also used in a variety of immune-mediated conditions for its antiinflammatory and immunosuppressive effects. Potential side effects include gastrointestinal symptoms (e.g. stomatitis, nausea, vomiting, diarrhea). Liver toxicity (including cirrhosis) and pulmonary fibrosis are possible after prolonged treatment, necessitating appropriate testing to monitor for these effects. A placebo-controlled trial demonstrated a significant effect in delaying progression of disability as determined by a composite measure, including measures of upper and lower extremity function. In this study, oral methotrexate was given weekly in doses of 7.5 mg, and there were no major adverse effects seen. A single-center open-label study of weekly oral methotrexate (20 mg) used in combination with interferon beta-1a given by weekly intramuscular injection for 6 months in 15 patients has been reported. Patients were selected after MRI scans with triple-dose gadolinium demonstrated at least two T1 gadolinium-enhancing lesions during the 3 months of prestudy scans. There was a 44% reduction (p=0.02) in the...
number of enhancing lesions compared with baseline. Nausea was the most common
untoward effect with this combination.

**Intravenous immunoglobulin**

Intravenous immunoglobulin G is used as an immunomodulatory agent in immune-
mediated conditions, including neurologic diseases such as Guillain-Barré syndrome and
myasthenia gravis. An Austrian co-operative, randomized, placebo-controlled 148-patient
study reported by Fazekas et al. using intravenous immunoglobulin G showed a
significant reduction in relapse rate (49%, \( p=0.006 \)) and a significant but unconfirmed
difference in change in EDSS after 2 years.\(^{[57]}\) Another placebo-controlled trial of
intravenous immunoglobulin G (0.4 g/kg per day for 5 days and then monthly for 1 day
for 2 years) showed significant reduction in clinical relapses but not in other outcomes.\(^{[58]}\)
There are no published reports of studies combining interferon or glatiramer acetate in a
systematic or extended manner.

**Cyclophosphamide**

In 1983, Hauser et al. reported that cyclophosphamide, an alkylating agent, reduced
clinical deterioration in patients with what was then called ‘chronic progressive MS’.\(^{[59]}\)
A subsequent multicenter Canadian trial using cyclophosphamide with or without plasma
exchange failed to show any effect compared to placebo.\(^{[60]}\) The placebo control group,
however, fared extraordinarily well on the primary outcome measure confounding the
determination of efficacy. The results of the Northeast Cooperative Study of
cyclophosphamide suggested that its effectiveness in slowing progression may be limited
to patients younger than age 41 years, who may be at an earlier stage of disease before
starting a slow, steady deterioration without relapses.\(^{[61]}\) A multicenter study of
cyclophosphamide combined with interferon beta-1a is under way.\(^{[62]}\)

**Plasma exchange**

Similar to intravenous immunoglobulin G, plasma exchange is an immunomodulatory
therapy used in a variety of indications, including Guillain-Barré syndrome and
myasthenia gravis. Several clinical trials in MS have yielded mixed results. A study by
Hauser et al.\(^{[59]}\) and the Canadian Cooperative trial\(^{[63]}\) failed to show significant benefit in
progressive forms of MS. A more recent sham-controlled cross-over study demonstrated
clinical improvement in 42% of patients with severe corticosteroid-resistant acute (less
than 2 months) demyelinative episodes.\(^{[64]}\) No definitive study combining plasma
exchange with current FDA-approved MS therapies has been published.
SECONDARY PROGRESSIVE MS

Mitoxantrone

Mitoxantrone is an anthracenedione-based chemotherapeutic agent that intercalates into DNA, causing cross-linking and breakage. Its antineoplastic effects have been used in the treatment of leukemia and certain carcinomas. In late 2000, it became the first treatment specifically approved for use in secondary progressive MS by the FDA in the USA. The results of the Mitoxantrone in Multiple Sclerosis (MIMS) trial have been reported and have been accepted by regulatory agencies worldwide as evidence supportive of efficacy in secondary progressive disease. This study was a randomized, placebo-controlled trial in patients with worsening MS, including those with relapses and secondary progression. The primary clinical endpoint, a composite score, showed a significant treatment effect. Enhancing activity on MRI was completely absent in the mitoxantrone-treated group at 1 year, which was a highly significant result. Time to worsening of EDSS was diminished, indicating an effect on slowing accrual of disability. Similar results were seen in earlier, smaller studies, including a study with 51 relapsing-remitting MS patients, which demonstrated a significant impact on attack rate and slowing progressive deterioration.

In general, mitoxantrone is well tolerated, with nausea as the most common immediate side effect. Menstrual irregularities are relatively common. Because life-threatening toxicity can occur (though rarely), mitoxantrone should be prescribed cautiously. It causes a vacuolar cardiomyopathy that may be dependent on the lifetime total dose exposure (risk is estimated at total doses >140 mg/m²). The recommended dosage schedule is 12 mg/m² given by intra-venous infusion every 3 months. Before initiation of therapy, an evaluation of the cardiac ejection fraction must be done. The MUGA scan is the preferred method because of its good reproducibility. It is recommended that mitoxantrone should not be given to any patient with a left ventricular ejection fraction <50%. There is now a case of treatment-related leukemia reported (in less than 1% of MS patients).

Interferon beta

The European study of interferon beta-1b included 718 patients with EDSS between 3.9 and 6.5. Treatment with interferon 8 MIU subcutaneously on alternate days was compared with placebo injections given for up to 3 years in this randomized, double-blinded, placebo-controlled study. Compared with placebo, there was a significant reduction in the active treatment arm with respect to confirmed worsening of 1.0 on the EDSS (p=0.0008), relapse rate (p=0.0002), new lesions on MRI (p=0.0008), and MRI lesion volume (p=0.0001). However, the North American trial of interferon beta-1b using a similar study design (one treatment arm also included dosing by body mass), failed to show a significant difference in the primary outcome measure of confirmed progression of disability measured by change on the EDSS. Secondary outcomes, including clinical relapse rate, enhancing lesions, and T2 lesion burden on MRI, were significantly better in
the interferon-treated group, recapitulating the results of the European study. Although the reasons for the differing results can never be known with certainty, it has been the subject of much post hoc analysis and speculation. Differences in duration of disease and relapsing activity before study entry are among the principal factors thought to be contributing to the discrepant results. The suggestion is that the differential treatment response is due to the fact that, in essence, these differences in pre-trial clinical course represent distinct subpopulations of secondary progressive MS patients: the effect of interferon is less apparent in later stages of secondary progressive disease when fewer relapses are occurring. Progression of disability in later stages may be driven more by a chronic interferon-unresponsive neurodegenerative process than by sporadic inflammation. Another contributing factor of note in the North American trial was the relatively small change on EDSS in the placebo-treated group reflecting the relative insensitivity of the EDSS to change over a 2-year study period.

Similarly, the SPECTRIMS trial of interferon beta-1a given subcutaneously three times weekly in patients with secondary progressive MS failed to find a significant difference in the primary outcome measure of change of 1.0 on the EDSS, but it also showed significant benefit on relapses and pre-determined MRI outcomes. Further analysis revealed a treatment effect when patients with relapses before study were considered separately and supported the hypothesis about the greater impact of interferon treatment in earlier secondary progressive MS with relapses.

A trial of interferon beta-1a 60 µg once weekly intramuscular injection has been completed, and the results have been reported. The Multiple Sclerosis Functional Composite (MSFC), developed by a National Multiple Sclerosis Society task force was the primary outcome measure in this trial. The potential advantages of this tool include the increased sensitivity to change of the functional measures used, the multidimensionality of the composite clinical assessment (including cognitive and upper extremity function in addition to gait, which is strongly emphasized in the 4.0 to 7.5 range of the EDSS), the high intra-rater and inter-rater reliability, and ease of administration.

The study showed a significant reduction (40%, \( p=0.033 \)) in the tendency toward progressive neurological impairment demonstrated by the MSFC in the interferon-treated group compared with the placebo group. Although all three dimensions of the MSFC showed a trend in the same direction (favoring the active treatment group), only the nine-hole peg test of upper extremity function was by itself significantly better than for controls (\( p=0.024 \)). Similar to the previous IFN trials in secondary progressive MS, there were significantly fewer relapses (33%, \( p=0.008 \)), and significantly fewer new and enlarging T2 and enhancing T1 lesions on MRI (\( p<0.001 \)) for both groups, but there was no difference detected in sustained progression of disability determined by change on EDSS.

Taken together, the four trials of the interferon formulations show clear benefit in reduction of attacks and changes on brain MRI but, at best, modest benefit for slowing measurable clinical progression.
PRIMARY PROGRESSIVE AND PROGRESSIVE-RELAPSING MS

Approximately 10% of patients have progressively worsening disability without any detectable exacerbations from the outset of the disease. This pattern seems to occur equally in men and women, often becoming apparent in the fourth or fifth decade of life. Although there is no proven effective therapy, progressive worsening (when occurring rapidly) is sometimes treated with attempts at immunosuppression. Several clinical trials are under way with existing agents, including glatiramer acetate and mitoxantrone. Approximately 6% of MS patients with progressive disease from the outset will develop one or more acute relapses. There are no definitive studies of efficacy with any of the above therapies. It seems reasonable to expect that any of the established therapies for relapsing patterns of disease activity would have a positive impact on the tendency to relapse.

FUTURE DIRECTIONS

Unquestionably, the agents now approved for use in many countries have transformed the therapy of MS over the past 10 years. However, many questions remain to be answered. Will initiation of immunomodulatory therapy have an impact on the accrual of disability in patients treated from the very first isolated symptoms compared with those whose treatment is delayed? How long a delay results in a worse outcome? How will this compare to that predicted by long-term natural history? Can any strategies improve the efficacy or ease of use (i.e. oral or other type of administration) for existing therapies? Can more efficacy be gained from combining therapies? Will better measurement of the disease process by MRI or other technologies allow for improved adjustment of treatments? Will we learn through MRI and genetic analysis which patients are likely to have more aggressive disease from the outset and which are likely to be more responsive or less responsive to the various therapeutic modalities? It is to be hoped that these questions can be answered through well-designed research studies, including new trials and data ‘mining’ from existing databases in the coming years.

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INTRODUCTION

Patients with primary progressive multiple sclerosis (MS) are a unique group with atypical clinical and magnetic resonance imaging (MRI) characteristics, which have resulted in their exclusion from the majority of therapeutic trials. This chapter reviews the few trials in primary progressive MS to date but first discusses the characteristics of primary progressive MS and their implications for treatment and clinical trials, particularly with regard to patient selection and therapeutic monitoring.

BACKGROUND

Approximately 10% of MS patients have a primary progressive course, characterized by a continuous accumulation of neurological deficit from symptom onset, without relapse or remission. There also is a small group of patients with predominantly progressive disease defined in two ways—progressive relapsing MS, characterized by progressive disease from onset with subsequent superimposed relapses, and transitional progressive MS, characterized by a single relapse before or after the onset of disease progression. The primary progressive, progressive relapsing, and transitional progressive subgroups appear to be similar and should at present be considered separately from relapsing-remitting MS and secondary progressive MS with regard to therapeutics. This chapter concentrates on primary progressive MS because it has been the best characterized of the three subgroups to date.

Differences between primary progressive MS and relapsing-remitting MS have been well described. The mean age of presentation of primary progressive MS is later than in relapsing-remitting MS, and relatively more men are affected resulting in an equal male-female ratio. Prognosis has been considered poorer, because time from disease onset to reach advanced disability is shorter than in relapsing-remitting MS. However, compared with the progressive phase in secondary progressive MS, both the rate of progression and the age of onset of progression are similar. MRI is atypical in primary progressive MS with a more marked discrepancy between magnetic resonance activity and disability than in other groups. Patients with primary progressive MS have a paucity of lesions, less gadolinium enhancement, and fewer new lesions developing over
The limited gadolinium enhancement on MRI suggests less inflammation, and this is supported by the pathological finding of significantly less inflammation in primary progressive MS than in secondary progressive MS. Differences in immunological and genetic profiles have also been suggested but are not proven.

If the mechanisms underlying impairment and disability are considered, more fundamental differences may become apparent. Whereas neurological deficit in relapsing-remitting MS appears to result from incomplete remission from relapses, in primary progressive MS, deficits arise from disease progression. These differences may relate to mechanisms of axonal loss, the probable correlate of fixed neurological deficit. In relapsing-remitting MS, axonal loss may be related to acute inflammatory demyelination, whereas in primary progressive MS, it may result from a more diffuse process with low-grade inflammation. This hypothesis is supported by the MRI finding that diffuse abnormalities of the brain and spinal cord are more common in primary progressive MS than in relapsing-remitting MS or secondary progressive MS; this has been confirmed pathologically in the spinal cord. Although inflammation is less in primary progressive disease, it clearly occurs. It may be that there is a different relationship between inflammation and axonal loss, perhaps with axons being more susceptible to damage.

These clinical, MRI, and pathological features suggest that primary progressive MS is a distinct subgroup of MS. However, the classification of primary progressive MS has only come into regular use in the past decade being reinforced by the Lublin and Reingold consensus definitions. Previously, poorly defined terms such as ‘chronic progressive’ MS have been used to describe any type of progressive disease course. Although there have been trials in progressive MS, few trials have specifically addressed primary progressive MS. This raises the question as to whether or not specific trials for primary progressive MS are required. The answer to this probably is yes, if two issues are considered. First, the proposed differences in the mechanisms underlying impairment and disability may have implications for the choice of therapeutic agent. If axons in primary progressive MS are more susceptible to damage than other forms of MS, therapeutic agents directed at axonal protection as well as at suppressing inflammation may be particularly useful in this group. Second, the atypical clinical and MRI characteristics pose particular problems in selecting patients for treatment and designing therapeutic trials. The implications of these characteristics for patient selection, choice of outcome measures for therapeutic monitoring, and duration and size of study are now discussed.

**PATIENT SELECTION**

Before treatment in any patient group is initiated, a secure diagnosis should be made, and this is particularly difficult in patients with primary progressive MS. The first step is to exclude other progressive diseases. Most patients with primary progressive MS present with a single progressive symptom, usually implicating the spinal cord. Therefore, other causes of progressive pathology, such as compressive spinal cord lesions, must be excluded; MRI plays a particularly important role in this step.

Second, the certainty of the diagnosis of MS has to be established. Conventionally, the Poser et al. criteria have been used, but patients with primary progressive MS do not
readily conform to these criteria. Patients with only a single clinical lesion cannot be
classified as having clinically definite MS, and so more emphasis has to be put on the
presence of oligoclonal bands and paraclinical evidence of dissemination in time and
space. To address the problem of certainty of diagnosis in primary progressive MS,
specific diagnostic criteria recently were developed. Three levels of diagnostic
certainty were defined—definite, probable and possible—based on clinical, cerebrospinal
fluid, MRI and neurophysiological findings. Evidence of intrathecal immunoglobulin
(Ig)G synthesis is of central importance and must be present for a definite diagnosis,
covered with one of the following MRI criteria: nine brain lesions, two spinal cord
lesions, or between four and eight brain lesions and one spinal cord lesion. These criteria
have as yet only undergone limited validation on retrospective data. The diagnostic
criteria for MS were recently revised and have incorporated these criteria for primary
progressive MS, with some simplification in that there are only two levels of diagnostic
certainty—possible MS and MS.

Finally, a history of progressive disease from onset, without relapse or remission, must
be established. This may be difficult because details of the initial presentation may fade
with the passage of time, and it may not be possible to distinguish retrospectively
between fluctuations in function and true neurological relapses. The difficulties in
establishing a diagnosis of primary progressive MS were highlighted in the recent study
of interferon beta-1a in which only 50 of 138 patients referred with a diagnosis of
primary progressive MS were enrolled. Of the 88 patients not included, 50% either did
not have a primary progressive course on detailed history or did not fulfill diagnostic
criteria for definite MS.

The timing of initiation of therapy also presents problems in this group. There is
growing evidence that axonal loss occurs early in the disease course of MS and, although not universally accepted, the US National MS Society recommended that
therapy should be initiated as soon as possible after diagnosis. In primary progressive MS it has been suggested that inflammation is more evident in early disease than in
established disease, and therapy may therefore be more effective early in the disease
course. However, the new diagnostic criteria propose that a disease duration of 1 year is
required before making a definite diagnosis of primary progressive MS. This means
that patients with very early primary progressive MS will be excluded from therapy as
few, if any, are diagnosed in the first year of the insidious onset of their symptoms.

In established disease it is not clear whether severity of disease should influence
initiation of therapy. Whereas in relapsing-remitting MS, frequent or severe relapses with
significant residual deficits often prompt treatment, the majority of patients with primary
progressive MS have a gradual course. Rate of disease progression may be a guide to
‘active’ patients because change in the expanded disability status scale (EDSS) in the
short term has been reported to predict faster disease progression in the longer term. The occurrence of new lesions on MRI also may predict future disease progression in
primary progressive MS.

Another problem with primary progressive MS is the increased incidence of general
medical problems caused by the higher mean age of presentation. In the study of
interferon beta-1a, 12.5% of patients not entered in the study were excluded on general
medical grounds, for example, because of ischaemic heart disease or spinal cord
compression. Cervical spondylosis is common in this age group, and spinal cord
compression may be present at entry into a clinical trial, or it may develop during the trial and confound clinical assessment. Patients with general medical problems may be more sensitive to any toxic effects of therapeutic agents.

**THERAPEUTIC MONITORING**

**Clinical outcome measures**

In any definitive therapeutic trial in MS, the primary outcome measure has to be clinical,[31] conventionally relapse frequency and severity, and disease progression. In primary progressive MS assessment of relapses is not applicable, so the clinical outcome is limited to disease progression. Currently the most widely used measure of disease progression is the EDSS.[32] However, there are limitations to its validity and reliability, and its responsiveness is poor.[33] Responsiveness of a clinical scale is particularly important in primary progressive MS, because disease progression is gradual and small changes may be clinically significant. Despite its limitations, the EDSS has remained the first choice for the majority of clinical trials. However, a functional composite measure that incorporates quantitative tests of arm, leg, and cognitive function—the multiple sclerosis functional composite measure (MSFC)[34]—was recently developed. Early evaluation has confirmed its validity and reliability [35,36] The MSFC is now being included in longitudinal clinical trials, which will provide further information, particularly on its responsiveness.

**MRI outcome measures**

MRI outcome measures are now widely used as surrogate markers of disease activity in MS, either as a primary outcome in preliminary short-term trials in relapsing-remitting MS and secondary progressive MS, or as a secondary outcome in definitive long-term trials in relapsing-remitting MS, secondary progressive MS, or primary progressive MS.[37] However, currently there are no valid MRI markers that can be used as a primary outcome in preliminary trials in primary progressive MS.[29] Owing to the rarity of primary progressive MS, the validity and reliability of MRI markers is particularly important because multicentre trials will be necessary and markers must be robust across centres.

Therapeutic trials in relapsing-remitting MS and secondary progressive MS usually assess conventional MRI markers of gadolinium-enhancement and changes in T2-weighted MRI lesion volume. However, in primary progressive MS, the rate of development of new lesions is low, and there are few gadolinium-enhancing lesions.[13] Cerebral T2 lesion load may be a responsive measure. Significant change has been demonstrated over 1–2 years,[38,39] but no correlation has been shown to date between T2 lesion load and EDSS in cross-sectional[4] or longitudinal studies.[38] Triple-dose gadolinium may increase the yield of enhancing lesions,[40] although this has not been confirmed[41] Fast fluid-attenuated inversion recovery (FLAIR) imaging may increase detection of subcortical lesions in this group[42] However, even with such optimization, the role of conventional MRI measures as markers of disease activity remains limited in
primary progressive MS. Conventional imaging of the spinal cord was expected to be more relevant than brain MRI, because clinical spinal cord involvement is common in primary progressive MS. However, no correlation was demonstrated between cord lesion load and disability in cross-sectional or longitudinal studies.

It appears likely that more pathologically specific markers of tissue destruction may be more clinically relevant in primary progressive MS. Although T1 hypointensity is thought to reflect more destructive lesion pathology, T1 hypointense lesion load in primary progressive MS did not correlate with EDSS in cross-sectional or longitudinal studies. Atrophy appears to be a more promising marker of disease progression in primary progressive MS, because it would be expected to reflect the overall tissue destructive process. Spinal cord cross-sectional area correlates strongly with disability, and significant spinal cord atrophy progression has been demonstrated in primary progressive MS in only 1 year. Spinal cord atrophy did not demonstrably correlate with progression in disability in the short term, but in a 5-year study, a weak correlation was seen between change in cord area and disability. Spinal cord atrophy therefore remains a promising marker of disease progression in the longer term. Using a measure of partial brain volume, significant correlation with disability cross-sectionally was demonstrated in primary progressive MS. A more sensitive and reproducible technique also confirmed whole brain atrophy and ventricular enlargement occurring over 1 year in patients with primary progressive MS.

Owing to the paucity of lesions in primary progressive MS, it appears likely that intrinsic changes in normal-appearing brain tissue (NABT), including normal-appearing white matter (NAWM), may make a major contribution to disability in this group. Magnetization transfer imaging, 1H magnetic resonance spectroscopy (MRS), and diffusion imaging are potentially powerful tools to study changes in NABT and NAWM as well as lesions. A significant reduction in the magnetization transfer ratio (MTR) in lesions and small but widespread reductions in NAWM were demonstrated in primary progressive MS. Studies using MTR histogram analysis identified abnormalities in MTR parameters in primary progressive MS in both brain and spinal cord but found no correlation between individual MTR parameters and disability. To date, there are limited longitudinal MTR data in primary progressive MS, with one small study finding no significant changes over 1 year, but another reporting a reduction in MTR of NABT over 2 years. Further evaluation of the role of MTR in monitoring disease progression is required. On MRS, there is a reduction in N-acetyl aspartate in lesions and NAWM in primary progressive MS, but longitudinal studies are required to evaluate the relationship between these changes and disability. Finally, a preliminary study of diffusion imaging in primary progressive MS demonstrated increased apparent diffusion coefficient in lesions, but further work is required to evaluate its validity and practicality as a disease marker.

Study duration and sample size

The choice of outcome measures is a major determinant of the duration and sample size of any study. In primary progressive MS, the primary outcome must be disease progression and the study must be sufficiently long to ensure that the disease will have
progressed in a significant number of patients. Until recently there have been limited data available on the rate of disease progression in primary progressive MS, but a study in Ontario, Canada has now extended the natural history data.\textsuperscript{[58]} From this database, sample size tables have been developed to give the number of patients and duration of follow-up required to detect a significant difference in disease progression.\textsuperscript{[59]} These sample size calculations will be useful in the planning of future therapeutic trials in primary progressive MS. However, they confirm the view that large multicentre trials with several hundred patients per treatment group will be required.

\section*{THERAPEUTIC TRIALS}

Currently there is no definitively proven disease-modifying treatment available for primary progressive MS. Several trials have been completed in chronic progressive MS but without clear distinction between primary and secondary progressive disease. Some of these trials have made reference to primary progressive MS, but there has been insufficient evidence available to recommend the use of these agents in this patient group. More recently, a number of trials have been specifically designed for primary progressive MS, and preliminary results from the first of these trials are now available.

\section*{Trials including patients with PP-MS}

\textit{Azathioprine}

Several randomized, controlled trials of azathioprine have been carried out in MS. A metaanalysis of these trials confirmed a slight clinical benefit.\textsuperscript{[60]} In one trial a subgroup of 51 patients with progressive disease from onset was included. Although analysis of the whole group showed a small beneficial effect, no significant effects were seen in the patients with progressive disease from onset.\textsuperscript{[61]}

\textit{Methotrexate}

A randomized, double-blind, placebo-controlled trial of low-dose oral methotrexate in chronic progressive MS demonstrated benefit on disease progression measured by a newly developed composite measure.\textsuperscript{[62]} The study included 18 patients with primary progressive MS, but the result was not significant when considering the primary progressive group alone.

\textit{Cladribine (2-chlorodeoxyadenosine)}

In the double-blind, placebo-controlled phase III trial of subcutaneous cladribine in progressive MS, 48 patients had primary progressive MS.\textsuperscript{[63]} No clinical efficacy was apparent for the overall study. A significant treatment effect on gadolinium-enhancing lesions was reported for the whole cohort but was not seen on subgroup analysis of the primary progressive group.
Intravenous immunoglobulin

A double-blind, placebo-controlled study of intravenous immunoglobulin was carried out in progressive MS, including 50 patients with primary progressive MS. The primary outcome measure was the EDSS, but there was no MRI evaluation. Results have not yet been published, but a recent large trial in secondary progressive MS was negative.

Trials specifically designed for primary progressive MS

**Interferon beta-1a**

An exploratory double-blind, placebo-controlled study of two doses of intramuscular interferon beta-1a (30 or 60 µg weekly) in 50 patients with primary progressive MS over 2 years was recently completed. The 60-µg dose was poorly tolerated, owing to flu-like reactions and increases in liver enzymes, but the 30-µg dose was well tolerated. No effect was seen on EDSS progression or the timed 10-m walk, although there was a non-significant trend favouring interferon beta-1a 30 µg on the nine-hole peg test. There was a suggestion of a treatment effect on T2 lesion load favoring the 30-µg dose, but no positive effects were seen on the other secondary MRI outcomes, including T1 lesion load, new lesions, and spinal cord and brain atrophy. Tertiary MRI outcomes included MTR and MRS. Peer-reviewed publication of results is awaited.

**Interferon beta-1b**

Interferon beta-1b was shown to delay disease progression in secondary progressive MS in patients both with and without superimposed relapses. A double-blind, placebo-controlled trial of subcutaneous interferon beta-1b (8 MIU on alternate days) in 70 patients with primary progressive MS and transitional progressive MS over 2 years has been completed. Clinical outcome measures included the EDSS, and MRI outcomes included lesion load, cervical cord area, MTR, and MRS. The results are not yet available.

**Glatiramer acetate**

A double-blind, placebo-controlled trial of subcutaneous glatiramer acetate (20 mg daily) over 3 years is currently under way. It is the largest trial in primary progressive MS to date and is the first definitive therapeutic trial. A total of 946 patients have been recruited from North America and Europe with the use of strict clinical criteria. The primary outcome measure is the EDSS, and secondary outcomes include the MSFC and MRI measures. The study will also provide important natural history data. Evidence of intrathecal IgG synthesis was sought in all subjects and was not present in almost 20%; the information provided on the characteristics of this subgroup will be of particular interest.
**Riluzole**

A small pilot cross-over study of the neuroprotective agent riluzole has been completed in 16 patients. [70] The primary outcome measure was spinal cord area. EDSS and T1 and T2 lesion loads were secondary outcome measures. Non-significant trends for a reduction in the rate of spinal cord atrophy and T1 hypointense lesion accrual were seen.

**Mitoxantrone**

A double-blind, placebo-controlled trial of mitoxantrone in 54 patients with primary progressive MS is under way.[71] Outcome measures include the EDSS, nine-hole peg test, and MRI measures.

**CONCLUSION**

Until recently, therapeutic trials in primary progressive MS have been a neglected area. Now, with the advent of disease-modifying drugs, this group should no longer be excluded from therapeutic trials. Design and recruitment to therapeutic trials in primary progressive MS present unique difficulties, but this pursuit is an important and worthwhile challenge. Certainty of diagnosis has been a key problem but is now being addressed by newly developed diagnostic criteria. Further work is required to validate reliable clinical and MRI markers of disease progression to facilitate future therapeutic trials and to monitor efficacy. Further elucidation of pathophysiology also is required to guide the development of therapeutic agents. The aim of future therapeutic agents should be to target the underlying pathological process, which in primary progressive MS may well be axonal loss.

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Fatigue in multiple sclerosis
Lauren B Krupp

INTRODUCTION

Fatigue is a common symptom in multiple sclerosis (MS) and can profoundly disrupt the occupational and social functioning of patients. [1–5] Approximately 75–90% of people with MS report fatigue, and for many patients it is a daily concern. [1,2,6] A number of recent studies, which have advanced our understanding of MS fatigue, are summarized in this review. [7–14]

DEFINITION AND MEASUREMENT OF FATIGUE

A useful working definition developed by a consensus conference of MS researchers and clinicians states that fatigue is “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities”. [15] The consensus conference definition emphasizes the person’s subjective experience. Self-report measures are widely used to assess fatigue and have the advantages of ease of administration, convenience in clinical settings, and a focus on the experiences and concerns of patients.

A number of instruments that are available to assess perceived fatigue in MS are listed in Table 36.1. The Fatigue Severity Scale (FSS) is useful in distinguishing fatigued versus non-fatigued groups. [3] The FSS measures the effect of fatigue on activities of daily living. It has been used in a variety of MS studies [7,8,16,17] and correlates strongly with other fatigue measures. [3,16,18] It is closely associated with perceived health. [19] The FSS was a sensitive outcome in several treatment trials of fatigue. [20–22] Versions of the FSS have been developed in several different languages and used with over 1000 patients and have been found to be reliable and internally consistent. [23]

Many MS fatigue scales are designed to assess

Table 36.1 Fatigue measures

| Fatigue Severity Scale (FSS) [3] |
| Fatigue Impact Scale (FIS) [6] |
| Multidimensional Assessment of Fatigue (MAF) [24,25] |
| Checklist of Individual Strength (CIS) [39] |
| Multidimensional Fatigue Inventory (MFI) [75] |
| Fatigue Assessment Instrument (FAI) [26] |
| Fatigue Scale (FS) [76] |
| Fatigue Descriptive Scale (FDS) [16] |
| Profile of Mood States (POMS) [29] |
multiple characteristics. The Multidimensional Assessment of Fatigue (MAF)\(^{24}\) is a measure of general fatigue that was developed for patients with rheumatoid arthritis and has been effective in studies of patients with MS.\(^{25}\) The dimensions include severity and frequency of fatigue, degree of interference in activities of daily living, and associated distress. The Fatigue Impact Scale (FIS) is a 40-item questionnaire that includes cognitive, psychosocial, and physical dimensions.\(^{6}\) Its shorter version, the 21-item Modified Fatigue Impact Scale (MFIS), has been recommended for studies on MS by a consensus conference.\(^{15}\) The FIS was a strong predictor of mental and general health in a population of 85 MS patients\(^{6}\) and was sensitive to treatment effects in a clinical trial.\(^{20}\) The Fatigue Assessment Instrument (FAI)\(^{26}\) is a 29-item questionnaire that identifies a severity factor and a situation-specific factor. The situation-specific factor addresses features of fatigue that are more specific to MS, such as the exacerbating effects of heat. Another multidimensional scale, the Fatigue Descriptive Scale (FDS),\(^{16}\) identifies several components of fatigue including asthenia and fatiguability. The FDS also generates a global score, which is strongly correlated with the FSS (\(r=0.87\)).\(^{16}\)

Other assessments of fatigue are contained within larger self-report inventories. Such measures include the tiredness-thinking measure within the Functional Assessment of Multiple Sclerosis (FAMS),\(^{27}\) the vitality subscale of the Medical Outcome Survey (MOS and Short-Form36),\(^{28}\) and the tiredness-vigor subscale of the Profile of Mood States (POMS).\(^{29}\)

One drawback of all self-report scales is that they are subject to retrospective bias. That is, how a patient in the office rates his or her fatigue over the past 1–2 weeks may reflect the degree of difficulty in getting to the doctor’s office for the appointment that day as well as their recollection of the recent past. Ecological momentary assessment methods, which involve frequent and random monitoring of affect and fatigue on a real-time basis, may overcome the problem of retrospective bias.\(^{30}\)

An alternative approach to fatigue measurement involves more objective or performance-based evaluations. Physiologically, fatigue is defined by a reduction in power output over time. A common measurement is the time-force curve during maximal effort (e.g. sustained muscle contraction). With this measurement approach, MS patients have been shown to have significantly greater motor fatigue than healthy controls or patients with chronic fatigue syndrome.\(^{31}\) Declines in central motor drive,\(^{32}\) decreased muscle torque during sustained contractions, and reduced motor evoked potentials\(^{33–35}\) have all been proposed explanations of the physiological findings.

Although more difficult to measure, cognitive functioning may also be susceptible to fatigue. In a study of 45 MS patients and 14 healthy controls in whom cognitive evaluation was performed before and after a continuous cognitively effortful task, the MS subjects declined on measures of memory and conceptual thinking during the testing session, while the controls continued to improve with practice.\(^{9}\) Kujala et al. demonstrated a similar decline in cognitive performance during the last few minutes of a vigilance task during a testing session in MS patients who were otherwise cognitively intact.\(^{36}\) These findings suggest that cognitively effortful tasks may be associated with a decline in performance over time. Performance-based measures of cognitive or motor
fatigue distinguish MS patients from healthy controls. However, in most studies to date these objective measures do not show significant correlations with perceived fatigue.\cite{9,21,32,35,37}

ASSOCIATION OF FATIGUE WITH OTHER CLINICAL CHARACTERISTICS

Mood

Many MS patients with severe fatigue have neither depressive symptoms nor any signs of a clinical affective disorder.\cite{3,38,39} However, more often, depressed mood or other psychological factors influence a person’s experience of fatigue. Measures of psychological distress are often correlated with self-reported fatigue measures with correlation coefficients ranging from 0.1 to 0.55.\cite{17,8,14,39,40}

Fatigue is lessened by feelings of control and exacerbated by focusing on bodily sensations.\cite{39} People who feel that they can create environments appropriate to their psychological and physical needs experience less fatigue and fatigue-related stress.\cite{25} in other medical groups with severe fatigue, fatigue correlates with low positive affect but does not correspond to elevated negative affect.\cite{41,42} The author has recently found a similar association between low positive affect and elevated fatigue in MS.\cite{43}

Neurologic impairment and disease course

Fatigue is only weakly associated with overall neurologic impairment.\cite{6,7,25,40} Some investigators, but not all, have found the correlation between fatigue and expanded disability status scale (EDSS) to be significant. The pyramidal functional system of the EDSS has been correlated with fatigue.\cite{44} However, other factors may account for the identified association between physical impairment and MS. For example, in another study the observed association between EDSS and fatigue was greatly attenuated after controlling for the effects of mood and lost statistical significance.\cite{8}

Fatigue may be a major handicap in patients with relapsing MS, and the symptom appears even more severe among MS patients with a progressive disease course.\cite{6,40,45} However, the greater severity of fatigue in progressive MS could be due to increased depressive symptoms in this MS subtype\cite{8} or to higher EDSS.\cite{7} Neither age nor sex has shown a meaningful association with fatigue. Perceived fatigue does not show an association with performance on conventional neuropsychological tests.\cite{25,46} Furthermore, medications found to ameliorate fatigue have shown inconsistent effects on cognitive function.\cite{46,47} Changes in cognitive function over the course of a testing session are not correlated with changes in perceived fatigue.\cite{9,37} Finally, neuroimaging studies have failed to identify an anatomical substrate for fatigue.\cite{8,48–50}
PATHOGENESIS OF FATIGUE

The pathogenesis of fatigue remains uncertain. While some have suggested involvement of premotor, limbic, basal ganglia, or brainstem areas as a cause of decreased motivation or motor readiness, there are no established anatomic markers of fatigue. Immune factors may contribute to fatigue. Medications such as interferon alpha and interferon beta sometimes produce prominent fatigue as an initial side effect.\(^{51,52}\) The mechanism for this effect is not known. However, the effects of interferon on neuro-endocrine pathways or on the induction of other cytokines such as interleukin (IL)-6 may contribute to the production of fatigue.\(^{53,54}\) In both human and animal studies, other cytokines, including IL-1 and tumor necrosis factor have also been associated with either sleep induction or fatigue.\(^{55-57}\) In a study of measures of circulating immune activation, an association between perceived fatigue as evaluated by two different fatigue scales was noted.\(^{58}\) However, others examining the relationship between inflammatory cytokines and fatigue have not replicated these findings.\(^{13}\) Given the sensitivity of circulating inflammatory cytokines to many variables and the challenges in their measurement, one can imagine that an association of this biologic marker with such a heterogeneous entity as fatigue would be difficult to detect consistently.

It is reasonable to speculate that fatigue may have a neuronal basis. Disruption of the neuroendocrine axis may relate to perceived stress, arousal, and fatigue.\(^{59}\) The strongest support to date comes from studies of altered cerebral metabolism. Positron emission tomography in subjects with MS identified a significant association between perceived fatigue as measured by the FSS and cerebral glucose availability.\(^{60}\) Decreases in the brain supply of glucose could cause fatigue either via decreased blood glucose or impaired cerebral glucose metabolism. Disruption of neurotransmitter systems, including serotonergic pathways, interferes with attention and could also cause cognitive fatigue.\(^{61}\) While an association between perceived fatigue and changes in the amplitude of event- and motorrelated evoked potentials has been noted in small patient samples,\(^{48,62}\) slowing of nerve conduction does not appear to be associated with fatigue.\(^{12,21,48}\) One of these studies lacked adequate controls for changes, owing to repeated test administrations (independent of fatigue) limiting the interpretation of the findings.\(^{62}\) Magnetic resonance imaging (MRI) studies have demonstrated conflicting results. Three of four studies did not identify a consistent relationship between cerebral atrophy, lesion burden, and measures of fatigue.\(^{8,48-50}\) However, additional investigation with functional MRI and other measures of neuronal function may support the presumed central neural basis for fatigue.

NON-PHARMACOLOGIC TREATMENTS

Among the non-pharmacologic treatments, education and support are very important. Patients are directly helped by validating fatigue as a genuine feature of MS. Exercise is a powerful method to combat deconditioning and enhance self-esteem.\(^{63}\) While a graded exercise program is useful, over-exertion can be detrimental. Carefully timed rest periods
during the working day and avoidance of environmental factors that worsen fatigue (such as heat) can lessen fatigue and enhance productivity.

A 1-year multidisciplinary rehabilitation program reduced fatigue and MS symptoms in a group of 20 progressive MS patients compared with a wait-list control group.\[64\] Behavioral therapy is another means for managing fatigue. When behavioral techniques have been applied to patients with chronic fatigue syndrome, there has been a significant reduction in depression and fatigue components caused by mood disorder.\[65–67\] Behavioral therapies on an individual or group basis can also be easily applied in MS.

**PHARMACOLOGIC TREATMENTS**

Often non-pharmacologic interventions must be supplemented with medications. Treatments shown to be effective in randomized controlled trials are amantadine (an antiviral agent that also has an antiparkinson effect),\[34,68,69\] modafinil (a non-dopaminergic agent approved for narcolepsy),\[20\] and pemoline (a central nervous system (CNS) stimulant).\[70\]

In a double-blind, multicenter treatment trial with a cross-over design, amantadine significantly improved fatigue relative to placebo.\[69\] In another study comparing pemoline and placebo, no significant differences emerged, but there was a trend in favor of pemoline.\[70\] In a placebo-controlled, randomized study with a parallel-group design, pemoline, amantadine, and placebo were compared. Amantadine was the most effective agent.\[34\] Side effects with either medication in this study were infrequent. More recently, modafinil was found to improve MS-associated fatigue.\[20\] In a cross-over, dose-escalation, single-blind study, modafinil at a dose of 200 mg/day was superior to placebo in reducing fatigue. Interestingly, higher doses of modafinil (400 mg/day) improved sleepiness but not fatigue. The beneficial effects with modafinil can be dramatic, yet modafinil lacks the side effects of many CNS stimulants. Some patients experience headache with the 400-mg dose. On the basis of the efficacy of amantadine and modafinil and their low side-effect profiles, these are the agents to consider first in pharmacologic management of fatigue.

As shown in Table 36.2, amantadine is usually prescribed at a dose of 100mg twice daily. Modafinil can be begun at 100 mg/day for 3 days and then increased to 200 mg/day, in the morning. An alternative approach is to administer the medication at a dose of 100mg morning and afternoon. Drug holidays administered 2 days a week may prolong the therapeutic effect for either agent. The dose of pemoline needs to be determined. Most patients do well on 18.75 mg/day or 37.5 mg/day, but liver function tests need to be monitored periodically.

Other medications that are anecdotally

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Usual maintenance dose</th>
<th>Maximum dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine 100 mg/day</td>
<td>100 mg/day in the</td>
<td>300 mg/day</td>
<td>Insomnia</td>
<td></td>
</tr>
</tbody>
</table>
reported to be useful for fatigue include CNS stimulants such as methylphenidate or dextroamphetamine. CNS stimulants should be used with caution, but in selected cases they have value. They are contraindicated in patients with abuse potential. A potential future therapy is 4-aminopyridine. In a study examining its long-term efficacy and safety, fatigue was reported to improve with therapy.[71] A pilot study in MS with 3,4-diaminopyridine reported subjective fatigue improvement in six of eight treated subjects but no change in physiological fatigue measures.[33] Unfortunately, seizures can occur with 4-aminopyridine, and this has interfered with further development of this therapy for MS.

For patients with concomitant depression and fatigue, the initial treatment of choice consists of antidepressant medication (see chapter 39). Fatigue is likely to be resistant to all therapy if the depression is not treated first. Even patients who deny depressive symptoms may have positive responses to antidepressant medication. Agents with the least sedating properties are preferable, such as fluoxetine, sertraline, nefazodone hydrochloride, desipramine, cirprolam, or venlafaxine.

In patients in whom fatigue is associated with sleep disorder, improved sleep hygiene is important. For some patients, exercise taken 6 hours before sleep can help. Medications for insomnia may also lower fatigue.

When fatigue is associated with anxiety, pharmacologic treatments that alleviate anxiety or panic attacks can reduce fatigue.

**IMPLICATIONS FOR PRACTICE**

The clinical management of fatigue should include an assessment of the various factors that
Fig. 36.1 Evaluation and treatment of fatigue
can cause fatigue as well as a step-wise treatment approach that encompasses non-pharmacologic and pharmacologic interventions (Fig. 36.1). With new-onset fatigue, the possibility of a relapse should be considered. Other questions also need to be addressed when the MS patient with increased fatigue is evaluated. One is whether infection is present or whether there has been increased heat exposure. One also needs to determine changes or additions of medications with potential fatigue side effects. Medications to review include antispasticity agents, β-blockers, tricyclic antidepressants, benzodiazepines, and anticonvulsants. At some point in their disease course, patients should be evaluated with a laboratory screen of blood tests (see Fig. 36.1) to exclude other fatigue-producing conditions. Testing should include thyroid function tests, a complete blood count, electrolytes, glucose, tests of liver function, erythrocyte sedimentation rate, and urinalysis and culture.

Since many MS symptoms may contribute to fatigue, the evaluation should include questions about pain, sleep, and depression. For example, patients experiencing poor sleep from painful spasms may experience increased energy the next day if nocturnal pain is controlled with small doses of medications such as tizanidine or baclofen. Assessment of mood is critical to the evaluation of fatigue. Most patients with MS have elevated depressive symptoms although they may not meet the criteria for major depression. A simple office approach to assess for mood disorders is to administer self-report questionnaires such as the Beck Depression Inventory[72] or the Center for Epidemiologic Studies Depression Scale (CES-D).[73] Methods for dealing with the overlap between self-reported depressive symptoms and somatic symptoms can enhance the specificity of the mood scales.[74] The evaluation should also include questions about the patient’s family history of psychiatric illness, the status of the family unit, and the presence or absence of related support systems. For patients in whom overwhelming fatigue is associated with severe depression, or in patients who are refractory to all forms of fatigue therapy including exercise, medications, and behavioral interventions, psychiatric referral may be of value.

Treatment requires a multidisciplinary approach that considers the various factors that may contribute to fatigue. Once these contributing factors have been addressed and other causes have been ruled out, there is good evidence that reassurance, education about the symptom, physical therapy, avoidance of heat, initiating rest periods, and methods for energy conservation are valuable. Medications, particularly amantadine or modafinil, are well tolerated and may be beneficial for many patients. Selection of the appropriate patients for pharmacologic intervention, periodic assessment of the response to therapy, and considerations of drug holidays can enhance the efficacy of pharmacologic intervention.

**IMPLICATIONS FOR STUDIES**

Fatigue is a frequent and often disabling symptom of MS. Clinical treatment trials are currently limited by the lack of a well-validated definition for fatigue. Future studies should include outcomes that address the motor, cognitive, and subjective components and involve self-report and performance-based outcomes. Studies of fatigue must also assess those variables most closely associated with fatigue. Included among the
assessments should be measures of psychological distress or depressive symptoms and neurologic impairment. As our understanding of fatigue continues to grow, improved therapies are likely to follow.

ACKNOWLEDGMENTS

This work was supported in part from the National Multiple Sclerosis Society (grant number RG3042-A-2), National Institutes of Health (grant number HD38107–01) and the National Institutes for Disability and Rehabilitation Research (grant number H133G990058).

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Management of spasticity in multiple sclerosis
François A Bethoux

INTRODUCTION

Spasticity has been defined as a velocity-dependent increase in resistance to passive muscle stretching caused by the exaggeration of tonic stretch reflexes.[1] Spasticity is frequently encountered in multiple sclerosis (MS), often with significant subjective and objective consequences. In a prevalence study of 301 MS patients, 52% reported cramps, and 56.5% had increased tone on examination.[2] Disease-modifying therapies usually do not provide symptom relief, and there are even reports of increased spasticity with interferon beta.[3] Although the pathophysiology of spasticity is incompletely understood, a wide array of symptomatic therapies are available to the clinician.

PATHOPHYSIOLOGY

The main mechanism leading to spasticity is the hyperexcitability of α-motor neurons, caused by decreased descending inhibitory signals secondary to lesions within the central nervous system (CNS).[4] The lack of inhibition of intramedullary oligosynaptic or polysynaptic pathways, physiologically mediated by the neurotransmitter γ-aminobutyric acid (GABA), results in hyperactivity of the stretch reflex. Two clinical models have been described. In the spinal model, reflex activity appears to build up more slowly, suggesting predominant involvement of polysynaptic pathways. In the cerebral model, monosynaptic pathways could be responsible for more rapid increase in reflex activity.[5] In clinical trials, spasticity from MS is often considered as spasticity of spinal origin, although the presence of diffuse lesions throughout the neuraxis would suggest a mixed pathophysiology.

CLINICAL FEATURES

The upper motor neuron syndrome can be divided into positive signs and symptoms (increased muscle tone, exaggerated tendon reflexes, spread of stretch reflex, clonus, synergy patterns, Babinski sign) and negative signs and symptoms (loss of dexterity, weakness), which most often coexist and which, in MS, are often associated with signs and symptoms of deficits in other neurologic systems (e.g. ataxia and sensory deficits).

Consequences of spasticity reported by patients or caregivers are muscle stiffness, spasms, pain, loss of extremity function, difficulty maintaining standing or sitting postures, and decreased ease of care or self-care (e.g. difficulty performing intermittent
catheterization, owing to adductor spasticity). Objective signs include exaggerated stretch reflexes, clonus, spasms, synergy patterns, co-contraction of agonist and antagonist muscles, increased resistance to passive movement with or without ‘clasp-knife’ phenomenon, decreased range of motion, and abnormal posture. Dynamic phenomena (abnormal movements) are related to reflex hyperexcitability, and static phenomena (decreased range of motion) are caused by changes in the rheologic properties of musculoskeletal structures. Spasticity often contributes to limitations in the ability to perform activities and to fulfill familial and societal roles, along with other neurologic impairments. It is important to remember that spasticity can also have beneficial consequences. For example, a patient may use extensor spasms to stand and perform pivot transfers, which would otherwise be compromised by severe paraparesis. It is also believed that spasticity decreases the risk of deep venous thrombosis and pressure ulcers by maintaining muscle tone in paralysed muscles. Spasticity increases with stress and noxious stimuli (e.g. pain, decubiti, urinary tract infection, ingrown toenail), and usually exhibits spontaneous fluctuations (typically increasing at night). Variations in ambient and core body temperature have been reported anecdotally to affect spasticity.

**ASSESSMENT**

**Impairments**

**Clinical evaluations**

The most common way to evaluate spasticity is to record the symptoms and signs listed above during a standard neurologic examination. This method is usually sufficient for routine clinical practice. However, for research purposes and clinical trials, more standardized, quantitative, and reliable measures are needed. The Ashworth scale, in its standard[6] or modified[7] version, is an ordinal measure of resistance to passive movement in the extremities. Satisfactory inter-rater and intra-rater reliability in trained evaluators has been reported. However, the Ashworth scale exhibits low sensitivity to change, and addresses only one aspect of spasticity. Limitations of the Ashworth scale have been summarized in a recent review of the literature.[8] The Spasm Frequency Scale[9] and a 10-cm visual analog scale for pain can be used to complement the Ashworth scale, but both are based on self-report rather than direct observation.

**Quantitative tests**

Quantitative tests are designed to be more reliable and more sensitive than clinical measures. Generally, they are too cumbersome to be used in routine clinical practice. They do not always correlate well with clinical measures. The pendulum test[10] requires the use of an electrogoniometer to quantify the number of swings and the degree of excursion at the knee after the leg of the patient is dropped from maximum extension. Additional data can be gathered by combining video or electromyographic (EMG) recordings with isokinetic dynamometry. The vibration inhibitory index compares the amplitude of the H-reflex before and after application of 60 Hz vibration to the Achilles
tendon. (The H-reflex is an EMG measure of excitability of motor neurons at rest.) This test is based on the observation that vibration inhibits the H-reflex in healthy non-spastic subjects.\textsuperscript{[11]}

Disability and subjective health status

Improving or preserving function and quality of life are the ultimate goals of spasticity management. Therefore, it is useful to incorporate these dimensions into the evaluation of the consequences of spasticity and treatment outcomes. However, the measures should be carefully chosen, since previously validated instruments can lack sensitivity and specificity in the context of spasticity management. For the same reason, results should be interpreted with caution. Potentially useful instruments include generic global disability scales (e.g. FIM\textsuperscript{TM}, Barthel Index) or disease-specific global disability scales (e.g. Incapacity Status Scale), measures of gait performance (e.g. Timed 25-foot Walk, Ambulation Index, Timed Up and Go Test, Dynamic Gait Index), measures of upper extremity function (e.g. Nine-Hole Peg Test, Box and Blocks Test), and generic (e.g. Short Form-36, Sickness Impact Profile) or disease-specific measures of quality of life (e.g. MS Quality of Life Inventory, MS Quality of Life-54).

TREATMENT

General considerations

The goals of spasticity management are to relieve symptoms, improve function or ease of care, improve posture, and prevent long-term complications such as fixed contractures. The treatment plan should address positive and negative manifestations of spasticity, and the dynamic and the static components. In addition, the interaction with other neurologic deficits, the role of extraneous factors (e.g. noxious stimuli, other medications), and the balance between beneficial and deleterious effects of spasticity on function should be taken into account. Complementary treatment modalities can be combined, following an integrated care model.

Rehabilitation

The rationale for the use of rehabilitation in the management of spasticity is mostly empirical. Although rehabilitative interventions (primarily physical therapy and occupational therapy) alone are not usually sufficient, they should be part of the plan of care at all stages. In mild to moderate spasticity, therapists can educate the patient about the consequences of spasticity, teach a home stretching exercise program, recommend ankle-foot orthoses or other devices as appropriate, and evaluate and treat functional consequences of spasticity. In severe spasticity with contractures, improvement of range of motion and posture can be sought through aggressive stretching, splinting, and serial casting, usually in addition to high doses of medications and sometimes surgical interventions. Physical treatments such as electrical stimulation and application of cold-packs may help, although the benefit is usually short-lived. They can be used at the
beginning of a therapy session to facilitate the exercises. A recent study in 14 MS patients showed an increase in spasticity after a cold bath compared with ambient temperature, in contrast to previously published findings.\[12\]

**Oral medications**

Oral antispastic medications are widely used, although a recent systematic review of the literature showed limited evidence supporting the efficacy and tolerability of these agents in MS.\[13\] Monotherapy, in association with stretching, is usually effective in mild to moderate spasticity. When spasticity is more severe, drugs can be combined, with tolerability being the main limiting factor. Most antispasticity medications can cause central nervous system (CNS) sedation, which is of particular concern in MS patients, a majority of whom complain of chronic fatigue. Therefore, they usually should be started at a low dose, with a gradual dose titration.

**Baclofen**

Baclofen is a structural analog of GABA, which binds to presynaptic and postsynaptic GABA-b receptors. Presynaptic binding results in membrane hyperpolarization, reduced influx of calcium, and decreased endogenous transmitter release. Postsynaptic binding increases potassium conductance and enhances presynaptic inhibition. Activation of GABA-b receptors may also cause inhibition of $\gamma$-motor neuron activity and decreased muscle spindle sensitivity.

Baclofen is rapidly absorbed after oral administration and has a mean half-life of 3.5 hours. Most of the drug is directly excreted by the kidney (15% is metabolized in the liver). As a consequence, the dosage should be reduced in patients with impaired renal function, and periodic monitoring of liver function has been recommended.

Side effects mainly consist of CNS depression (sedation, drowsiness, fatigue, confusion, dizziness). Baclofen can potentiate the effect of antihypertensive agents. Abrupt discontinuation of treatment can result in a withdrawal syndrome with severe muscle stiffness, paresthesias, hallucinations, confusion, fever, and seizures. Baclofen overdose can produce hypotonia, respiratory depression, hypotension, and coma. Another common problem is the development or worsening of muscle weakness with baclofen, probably both by direct action of the medication and indirectly through unmasking of underlying weakness.

Treatment is usually initiated at 5–10 mg/day and increased by 5 mg or 10mg increments until the desired effect is obtained or undesirable side effects occur. The recommended maximum total dose is 80 mg/day, but daily doses above 100 mg have been used.

Early trials showed that baclofen is effective in reducing spasticity in MS patients, with a more prominent benefit on spasms.\[14,15\] Brar et al. studied the effect of low-dose oral baclofen and muscle stretching, alone or combined, compared to placebo, in 30 MS patients with mild to moderate spasticity, using a double-blind cross-over design.\[16\] There was significant improvement of spasticity with baclofen compared with stretching or placebo. Adding stretching to baclofen resulted in further improvement, although the improvement was not statistically significant. In contrast, a more recent double-blind,
cross-over trial of oral baclofen versus placebo in 13 mildly to moderately disabled MS patients showed no significant improvement on muscle tone or gait characteristics with treatment treatment.[17]

**Tizanidine**

Tizanidine, an imidazoline derivative, is a central α-2 adrenergic receptor agonist. Tizanidine inhibits the release of excitatory amino acids from the presynaptic spinal interneurons, and it may facilitate the action of glycine. It is well absorbed and undergoes extensive first-pass hepatic metabolism. Therefore, tizanidine should be used with caution in patients with liver dysfunction, and monitoring of liver function is recommended. The usual starting dose is 2–4 mg/day. The maximum recommended dose is 36 mg/day, divided into three or four doses. Sedation and drowsiness are frequently reported by patients. Other side effects include dry mouth, dizziness, hypotension, elevated liver enzymes, and hallucinations. Association with antihypertensive agents should be avoided or done with caution, owing to the risk of potentiation.

Tizanidine has been shown to be effective in spasticity from MS, although functional improvement was not demonstrated[18] Its efficacy appears comparable to that of baclofen.[19–21] Weakness was reported less often with tizanidine than with baclofen.[22] Results of a double-blind, placebo-controlled trial in 187 MS patients published by the UK Tizanidine Study Group showed significant reduction of Ashworth scores in the treatment group, with no significant between-group difference in muscle strength. Again, no effect was seen on measures of disability.[23]

**Benzodiazepines**

Benzodiazepines act by decreasing monosynaptic and polysynaptic reflexes in the spinal cord. This effect is mediated by the functional coupling of a benzodiazepine-GABA-a receptor-chloride ionophore complex. Long-acting benzodiazepines (e.g. diazepam, clonazepam, chlordiazepoxide) and short-acting benzodiazepines (e.g. oxazepam, lorazepam) differ in that the former produce pharmacologically active metabolites.

Diazepam is the oldest antispasticity medication. It is well absorbed and reaches a peak blood level within 1 hour. It is 98% protein-bound, and its half-life is between 20 and 80 hours. Its hepatic metabolism produces active metabolites (nordiazepam and oxazepam). It crosses the placental barrier and is excreted into breast milk. CNS depression is the main adverse effect, and is potentiated by alcohol. Overdose can lead to coma and respiratory depression. Abrupt discontinuation can result in a withdrawal syndrome with anxiety, tremor, agitation, insomnia, possible psychotic manifestations, and seizures. The severity of withdrawal symptoms is dose-dependent.

A double-blind, cross-over study by From and Heltberg comparing baclofen with diazepam in 17 MS patients showed no difference in efficacy between the two agents.[24] Sedation was more frequently reported with diazepam. Deterioration of gait performance caused by weakness was observed in one out of two ambulatory patients, both with diazepam and baclofen. An open trial comparing baclofen (n=33, 80% MS), clonazepam (n=25, 100% MS) and placebo (n=10, 100% MS) showed comparable efficacy of both active drugs, but patients with more severe spasticity at baseline appeared to respond
better to baclofen. Because of the risk of sedation, benzodiazepines are often prescribed at a low dosage, in combination with other antispastic agents.

**Gabapentin**

Gabapentin was introduced in 1994 as an add-on therapy for patients with refractory partial seizures. Its structure is similar to that of GABA, but it does not bind to conventional CNS receptors. It is well absorbed and reaches peak serum concentration after 2–3 hours. It is not bound to proteins and is excreted in its original form in the urine. Adverse effects, including nystagmus, diplopia, somnolence, ataxia, and dizziness, have been reported in a small percentage of patients. There is no evidence of toxicity on any major organ system. Dosages up to 3600 mg/day or higher (in divided doses) have been used. Gabapentin also is used to treat uncomfortable positive sensory symptoms (such as paresthesias and neuropathic pain).

Dunevsky and Perel reported improvement of Ashworth scores and functional status in two MS patients treated with gabapentin at the dose of 400 mg/day. A recent double-blinded placebo-controlled trial of gabapentin in 21 veterans with MS (19 of them men) showed significant improvement of subjective and objective impairment in the treatment group. There was no significant difference in disability measured by the expanded disability status score (EDSS) between the two groups, but EDSS is unlikely to be very sensitive to changes in functional performance related to spasticity relief.

**Dantrolene sodium**

Dantrolene sodium, a hydantoin derivative, acts peripherally by reducing the action potential-induced release of calcium from the sarcoplasmic reticulum of skeletal muscle fibers. This results in partial excitation-contraction uncoupling, which appears to be more prominent on fast-twitch extrafusal fibers. Approximately 70% of an oral dose of dantrolene sodium is absorbed. Peak serum concentration is reached after 3–6 hours, and the drug is largely metabolized by the liver, with production of an active metabolite (5-hydroxydantrolene). The molecule is lipophilic and therefore easily crosses cell membranes. In particular, it crosses the placental barrier.

Side effects include CNS sedation, gastrointestinal symptoms, and hepatotoxicity, which can be severe with necrosis of the liver. The incidence of fatal hepatitis is 0.3%. Therefore, liver function should be tested before, and periodically after onset of treatment. Dantrolene sodium is also used to treat malignant hyperthermia and the neuroleptic malignant syndrome. Toxicity, the risk of weakness, and modest efficacy in early clinical trials explain the limited use of dantrolene sodium in MS.

**Clonidine**

Clonidine acts as an α-2 agonist throughout the CNS. It is primarily used as an antihypertensive agent. The effect of clonidine on blood pressure appears to be mediated by inhibition of neurons in the locus coeruleus, resulting in decreased sympathetic outflow. The medication is readily absorbed, and peak plasma concentration is reached after 3–5 hours. It is metabolized by the liver and excreted in unchanged form in the
urine, in equal proportions. Side effects include bradycardia, hypotension, drowsiness, dry mouth, constipation, dizziness, ankle edema, and depression.

Trials of clonidine, mostly in patients with spinal cord injury, have shown a positive effect on spasticity.\cite{30,31} It is usually combined with other medications such as baclofen. Poor tolerance is a concern, particularly the risk of hypotension in MS patients with dysautonomia. The transdermal patch appears to be as effective as the oral form against spasticity and may decrease the occurrence and severity of side effects.\cite{32}

### Other medications

Cyproheptadine, a histamine and serotonin antagonist, was found to be effective against clonus in an open trial of patients with spasticity of spinal origin.\cite{33} Side effects mainly consist of CNS sedation and anticholinergic symptoms. Cannabinoids have been reported to improve tremor and spasticity, both in animal models of MS\cite{34} and in MS patients.\cite{35}

### Local treatments

Local treatments are used to provide short- or long-term relaxation of specific muscles or muscle groups, to facilitate stretching and range of motion exercises, to improve comfort, or to improve function. If the spasticity involves an entire limb or several limbs, as is usually the case in MS, local treatments can be administered in combination with systemic agents.

#### Local anesthetic agents

Lidocaine, etidocaine and bupivacain are examples of local anesthetic agents that can be administered via perineural or intramuscular injection. They exert a blocking action on sensory and motor nerves, muscle fibers, and the neuromuscular junction. Small-diameter nerve fibers and fibers that have been recently and repetitively stimulated are more sensitive to anesthetic block. Onset of action is rapid (within minutes) and duration varies according to the lipid solubility and protein affinity of the anesthetic (usually a few hours). Systemic side effects include CNS stimulation, cardiovascular depression, and rarely hypersensitivity reactions. Therefore, resuscitation equipment should be available. Intensive use of local anesthetic should be avoided in patients with liver failure, since the agents are metabolized by the liver. Owing to their short duration of action, local anesthetics are used to evaluate the potential benefit of more long-lasting local procedures or to facilitate therapy.

#### Chemical neurolysis

Chemical neurolysis produces a nerve block by damaging nerve structures. Phenol and ethyl alcohol are the two chemical agents used for these procedures. Both work by denaturing proteins and causing tissue necrosis. The destruction is non-selective and depends on the concentration of the chemical administered. Regrowth of axons is expected and accounts for the reversibility of the effect. However, damage to the microcirculation may result in fibrosis impairing nerve regeneration. The main side
effects are local—pain during the injection and chronic dysesthesia. Onset of effect is rapid. Duration of effect is highly variable but is usually several months (up to 36 months). Both perineural and intramuscular injections can be performed. Injection of purely or largely motor nerves (e.g. the obturator nerve for adductor spasticity) is preferred, to minimize the risk of chronic dysesthesias.

**Botulinum toxin**

Botulinum toxin (BT) is increasingly used in various indications, including spasticity (which remains an off-label indication). BT is produced by the anaerobic organism *Clostridium botulinum* and is a very potent toxin that blocks the release of acetylcholine by presynaptic terminals at the neuromuscular junction. Of the seven known serotypes of BT, only BT-A and more recently BT-B are available in preparation for injecting. BT is injected into the muscle and diffuses approximately 30 mm around the injection site. Detection EMG or electrical stimulation can be used to locate small and deep muscles, particularly in the distal upper extremity. The therapeutic effect appears after 24–72 hours, peaks at 2–4 weeks, and usually lasts 12 weeks or more. The reversibility of the effect of BT is due to nerve sprouting and creation of new neuromuscular junctions. Repetition of the injection usually produces an identical or augmented effect. Muscle atrophy is commonly observed. Partial muscle weakness is a logical consequence of BT injection. Therefore, target muscles should be determined with care to avoid negative functional consequences.

The development of antibodies to BT-A can lead to resistance to therapy and has been linked to higher doses of toxin injected, frequent injections, and higher protein load in the preparation.\(^{[36]}\) For this reason, it is recommended that a maximum dose of 400IU per visit is administered and that injections are repeated no more than every 3 months. More recent preparations of BT-A have a reduced protein load. The frontalis test can be used to detect resistance to BT-A clinically; it involves injecting 15IU of BT in the corrugator muscle on one side, and evaluating the ability of the patient to move this muscle after 2 weeks. Several types of assays are available to detect antibodies to BT-A in the serum.

Systemic side effects of BT are rare and are usually minor and reversible. BT should be used with caution in patients with disorders of the neuromuscular junction and in patients taking aminoglycosides, which may interfere with neuromuscular transmission. Cost can be an issue, since the injections must be repeated to maintain a long-term effect.

A double-blind, placebo-controlled, cross-over trial of BT in 10 non-ambulatory MS patients showed significant improvement of spasticity scores and ease of care with BT.\(^{[37]}\) BT or placebo was injected in the thigh adductor muscles with cross-over injection at 3 months. Kerty and Stein reported improvement of adductor spasticity in two of five patients with advanced MS.\(^{[38]}\) Borg-Stein et al. noted improvement of spasticity and function in two MS patients treated with BT.\(^{[39]}\) Despite these promising results, controlled studies with standardized evaluation of functional outcomes are needed to evaluate further the indications for BT in MS.
Neuro-orthopedic interventions

Neuro-orthopedic interventions are considered when there are contractures resulting from severe spasticity. Procedures include tendon lengthening (e.g. of the Achilles tendon), tendon transfer, neurectomy (e.g. obturator neurectomy for adductor spasticity), and less frequently, intramuscular lengthening. Owing to the risks related to surgery, indications should be evaluated with caution, and postsurgical care should be planned carefully. It is recommended that these interventions are performed during periods of disease stability, and expectations in terms of ease of care, posturing, or function must be realistic. Surgery is usually followed by aggressive stretching, serial casting, or splinting to avoid recurrence of contractures. MS patients often are reluctant to consider such interventions because of fear of complications or because of their destructive character, but they can be very helpful in selected cases.

Other surgical treatments

Intrathecal therapies

Intrathecal baclofen (ITB) therapy is approved in the USA by the Food and Drug Administration (FDA) for the treatment of severe spasticity of spinal or cerebral origin that is refractory to oral antispastic medications, or when oral medications are not tolerated. The medication is delivered directly into the intrathecal space via a programmable infusion system, consisting of a battery-powered pump implanted subcutaneously or subfascially in the lower abdominal wall and also an intraspinal catheter tunneled subcutaneously to the pump catheter port. The catheter tip is usually placed at the lower thoracic level, providing relief of spasticity in the low back and legs. Higher catheter placement has been reported, particularly in cerebral palsy and spinal cord injury patients, to treat upper extremity spasticity. The pump contains a reservoir for the medication, which can be accessed for refills through a port. The maximum interval between refills is 90 days to ensure that the medication remains stable. The pump can be interrogated and programmed non-invasively through an external computer, which exchanges information with the pump via telemetry. Safety features include a low reservoir volume alarm and a low battery alarm to prevent withdrawal.

ITB administration allows effective cerebrospinal fluid (CSF) concentrations to be achieved with much smaller doses of baclofen (and resultant plasma concentrations 100 times less) than those with oral administration. The lumbar-cisternal concentration gradient is estimated at 4:1, accounting for the reduced incidence of CNS sedation compared with oral baclofen.

A test injection of intrathecal baclofen must be performed before pump implantation. The dose injected usually varies between 25 and 100 µg. The effect of intrathecal baclofen on lower extremity spasticity and weakness is evaluated periodically over the next 4–8 hours. Vital signs and any adverse effects are monitored during the same period. There are only a few contraindications to ITB therapy—known hypersensitivity to baclofen, active infection at the time of screening injection or surgery, and any severe concomitant pathology that would preclude surgery.
Potentially life-threatening complications of ITB therapy include overdosing and abrupt withdrawal (see above). Overdose is generally related to procedural errors. Abrupt withdrawal can be related to procedural errors, an empty reservoir, catheter malfunction, or pump malfunction. Other complications include infections, wound dehiscence, seroma, and CSF leak. Causes of catheter malfunction include catheter fracture, subdural migration, dislodgement, and fibrosis at the tip of the catheter. Pump malfunctions are rare, and include unexpected battery failure and rotor lock. Specific procedures are followed for patient management and troubleshooting of complications and malfunctions. Other drawbacks of ITB therapy are cost, the need for periodic refills and adjustments, and the need to undergo repeat surgery when the battery reaches the end of its life (usually every 5 years).

ITB has been used for over 10 years in the treatment of refractory lower extremity spasticity in MS and other CNS pathologies, and several studies have demonstrated its efficacy.[9,40–44] Improvement of bladder function has also been reported, but bladder dysfunction is never a primary indication for ITB. A recent publication reports the frequency of adverse effects and complications of ITB therapy from a survey of 40 centers (936 pump placements).[45] The most common side effects after screening intrathecal injection of baclofen were nausea and vomiting, sedation, hypotension, and urinary retention. The most common complications during hospitalization after pump implantation were CSF collection, constipation, headache, and CSF leak. The most frequent long-term complication was infection, which was also the most common reason for early pump replacement. The catheter had to be replaced for malfunction in 7% of cases.

ITB has traditionally been used in non-ambulatory MS patients with severe spasms. In this population, ITB has been shown to provide relief of discomfort and pain related to spasticity, greater ease of care, improved posture, and improved ability to transfer.[45,46] Interestingly, an increase in upper extremity MEP amplitude was reported in a sample of 11 patients with severe spastic quadriparesis treated with ITB (compared with pre-ITB testing), but the authors did not indicate if this was correlated with changes in upper extremity spasticity, strength, or function.[47]

More recently, ITB has been used increasingly in ambulatory MS patients.[48,49] This represents a more challenging patient subgroup, in particular because of the potential risk of loss of function from increased lower extremity weakness. On the other hand, these patients have a greater potential for reduction of disability or handicap with ITB, because they are more likely to be involved in household- and work-related activities. New outcomes measures, particularly easy-to-use measures of gait performance, need to be validated for this purpose.

Opiates and clonidine also have been used intrathecally to treat intractable pain and spasticity in MS, alone or, more frequently, in combination with baclofen.[50,51] A recent publication reports significant improvement of bladder function in spinal cord injury patients treated with intrathecal clonidine. The authors recommended combining clonidine with baclofen in order to achieve better tolerance.[52]
Neurosurgical interventions

Historically, stereotactic electrocoagulation of different parts of the brain (e.g. globus pallidus, thalamus, cerebellum), cerebellar stimulation, cordectomy, and myelotomy have been performed, but currently these procedures are not warranted in the treatment of spasticity. Selective posterior rhizotomy has been used with some success, particularly in cerebral palsy. The rationale for posterior rhizotomy is to decrease afferent signals to the spinal cord, disrupting the reflex arc involved in dynamic phenomena related to spasticity. Indications, contraindications, and surgical techniques have been refined over the years. For many reasons, this treatment modality is not commonly used in MS, although positive results have been published.⁵³

CONCLUSIONS

The paucity of scientific evidence and the lack of specific guidelines for the management of spasticity in MS make it difficult for the clinician to design treatment algorithms taking into account all of the available modalities. Training, interests, anecdotal experience, and the proximity of specialized centers heavily influence practice habits. Education of the patients and prevention of longterm complications are essential. Oral medications often provide adequate relief. More invasive and costly interventions, such as intrathecal baclofen therapy, are probably underused, or could be considered earlier instead of as a ‘last resort.’ Their success requires thorough assessments and a realistic treatment plan, ideally involving a multidisciplinary team.

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INTRODUCTION

Over 80% of multiple sclerosis (MS) patients have symptoms of lower genitourinary tract dysfunction. More than 96% of patients with the disease for 10 years will have had urological manifestations. The effect of MS on the genitourinary tract can range from bladder and urethral dysfunction to impotence. Consequently, genitourinary symptoms can be a source of considerable frustration and distress for the patient with MS; urologic involvement presents most commonly as either lower urinary tract (bladder and urethral) dysfunction (LUTD) or sexual dysfunction. Because LUTD and sexual dysfunction can have a significant impact on quality of life, a working knowledge of the pathophysiology, evaluation, and treatment of these conditions is essential for the MS specialist, who is often called upon to manage these severe, debilitating symptoms.

NEUROLOGIC EFFECTS ON THE URINARY TRACT

Although MS plaques can occur anywhere within the central nervous system (CNS), involvement in the cervical spinal cord, predominantly the lateral corticospinal (pyramidal) and reticulospinal tracts, is common. Because innervation of the detrusor and external urethral sphincter is mediated by these tracts, many MS patients will experience LUTD. 

Suprasacral spinal cord effects

Autopsy studies showed that lesions of the suprasacral spinal cord are extremely common in MS patients. Cervical cord plaques are the most common, occurring in up to 80% of patients in some series. The result is loss of supraspinal suppression of autonomous bladder contractions, resulting in detrusor hyperactivity (detrusor hyper-reflexia) and urgency incontinence in the majority of patients (>60%). Spinal lesions also disrupt reticulospinal pathways from the pons involved in the synergistic integration of urethral sphincteric and detrusor activity. This disruption results in a continuum of three main abnormalities: detrusor sphincter dyssynergia (DSD), incomplete sphincteric relaxation (ISR), or sphincteric paralysis.
Sacral cord effects

Lower motor neuron symptoms thought to reflect lesions in the sacral cord or conus medullaris are reported in up to 63% of patients.\textsuperscript{[1–3]} In contrast, autopsy studies showed only an 18% incidence of sacral plaques.\textsuperscript{[16]} Mayo and Chetner found 63% of patients with detrusor hypocontractility, but only 5% displayed true areflexia.\textsuperscript{[14]} This has led some authors to question the contribution of sacral plaques to overall symptoms of LUTD.\textsuperscript{[13–15]} Animal studies demonstrated that intact spinal afferents and efferents are crucial to the facilitation of sustained detrusor contractions.\textsuperscript{[18,19]} Plaques in these afferent or efferent pathways inhibit facilitated contractions, thereby causing impaired emptying and urinary retention. As a result, some patients may suffer from paradoxical detrusor hyperactivity in the absence of a coordinated detrusor contraction and, thus, failure to empty the bladder. Although abnormal sacral nerve function, as demonstrated by prolonged reflex latencies, is documented by several authors and may help to secure the diagnosis of MS, the contribution of these reflex pathways to bladder dysfunction remains uncertain.\textsuperscript{[1,3,18–21]}

Intracranial plaques

Intracranial plaques are common in MS patients, occurring in 60–90%.\textsuperscript{[21–24]} Although the most commonly involved area is the periventricular white matter, plaques can occur in nearly all areas of the intracranial white matter. Accordingly, the presence of disease in the supraspinal CNS may account for urologic dysfunction (detrusor hyper-reflexia). In a study of 90 MS patients, there was no correlation between findings on magnetic resonance imaging (MRI)—atrophy, number of lesions, and nature or size of a lesion—and any urodynamic parameter.\textsuperscript{[25]} Other studies demonstrated significant correlation ($p<0.001$) between urinary symptoms and lesions in the midbrain.\textsuperscript{[26,27]} While lesions in the midbrain are highly correlated with urologic manifestations, the urologic significance of clinically isolated pontine lesions in the absence pyramidal findings remains in question.\textsuperscript{[28,29]}

CLINICAL PRESENTATIONS

Lower urinary tract symptoms are varied and include frequency and urgency (occurring in 31–85% of patients), incontinence (in 37–72%), or obstructive symptoms and urinary retention (in 2–52%).\textsuperscript{[1–9]} Although the incidence of lower urinary tract symptoms ranges between 52% and 97%, the presence or absence of symptoms is an unreliable indicator of the extent of bladder dysfunction.\textsuperscript{[4,12,30,31]} Betts et al. found that only 47% of patients with elevated post-voiding residual (PVR) volumes had the sensation of incomplete emptying.\textsuperscript{[13]} Conversely, 83% of patients complaining of incomplete emptying had PVR volumes >100ml.\textsuperscript{[13]} Koldewijn et al. detected urodynamic evidence of urinary tract dysfunction in 100% of patients with urologic symptoms and in 52% of patients without symptoms.\textsuperscript{[4]}
Although several studies have shown that duration of disease, increased age of diagnosis, and degree of motor or sensory dysfunction correlate well with degree of urologic impairment, LUTD correlates best with pyramidal tract involvement and overall disability as measured by the Expanded Disability Status Scale (EDSS).\textsuperscript{[4,28,31–36]} In contrast, Awad et al. found that pyramidal tract dysfunction, independent of the level of disability measured by the EDSS, was most closely related to LUTD.\textsuperscript{[15]} Thus, ataxia, gait disturbance, lower extremity weakness, or numbness or paresthesias may indicate occult urologic dysfunction. The degree of lower extremity motor dysfunction may be the best predictor of urologic dysfunction and bladder dysfunction. This correlation is so significant that LUTD is rarely seen in the absence of pyramidal dysfunction.\textsuperscript{[4,35]} In assessing different types of MS, secondary progressive MS is the only course of MS associated with an increased risk of progressively deteriorating bladder function ($p<0.05$).\textsuperscript{[4]}

Urinary symptoms may be age-related and follow a bimodal distribution. Patients under the age of 40 years are most bothered by bladder storage and voiding symptoms, although these findings may be related to the inherent expectations of younger patients compared with their older counterparts. Patients over the age of 50 years are also greatly bothered with bladder symptoms, which may be related to their longer duration of disease or to the cumulative effect of other causes of bladder dysfunction, such as benign prostatic hyperplasia in men or genuine stress incontinence in women.\textsuperscript{[31]} Although increasing duration of disease is linked to increased frequency of overall symptoms, no single urologic symptom is more prevalent in patients with longstanding disease. No significant relationship has been found between the incidence of overall symptoms and sex. However, men with MS report a higher incidence of obstructive symptoms than women, which may be related to age-related changes in the prostate or to the severity of DSD in males.\textsuperscript{[4]} As a result of urinary tract dysfunction and stasis of urine, patients may develop bladder calculi, renal calculi, frequent urinary tract infections, often involving atypical organisms.\textsuperscript{[37]}

**EVALUATION OF VOIDING DYSFUNCTION**

**History**

Clearly, a history of lower extremity sensory or motor loss (pyramidal tract dysfunction) can be a sign of unrecognized urologic pathology.\textsuperscript{[15]} A history of visual disturbance (diplopia, oscillopsia) or dizziness may point to pontine pathology (e.g. internuclear ophthalmoplegia). Because the central co-ordinating center for bladder and sphincter integration lies in the pontine tegmentum, a history suggestive of pontine pathology may be pertinent to the diagnosis of occult bladder or sphincteric dysfunction. Patients should be asked about frequency of daytime urination, nocturia, urgency, urge or stress incontinence, degree of bladder emptying, and the ease with which micturition is initiated. However, the disparity in symptoms and underlying pathology supports the need for the objective measurement of PVR (see Ancillary testing). Patients who strain or push in order to urinate also may suffer from LUTD and incomplete emptying, thereby placing themselves at risk of other urologic complications (bladder calculi, infection,
bladder diverticuli, and lower urinary tract decompensation). Use of protective devices should be determined and an incontinence-specific quality of life instrument may be of benefit to assess overall daily impact of these urinary symptoms.\textsuperscript{38,39} Assessment of fluid intake is important, since many patients attempt to remedy their bladder symptoms by decreasing their fluid intake. This may cause hyperconcentration of urine, thereby leading to more irritative symptoms. To help in this determination, a diary of fluid intake and voiding can be beneficial.

A current and past medication profile should be obtained, since many medications that are used to treat MS have neuroleptic or anticholinergic side effects. These medications may cause inappropriate bladder relaxation and exacerbate urinary retention. \(\alpha\)-Adrenergic agonists used in many cold preparations as decongestants can impair bladder emptying by stimulating \(\alpha\)-receptors in the bladder neck and prostate. In women, \(\alpha\)-blockers used as antihypertensives can exacerbate stress incontinence. Because bladder cancer has been linked to the use of cyclophosphamide, a patient’s medication history should be thorough, including dates and courses of treatments and whether 2-Mercaptoethane sulfonate (MESNA) was given concomitantly. The wide use of corticosteroids and immunosuppressive agents in the MS population can contribute to urinary tract infections caused by especially virulent organisms.\textsuperscript{37}

Past medical and surgical history is especially important in the MS patient because competing pathologies may have an adverse impact on LUTD. A history of prior urethral instrumentation, (including catheterization) or injury may suggest the presence of urethral stricture as a cause for voiding dysfunction. A history of prior prostate or urethral surgery should alert the clinician to the possibility of postoperative urethral stricture. In males who are in their fifth or sixth decade, benign prostatic hyperplasia can likewise act as a confounding variable and mimic neurologic bladder dysfunction. In both sexes, diabetic cystopathy may adversely affect bladder emptying and predispose to infection or complicate diagnosis or treatment.

Women with MS should be questioned also about surgical and medical history. A history of prior incontinence or vaginal prolapse surgery may raise a suspicion of concomitant anatomic factors affecting continence (e.g. urethral hypermobility, urethral stricture, obstruction). Those with a history of prior incontinence surgery, hysterectomy, abdominal-perineal resection, or urethropelvic surgery are at increased risk of having combined anatomic and neurologic deficits. Obstetrical history is important, including any history of birth-related trauma or complications. Women may note a cyclical nature to their MS symptoms with worsening the week before their menstrual cycle. Many women with MS note the regulating effect of oral contraceptive preparations on their MS symptoms.

Gastrointestinal disturbances can have a significant effect on voiding dysfunction. Chronic constipation, a common symptom of MS, can contribute significantly to incontinence not only from mechanical compression but from sacral nerve feedback as well. Conversely, anticholinergic medications used to treat detrusor hyperactivity can exacerbate constipation.
Physical examination

The general physical examination is of significant help in the management of urologic dysfunction. The abdominal examination may reveal surgical scars, indicating prior urologic or gynecologic surgery. Fecal impaction may be detected on abdominal examination as well as digital rectal examination. Rectal tone should be assessed, as should the bulbocavernous reflex (S2–S4) as a measure of sacral reflex integrity. In men, rectal examination also aids in assessing prostate size and its possible contribution to voiding dysfunction. A testicular examination is also important to aid in cancer screening. In women, the vaginal examination helps to exclude coexisting vaginal pathology (pelvic prolapse, urethral hypermobility, cystocele, rectocele, urethral diverticulum, or atrophic vaginitis). Coexisting vaginal pathology may significantly contribute to both incontinence and voiding dysfunction. Examination of the genitalia is crucial since patients managed with an indwelling catheter may develop traumatic hypospadias (in males) or urethral erosion (in females).

A directed neurologic examination (L1–S4) may help to suggest the extent of urologic dysfunction. In addition to the high correlation between lower extremity dysfunction and bladder dysfunction, cerebellar signs (such as ataxia or dysdiadochokinesis) are correlated with detrusor areflexia. Extensor plantar responses (Babinski sign) may be seen in 70–95% of patients with bladder dysfunction and in 70% of patients with DSD. However, poor specificity limits its use as a diagnostic tool. Similarly, many patients will display hyperactive deep tendon reflexes, but this finding alone is not a good indicator of detrusor hyper-reflexia or bladder dysfunction (sensitivity 76%, specificity 58%). Sensory abnormalities may be seen in association with bladder dysfunction, especially abnormalities of lower extremity vibratory sensation. An assessment of upper extremity strength and dexterity is important because this may play an integral role in determining the options for bladder management. The association between cranial nerve findings and urinary tract abnormalities is not well established. Betts et al. evaluated 16 patients and found the presence of internuclear ophthalmoplegia correlated with bladder dysfunction. However, most of these patients demonstrated concomitant pyramidal tract dysfunction, raising the question of the significance of isolated internuclear ophthalmoplegia. In similar work at University of Texas Southwestern, the incidence of vesicourethral dysfunction in patients with internuclear ophthalmoplegia approached 97%.

Ancillary testing

Urinalysis

Urinalysis is an integral part of the urologic evaluation. In most instances, a multicomponent dipstick suffices for screening. Method of collection is of prime importance, since many patients are treated inappropriately because of a falsely contaminated specimen. Urine should be collected as a midstream, clean-catch specimen. However, because of spasticity or obesity, many patients are unable to provide a truly clean and uncontaminated specimen. In these instances, or in patients with repeated
infections, sterile catheterization provides the most reliable way of ensuring proper specimen collection. Leukocyte esterase and nitrite are good screening tests for urinary tract infection. The specificity of these tests is fairly high and the presence of infection in their absence is rare. Urine specific gravity is a useful test to determine state of hydration, since many patients with MS restrict their fluids in an attempt to control incontinence and frequency. The presence of blood in the urine, although often seen with infection, is a worrisome sign, and raises suspicion of a bladder stone or tumor, especially in the patient who has had multiple courses of cyclophosphamide.

**Upper urinary tract imaging**

Baseline radiographic assessment of the MS patient remains an important part of the initial urologic evaluation. In a review of 14 series comprising 2076 patients, Koldewijn et al. found the incidence of hydronephrosis or renal complication to be 0.34%.[4] All seven affected patients had DSD (Fig. 38.1). Although there are isolated reports of severe morbidity and mortality from upper tract disease in MS,[40,41] progression to upper tract deterioration is usually the exception.[4,17,31] Studies advocating initial surgical intervention for mild hydronephrosis are largely historical and often antedate the widespread acceptance of clean intermittent catheterization as a treatment alternative.[40,42] Upper tract deterioration is linked to two main risk factors, DSD (in the male) and the presence of an indwelling catheter (1.7%).[3,12,22] In these high-risk patients, a baseline renal ultrasound is advisable, since it may diagnose clinically silent calculi, identify parenchymal scarring, and provide comparison for longitudinal monitoring.

**Lower urinary tract imaging**

In the incontinent or otherwise symptomatic woman, an initial lateral voiding cystourethrogram or videourodynamics (urodynamic evaluation performed with concomitant fluoroscopic bladder imaging) may aid in the assessment of the bladder neck support, urethral hypermobility, and bladder diverticuli. As patients who are relatively young or middle-aged may have competing symptomatologies, such as genuine stress incontinence and urge incontinence, this type of imaging may be beneficial in determining the relative contribution of anatomic factors (urethral hypermobility or cystocele) to voiding dysfunction or incontinence. Videourodynamics may also be of benefit in the more accurate determination of DSD (see Fig. 38.1). In the patient with no stress incontinence or with good pelvic floor support on physical examination, lower tract radiologic imaging may not be necessary.
Fig. 38.1 Detrusor sphincter dyssynergia (DSD). This cystourethrogram demonstrates DSD in a 40-year-old man with relapsing-remitting MS who presented with poor bladder emptying. Note the columnation of the radiographic contrast down to the external sphincter (bold arrow). The two round densities at the bottom of the screen are electromyography leads. In the accompanying urodynamic tracing, sphincter activity increases dramatically and is accompanied by attempted voiding at a detrusor pressure of over 45 cmH₂O. Note the virtual absence of flow and near complete retention.
**Urodynamic evaluation**

Urodynamic evaluation of the patient with MS not only allows for proper identification of any underlying bladder and sphincteric abnormalities but also aids in the individualization of bladder management. During this study, the bladder is filled via a small (6–7F) multilumen catheter. Measurements of bladder pressure are continuously made during both filling and voiding. Concomitant rectal manometry is performed to record and correct for the effect of intraabdominal contents on bladder pressure. Electromyographic monitoring of the external sphincter is performed during the study to assess bladder and sphincteric co-ordination (Fig. 38.2).

Blaivas et al. found that 73% of MS patients without urodynamic evaluation were treated inappropriately.\[^{10}\] Indeed, 73% of patients with symptoms suggestive of obstruction were found to have detrusor areflexia. In equivocal cases, urodynamic evaluation may lend support to a suspected diagnosis of MS in 10–14% of patients.\[^{1,13,31}\] Within the MS patient population, the incidence of abnormal urodynamic findings is as high as 100% in some series.\[^{3}\] In a meta-analysis of 22 series and 1882 patients, the incidence of normal urodynamic findings was only 9% (Table 38.1). However, because most published series deal with symptomatic patients referred specifically for urological evaluation, there has been a significant reporting bias toward patients with advanced disease and pyramidal dysfunction. To date there are few prospective studies dealing with asymptomatic bladder dysfunction. In one prospective study, 52% of patients (21/40) demonstrated silent urodynamic abnormalities. The incidence of positive urodynamic findings in patients with lower urinary tract complaints was 98%.\[^{22}\] Once a urodynamic diagnosis is rendered, therapy may be tailored to each patient’s storage and emptying function, thereby eliminating a trial and error method of management.

Detrusor hyper-reflexia is defined as bladder over-activity caused by a disturbance of nervous control mechanisms; it is the most commonly
**Fig. 38.2** Normal urodynamic tracing. Note how the bladder accommodates a large volume at a very low pressure.

$P_{ves}$, total bladder pressure (vesical pressure, cmH$_2$O), a measured value from the dual lumen urethral catheter

$P_{abd}$, abdominal pressure (cmH$_2$O), a measured value derived from a rectal catheter

$P_{det}$ is calculated by the formula $P_{ves} - P_{abd}$ and represents the true detrusor pressure (cmH$_2$O) in the absence of abdominal effects

*Flow*, the rate of urinary flow (ml/s)

*V$_{H2O}$*, the volume infused (ml)

*Volume*, volume voided (ml)

*EMG*, muscle activity of the pelvic floor and external sphincter, by electromyography
encountered urodynamic abnormality in MS (Fig. 38.3; see Table 38.1). The incidence of detrusor hyper-reflexia varies directly with the level of the neurologic lesion.\[^{23}\] Patients with a higher predominance of cervical plaques have a higher incidence of detrusor hyper-reflexia. In 22 published series evaluating primarily symptomatic MS patients, 62% of patients (1194 of 1882) were found to have detrusor hyper-reflexia as their primary urodynamic diagnosis (see Table 38.1). This is not surprising given the high incidence of cervical and intracranial plaques in MS.\[^{10,19,20,31}\] Commonly, detrusor hyper-reflexia is manifested as urgency, frequency, and generalized irritative symptoms. Among patients with detrusor hyper-reflexia, 67%
display synergic voiding, and 43% display DSD. Patients in the latter group may suffer from both storage and emptying failure, complicating their management.

Detrusor hypocontractility can be seen in up to 63% of patients with or without associated hyper-reflexia. True areflexia is seen in only 20% of patients and may be associated with hesitancy and elevated PVR volume (see Table 38.1). Hypocontractility may be related to cerebellar plaque involvement, lack of cortical facilitory input, or sacral cord involvement. Some evidence suggests that areflexia is a temporary condition that may progress to hyper-reflexia in 57–100% of patients.

Urethral dysfunction, ISR, and DSD represent a continuum, which may be seen in 12–84%.

**Table 38.1 Published series of urodynamic findings in MS**

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Detrusor hyper-reflexia</th>
<th>DSD</th>
<th>Hypercontractility Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen and Bradley</td>
<td>52</td>
<td>33 (63)</td>
<td>16 (31)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Awad et al.</td>
<td>57</td>
<td>38 (66)</td>
<td>30 (52)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Beck et al.</td>
<td>46</td>
<td>40 (87)</td>
<td>–</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Betts et al.</td>
<td>70</td>
<td>63 (91)</td>
<td>–</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blaivas et al.</td>
<td>41</td>
<td>23 (56)</td>
<td>12 (30)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Bradley et al.</td>
<td>99</td>
<td>58 (60)</td>
<td>20 (20)</td>
<td>40 (40)</td>
</tr>
<tr>
<td>Bradley</td>
<td>302</td>
<td>127 (62)</td>
<td>–</td>
<td>103 (34)</td>
</tr>
<tr>
<td>Eardley et al.</td>
<td>24</td>
<td>15 (63)</td>
<td>6 (27)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Goldstein et al.</td>
<td>86</td>
<td>65 (76)</td>
<td>57 (66)</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Gonor et al.</td>
<td>64</td>
<td>40 (78)</td>
<td>8 (12)</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Hinson and Boone</td>
<td>70</td>
<td>44 (63)</td>
<td>15 (21)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Koldewijn et al.</td>
<td>212</td>
<td>72 (34)</td>
<td>27 (13)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Mayo and Chetner</td>
<td>89</td>
<td>69 (78)</td>
<td>5 (6)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>McGuire and Savastano</td>
<td>46</td>
<td>33 (72)</td>
<td>21 (46)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Peterson and Pederson</td>
<td>88</td>
<td>73 (83)</td>
<td>36 (41)</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Philip et al.</td>
<td>52</td>
<td>51 (99)</td>
<td>16 (37)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Piazza and Diokno</td>
<td>31</td>
<td>23 (74)</td>
<td>9 (47)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>
Schoenberg et al.\cite{49} & 39 & 27 (69) & 20 (5) & 2 (6) & 6 (15) \\
Sirls et al.\cite{50} & 113 & 79 (70) & 15 (28) & 17 (15) & 7 (6) \\
Summers\cite{51} & 50 & 26 (52) & 6 (12) & 6 (12) & 9 (18) \\
Van Poppel and Baert\cite{37} & 160 & 105 (66) & 38 (24) & 38 (24) & 16 (10) \\
Weinstein et al.\cite{52} & 91 & 64 (70) & 16 (18) & 15 (16) & 11 (12) \\
Total & 1882 & 1194 (62) & 373/1464 (25) & 394 (20) & 188 (10) \\

(mean 25.4\%) of patients (see Fig. 38.1; Table 38.1).\cite{10,13,45} Consequently, a variety of clinical effects may be seen, ranging from retention to complete incontinence.\cite{47–50} DSD is correlated with cervical plaques as well as with increased levels of cerebrospinal fluid myelin basic protein (p<0.05).\cite{1,4,23} Most commonly, DSD presents with incomplete emptying and stranguria (symptoms also seen with hypocontractility). DSD is the most extreme defect in this continuum and is seen when a detrusor voiding contraction is accompanied by concomitant internal or external sphincter contraction.\cite{10} In sharp contrast to the dyssynergia seen in spinal cord injury patients, DSD seen in the MS population is rarely associated with upper tract dysfunction, but rather with local symptoms of incomplete emptying, elevated PVR volume, bladder calculi, and infection.\cite{4,10,33,41,45,46} The reason for this distinction is unclear, but it may be related to the protective effect of the poorly sustained detrusor contractions, which are seen in up to 50\% of MS patients with detrusor hyper-reflexia. Alternatively, the hyper-reflexia and degree of external sphincter spasm seen in MS may be less severe than that seen in spinal cord injury.\cite{45–47}

Although the diagnosis of DSD is most commonly made by electromyography (EMG), the proper method for the diagnosis of DSD is unclear.\cite{48} The utility of urethral EMG versus anal EMG, wire or patch electrodes, urethral pressure gradients, and videourodynamic urethral assessment is also debated.\cite{10,11,49–53} The necessity for sphincteric assessment and diagnosis of DSD has been questioned.\cite{10,12,22,35} Sirls et al. found sphincteric evaluation by EMG unhelpful in the management of 15 patients with DSD and felt its only utility was in securing the diagnosis of MS.\cite{31}

ISR is similar to DSD but of lesser magnitude and less commonly associated with lower urinary tract complications. Rather, ISR may manifest itself by a weak force of stream or stranguria. Sphincteric paralysis (flaccidity) is seen in fewer than 15\% of patients and may manifest itself as sphincteric incontinence.\cite{2}

Because MS is a dynamic disease characterized by exacerbations, remissions, and progression, changes in lower urinary tract function over time and in response to therapy can occur. In studies of selected patients, 15–55\% of patients demonstrate changes on repeat urodynamic testing.\cite{44} Of note is the fact that once DSD is noted on urodynamic evaluation, it rarely remits.\cite{10,44} However, there have been few studies evaluating the natural progression of urologic findings in patients who are mildly symptomatic or asymptomatic. Furthermore, longitudinal studies following MS patients over time and in response to systemic treatment are currently lacking.
MANAGEMENT OF THE PATIENT WITH MS AND URINARY SYMPTOMS

Urologic treatment and therapeutic guidelines

In low-risk patients (those without indwelling catheters or DSD), most authors currently cite a low incidence of renal complications and upper urinary tract deterioration. These findings may support a rather conservative approach to upper urinary tract management, discouraging the routine use of yearly upper tract monitoring except in high-risk patients, patients with changing urologic symptoms, and patients with progression of disease. Aggressive surgical management for mild hydronephrosis, as practiced in the past, has largely been replaced by clean intermittent catheterization. Although pyelonephritis is rare, its treatment may be complicated by atypical organisms (Pseudomonas spp in 34%, Proteus spp in 30%, Providencia spp in 25%).

Treatment decisions should take into account the patient’s level of disability, ability to function independently, manual dexterity, competing medical problems, and social support networks. A team approach involving the patient’s treating neurologist, urologist, and rehabilitation specialist is essential to optimize patient care. An empiric trial-and-error method is to be discouraged, since it may be time consuming and costly and may leave many patients improperly treated and at risk of potential complications. Rather, an accurate understanding of each patient’s underlying pathology should be established, based on objective parameters such as flow rate, PVR volume, and urodynamic evaluation. For treatment purposes, patients may be separated into those with storage problems, those with emptying problems, and those with both. In most patients, conservative measures are an effective means of initial management.

Conservative therapy for bladder storage disorders

Symptoms arising from storage disorders (frequency, urgency, nocturia, and incontinence) are the most common cause for urologic consultation. As nearly two-thirds of patients suffer from detrusor hyper-reflexia, treatment usually involves pharmacologic therapy to suppress uninhibited bladder contractions. Traditionally, the use of atropine-like drugs, which competitively bind the acetylcholine receptor, thereby blocking muscarinic effects, represented the cornerstone of treatment. A variety of drugs can be used (Table 38.2). Dosages of these drugs are titrated to therapeutic response or until anticholinergic side effects become intolerable. The use of imipramine in MS may be tempered by its α-agonistic properties, thus impairing bladder emptying in patients with DSD. Concomitant use of other antidepressants in the MS population also limits the effective use of imipramine. When monotherapy fails to improve detrusor storage, medications with pure anticholinergic properties (e.g. hyoscyamine, propantheline) may be combined with those having additional direct smooth muscle relaxant properties (e.g. oxybutynin, flavoxate).

Oxybutynin is one of the most widely prescribed of these medications and has produced a fair to good response in 67–80% of MS patients. Anticholinergic side effects (decreased salivation, blurred vision, and constipation) occur in 57–94% of patients and...
can have a significant effect on patient compliance. Attrition rates of up to 50% have been reported in long-term studies. These side effects are especially troublesome in the MS population, since blurred vision may be mistaken for deterioration caused by optic neuritis, and constipation is a frequent problem in MS patients. A once-daily preparation of this medication has recently been released; it has similar efficacy to that of conventional oxybutynin. The advantage of this long-acting form over conventional immediate-release oxybutynin is a reduction of anticholinergic side effects and in increased patient compliance.

The new selective muscarinic receptor blocker, tolterodine shows promise in relieving urgency and frequency with a lower incidence of anticholinergic side effects. Again, patient compliance is enhanced and side effects are lessened, thereby providing a more favorable drug treatment profile. In patients with severe hyperreflexia who fail to respond to single-agent therapy, anticholinergic medications may be ‘stacked’ by combining different medications in an effort to maximize the synergy of drugs with antimuscarinic and smooth muscle relaxant properties (e.g. oxybutynin plus hyoscyamine). In some patients, clean intermittent catheterization can be combined with anticholinergic therapy; this may be especially beneficial in patients with both storage and emptying failure. In these patients, urinary retention is promoted by anticholinergics, thus alleviating storage problems, while emptying is accomplished by clean intermittent catheterization.

In an attempt to avoid anticholinergic side effects from oral medications, a variety of intravesical medications (e.g. verapamil, lidocaine, oxybutynin) have been tested for treatment of detrusor hyper-reflexia. These agents are crushed, suspended, and instilled into the bladder

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>How supplied</th>
<th>Use</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyoscyamine</td>
<td>Anticholinergic</td>
<td>Sublingual Extended release</td>
<td>Detrusor Hyper-reflexia</td>
<td>0.125mg every 4 hours, 0.375mg every 12 hours</td>
</tr>
<tr>
<td>Probanthine</td>
<td>Anticholinergic</td>
<td>Oral</td>
<td>Detrusor Hyper-reflexia</td>
<td>7.5–15 mg every 8 hours</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>Musculotropic</td>
<td>Detrusor Hyper-reflexia</td>
<td>100–200 mg every 8–12 hours</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Anticholinergic/Musculotropic</td>
<td>Detrusor Hyper-reflexia</td>
<td>2.5–5mg every 8 hours</td>
<td></td>
</tr>
</tbody>
</table>
via sterile catheterization. The most commonly used intravesical agent is oxybutynin. The therapeutic response to intravesical oxybutynin in MS patients has exceeded 86% in selected studies. However, the inconvenience of this route of administration has contributed to a high attrition rate and has tempered enthusiasm for this treatment method.\[78\] Nevertheless, in a select group of patients already on intermittent catheterization treatment, intravesical oxybutynin may lead to a significant improvement in continence with fewer side effects.\[78–84\]

Newer intravesical medications, capsaicin and resiniferatoxin, also show promise for the intravesical treatment of detrusor hyper-reflexia. These compounds exert a selective action on C-sensory fiber axons, which are thought to play an important role in bladder reflex pathways following spinal cord insult. When instilled intravesically, capsaicin exerts a neurotoxic effect on afferent C-fiber axons, causing depletion of substance P and calcitonin gene-related peptide (CGRP).\[85–92\] In a study of 18 patients, 61% of patients treated with capsaicin demonstrated excellent results and 17% demonstrated clinical improvement.\[89\] The duration of patient response ranged from 3 to 6 months. Optimism for capsaicin has been tempered by its side-effects, including pain on instillation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Condition</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>Antimuscarinic</td>
<td>Oral</td>
<td>Detrusor hyper-reflexia</td>
<td>2mg every 12 hours</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tricyclic antidepressant</td>
<td>Oral</td>
<td>Detrusor hyper-reflexia</td>
<td>25 mg every 8 hours or 50 mg bedtime</td>
</tr>
<tr>
<td>DDAVP</td>
<td>Vasopressin analog</td>
<td>Intranasal Oral</td>
<td>Nocturia or frequency</td>
<td>1–2 puffs at bedtime 0.05–0.2 mg every 12 hours</td>
</tr>
<tr>
<td>Doxazosin/Terazosin</td>
<td>α-blocker</td>
<td>Oral</td>
<td>Sphincter dyssynergia at bedtime</td>
<td>4–12mg orthostatic hypotension, asthenia, 5–10 mg incontinence</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>α-2 agonist (experimental) (spasmolytic)</td>
<td>Oral</td>
<td>Sphincter dyssynergia 8 mg every 8 hours</td>
<td>Asthenia drowsiness, weakness</td>
</tr>
</tbody>
</table>
Resiniferatoxin lacks these side effects and is 1000-fold more potent than capsaicin. Thus, it may represent a more attractive form of intravesical therapy. In studies evaluating the effects of resiniferatoxin, the mean bladder volume at initial urge was not affected, although total bladder capacity was increased by an average of 105 ml \((p<0.001)^{[86]}\). These preliminary results suggest a difference in the urodynamic effect between capsaicin and resiniferatoxin that merits further evaluation. As capsaicin and resiniferatoxin are not approved by the Food and Drug Administration, their use in the USA is at the present time limited to investigational protocols.

Detrusor hyper-reflexia can also be treated by decreasing urine production. In multiple placebo-controlled trials evaluating MS patients, 1-desamino-8-D-vasopressin (DDAVP) nasal spray has shown significant efficacy in reducing the incidence of nocturia and enuresis and increasing sleep time.\(^{[93-95]}\) The use of DDAVP can be especially helpful in the management of patients with detrusor hyper-reflexia who cannot tolerate anticholinergic medication or who suffer from concomitant emptying failure because of DSD or hypocontractility. In a phase I clinical trial, doses of 10–20 µg were found to provide a significant decrease in nocturnal urinary volumes without hyponatremia. Increased dosages to 60 µg were no more efficacious and were accompanied by a trend toward lower serum sodium levels.\(^{[94]}\) Recently, DDAVP has become available in a tablet preparation, which is more convenient for some patients (see Table 38.2).

**Conservative therapy for emptying failure (hypocontractility and sphincter dyssynergia)**

Despite problems encountered with storage failure due to detrusor hyper-reflexia, 42% of MS patients also suffer from emptying difficulties due to DSD, unsustained voiding contractions, or detrusor hypocontractility (see Table 38.1). In a select group of MS patients, timed voiding or double voiding may be sufficient for adequate emptying. However, in most patients, intervention is required to prevent infection, calculi, or overflow incontinence. Attempts to manage these patients conservatively with \(\alpha\)-1-blocking agents (e.g. prazosin, terazosin, doxazosin) and muscle relaxants (e.g. diazepam, baclofen, dantrolene) have had mixed results (see Table 38.2).\(^{[96,97]}\) Anecdotal success has been reported with the use of tizanidine, a new spasmolytic with centrally acting \(\alpha\)-2-adrenergic properties. Use of \(\alpha\)-blockers and muscle relaxants in patients with emptying failure should be limited to patients with urodynamically proven DSD and not detrusor hypocontractility.

Clean intermittent catheterization is the primary means of management for patients with emptying difficulties, and it may aid in bladder rehabilitation.\(^{[98]}\) Urodynamic evaluation may facilitate the decision for this treatment by defining bladder storage capabilities and selecting optimum catheterization interval.

**Surgical management of bladder dysfunction**

When conservative management fails in the management of LUTD, more aggressive surgical options may be entertained. A variety of factors should be considered including the patient’s degree of manual dexterity, social support systems, and disability status, a life expectancy of 20–50 additional years, and the urodynamic parameters. Thus, short-
term solutions may need to be dismissed in favor of a more comprehensive long-term approach. Surgical options include a suprapubic cystostomy, a sphincterotomy, sphincteric stents, an augmentation cystoplasty (surgical enlargement using an intestinal patch) with or without a catheterizable limb, an incontinent vesicostomy, or a supravesical diversion (Figs 38.4 and 38.5).[99–101]

Suprapubic cystostomy (see Fig. 38.4) may be an attractive initial plan for patients in whom conservative management fails, since it has several distinct advantages over a conventional indwelling catheter. Complications of urethral

Fig. 38.4 Suprapubic tube placement using percutaneous trocar technique.
erosion (in the female) and traumatic hypospadias (in the male), often seen in the patient with chronic Foley catheterization (prompted by using successively larger catheters), are avoided. Personal hygiene and catheter care is simplified because the catheter is readily accessible and is remote from vaginal or perineal soilage. Commonly, the tube can be placed percutaneously under local anesthesia. This therapeutic approach is reversible; the tube may be removed without difficulty and the site will heal in 1–2 days. It may not be a good long-term option for younger patients because of the risk of bladder calculi, infection, and the development of squamous cell carcinoma.¹⁰²–¹⁰⁴

In the male patient with detrusor hyperreflexia and DSD who cannot be managed by conservative measures, an outlet-reducing procedure such as a sphincterotomy (endoscopically cutting the external sphincter; see Fig. 38.5) or a urethral stent (Fig. 38.6) may help to facilitate bladder emptying. In both treatment options, a condom catheter may be necessary to manage the resulting incontinence. These procedures are best
Fig. 38.6 *Urolume prosthesis (American Medical Systems)* bridging the external sphincter, thereby preventing DSD.

reserved for the patient with limited hand function for whom clean intermittent catheterization is not an option. Documentation of adequate detrusor contractility is imperative because patients with hypocontractile bladders may carry an unacceptably high residual volume even after the procedure.\(^{100,101}\)

Surgical bladder augmentation for detrusor dysfunction is usually reserved for the patient in whom all other conservative options have been exhausted. As the course of MS is by nature dynamic and progressive, permanent procedures using intestinal segments should be undertaken only after careful consideration of the current course of disease and overall prognosis. Patients undergoing augmentation cystoplasty should be assessed for manual dexterity since most will continue to require some degree of clean intermittent catheterization.\(^{59}\) In most cases, surgical augmentation is combined with a catheterizable abdominal stoma, which allows easy catheterization especially in the chair-bound patient,
the patient with lower extremity spasticity, or in the patient with poor dexterity who can not perform urethral catheterization (Fig. 38.7).

When the patient, a family member, or a caregiver cannot perform clean intermittent catheterization, and conservative management has failed, cutaneous ileovesicostomy has been used successfully for both storage and emptying abnormalities in the MS patient (Fig. 38.8). In this procedure, a segment of ileum is used to construct a chimney emanating from the bladder to allow cutaneous drainage to an external collection device.\[99\] The advantages of this procedure over supravesical diversion are preservation of the bladder and ureterovesical junctions (if competent), lack of a defunctionalized bladder, and decreased blood loss. Although some patients are reluctant to proceed with major surgical intervention, most are

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**Fig. 38.7 Catheterizable augmentation cystoplasty using ileocecal segment.**
An ileocecal segment is used, not only to augment the existing bladder but to provide an alternative access to the bladder via an efferent stoma. This allows patients to catheterize themselves while sitting or fully clothed. (From Sutton et al.\[134\]).
pleasantly surprised with the improvement that this procedure provides in quality of life and daily management of their incontinence.

**Surgical management of urethral incompetence**

The treatment for urethral incompetence includes the use of injectable bulking agents (e.g. collagen, polytetrafluoroethylene (PTFE), fat), urethral inserts, conventional bladder suspension procedures, and compressive slings. In women with urethral incompetence or destruction due to indwelling catheterization, transvaginal bladder neck closure and suprapubic drainage may serve as a minimally invasive way of dealing with intractable incontinence. Surgical intervention for urethral insufficiency should consider a variety of factors such as voiding efficiency, ability to perform clean intermittent catheterization, stability of disease, and general overall health. Patients should be informed of the risk of postsurgical urinary retention, which may adversely affect the amount of nursing care they require and their quality of life. The artificial urinary sphincter has had a limited role in the management of incontinence in MS. This is primarily due to the significant incidence of detrusor hyper-reflexia in MS and its association with upper tract deterioration in patients undergoing artificial urinary sphincter placement. Before any outlet-enhancing procedure is performed, adequate bladder storage and voiding function should be confirmed, as patients with poorly sustained voiding contractions are at risk of postoperative urinary retention.

**SEXUAL DYSFUNCTION**

As MS affects people in mid-life, issues concerning sexual dysfunction are an important factor in determining quality of life. MS adversely effects sexual functioning in up to 91% of males and 72% of females. In 64% of males and 39% of females, sexual activity ceases or is unsatisfactory. In addition to physiological disturbances, psychosocial stressors can influence sexual functioning. Mattson et al. found associated marital relationship problems in 71% of MS patients with complaints of primary sexual dysfunction.

**Male sexual dysfunction**

Men with MS report a variety of sexual symptoms, including erectile dysfunction, decreased
Fig. 38.8 Ileovesicostomy. The ileovesicostomy allows the bladder to be tubularized and brought toward the abdominal wall. As the bladder will rarely reach the skin on its own, an interposed segment of ileum is used to bridge this gap. The bladder is allowed to drain freely, and a relatively maintenance-free appliance is placed on the skin.

sensation, fatigue, and decreased libido resulting in orgasmic dysfunction. The onset of erectile dysfunction has been reported from 3.7 to 9 years after diagnosis. Yet, despite impotence rates as high as 80%, more than 75% of patients report a continued interest in sexual activity. Sexual dysfunction has been shown to parallel the level of overall disability. However, other studies demonstrated erectile dysfunction to be independent of disability and more closely related to bladder and pyramidal dysfunction alone. In a study by Betts et al., 100% of 48 patients with erectile dysfunction were found to have concomitant bladder dysfunction. However, the absence of bladder or pyramidal dysfunction does not ensure adequate sexual function, since up to 50% of patients without pyramidal symptoms suffer from sexual impairment.

Several authors have studied the physiologic basis of erectile dysfunction using pudendal reflex latencies and tibial, pudendal, and cortical evoked potentials. These studies have shown consistent deficits in cortical and pudendal evoked potentials without consistent changes in sacral reflex latencies (bulbocavernosus). Thus, it is
thought that MS-related impotence is related to suprasacral mechanisms. Abnormal pudendal evoked potentials also are predictive of ejaculatory dysfunction.\[112\] In addition to neurophysiologic abnormalities, nocturnal penile tumescence studies have demonstrated a significant psychogenic component in over 50% of patients.\[113\] In these patients, marital and sexual counseling may be beneficial.

### Evaluation

The evaluation of sexual dysfunction should begin with a thorough sexual and urologic history. Patients should be questioned about a variety of topics (Table 38.3). A number of patients complain of decreased libido. However, close questioning may discriminate patients who have a physiologically decreased desire for sex from those in whom MS has made sexual activity an anxiety-laden burden. If morning erectile activity is normal, it confirms erectile integrity. Erections that spontaneously detumesce may indicate a venous leak or steal phenomenon. Spasticity and fatigue are often severely limiting factors for sexual activity and can play a role in both patient positioning and desire for sex. The presence of an understanding, stable partner cannot be overestimated, making it preferable for the patient’s partner to be present for this portion of the office visit. Physiologic evaluation for erectile dysfunction has centered around the use of penile Doppler flow evaluation and nocturnal penile tumescence monitoring. Although these are helpful in selected patients, many physicians have gone to a more practical approach for a number of reasons. First, these tests are expensive and carry a variable degree of false positives and negatives. Second, they may not accurately reproduce what happens in a patient’s sexual encounter at home. Finally, the options for management are often not altered by the results of the testing. The one clear benefit of these tests is their ability to discern psychogenic impotence from physiologic dysfunction.

### Treatment options

Treatment decisions should take into account a variety of factors, including the patient’s degree of manual dexterity, the stability of the patient’s current relationship, the degree of disability, and the course of the disease. The approach to treatment should involve the neurologist, rehabilitation physician, and urologist. Treatment options are outlined in Table 38.4 and illustrated in Fig. 38.9.

An initial course of sexual counseling may aid in treatment of any psychological factors and also help to develop a better understanding between the patient and his partner, thereby promoting intimacy. There are few studies involving impotence treatment specifically in the MS patient, and much of what is known is extrapolated from general studies involving neurogenic impotence.\[109,110\] Although the possibility for recovery of erectile activity is low (2%), non-surgical options, such as oral agents (sildenafil), vacuum erection devices, and intracorporal injection therapy (prostaglandin E1 or papaverine), play a more prominent role than prosthetic implantation since most patients are reluctant to undergo surgery for impotence.\[115\]

Oral therapy for impotence, though receiving a recent interest in popularity, is not a new concept. Probably the oldest oral treatment option available is yohimbine, which first
saw clinical use in the 1950s. Since that time, a number of clinical studies have produced varied results. In a meta-analysis by Ernst and Pittler, yohimbine was found to be slightly superior to placebo (odds ratio 3.85, 95% CI 2.2–6.7).\textsuperscript{[118]} Side effects include anxiety (18%), headache (13%), urinary frequency (32%), and vertigo (14%).\textsuperscript{[119]} The American Urological Association’s guidelines panel on erectile dysfunction recommended that yohimbine should not be used as treatment for organic erectile dysfunction.\textsuperscript{[120]} The use of yohimbine in MS patients has never been tested. With the recent advent of newer oral therapy for erectile dysfunction, most patients will elect to pursue this option first.

Studies are under way evaluating use of oral sildenafil in men with MS. However, studies in patients with spinal cord injury show a nearly 70% success rate when used in combination with vibratory stimulation.\textsuperscript{[121]} Sildenafil (50–100 mg) is taken 1 hour before intercourse and requires psychological or tactile stimulation. Caution should be exercised with the use of sildenafil, since there are a number of drug interactions (e.g. macrolide antibiotics, cimetidine, oral antifungal agents) that should be considered. Its use in patients with known cardiac disease is severely cautioned. The use in patients taking topical or oral nitrate therapy is absolutely contraindicated.

<table>
<thead>
<tr>
<th>Table 38.3 Sexual questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males and females</strong></td>
</tr>
<tr>
<td>1. How was your sexual functioning before MS? Please explain.</td>
</tr>
<tr>
<td>2. How has MS changed your sexual functioning? Please explain.</td>
</tr>
<tr>
<td>3. Describe your level of libido (desire for sex)?</td>
</tr>
<tr>
<td>4. Are you able to have orgasms? Do they occur either sooner or later than you would like?</td>
</tr>
<tr>
<td>5. How understanding is your partner of your sexual dysfunction? Is your partner willing to alter the way you have sex in order to make it more satisfying for you?</td>
</tr>
<tr>
<td>6. Does fatigue or spasticity limit your sexual functioning? How?</td>
</tr>
<tr>
<td>7. Do you have decreased genital sensation?</td>
</tr>
<tr>
<td><strong>Males only</strong></td>
</tr>
<tr>
<td>8. Do you wake up with morning erections? How firm are they? Do you have erections with masturbation or oral sex?</td>
</tr>
<tr>
<td>9. Are your erections with stimulation firm enough for penetration?</td>
</tr>
<tr>
<td>10. Do you lose your erection soon after penetration?</td>
</tr>
<tr>
<td><strong>Females only</strong></td>
</tr>
<tr>
<td>11. Is intercourse painful for you?</td>
</tr>
<tr>
<td>12. Do you have a problem with vaginal dryness during intercourse?</td>
</tr>
</tbody>
</table>
**Fig. 38.9** Examples of treatments for erectile dysfunction.

### Table 38.4 Treatment of sexual dysfunction

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cost</th>
<th>Covered By Insurance</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual counseling</td>
<td>M/F $50–100/hr</td>
<td>No</td>
<td>Promotes a healthy relationship, helps partner, fosters intimacy</td>
<td>None</td>
</tr>
<tr>
<td>Vibratory stimulation</td>
<td>M/F $25–350</td>
<td>No</td>
<td>Inexpensive</td>
<td>None</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>M $100/month</td>
<td>Sometimes</td>
<td>Natural and spontaneous</td>
<td>Poor efficacy in organic erectile dysfunction, cost</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>M/F $9–11/dose</td>
<td>Sometimes</td>
<td>Spontaneous and easily taken</td>
<td>Cost, contraindicated in patients with nitrates or cardiac disease, may need vibratory assistance</td>
</tr>
<tr>
<td>Vacuum erection devices</td>
<td>M $250–350/unit</td>
<td>Usually</td>
<td>One time cost, few complications</td>
<td>Penis feels cool, may look blue, less</td>
</tr>
<tr>
<td>Treatment</td>
<td>M</td>
<td>Cost</td>
<td>Usual Duration</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------</td>
<td>---</td>
<td>------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Injection pharmacotherapy</td>
<td></td>
<td>$10–20/dose</td>
<td>Usually</td>
<td>Provides a reliable firm erection</td>
</tr>
<tr>
<td>Penile prosthesis</td>
<td>M</td>
<td>$8–10000</td>
<td>Usually</td>
<td>High patient and partner satisfaction, most reliable erection</td>
</tr>
</tbody>
</table>

- Side effects, which are usually limited to nasal congestion, headache, flushing, and dyspepsia, are seen in 6–18% of patients.\[122\]

Although studies in men with MS are lacking, vibratory stimulation may be utilized as an adjunct to virtually any type of erectile therapy and has been well studied in the spinal cord injury population.\[123\] Vibratory stimulation may enhance erections and may be used to decrease the orgasmic threshold for both men and women.

Vacuum erection devices have been used successfully in a variety of patients with erectile dysfunction, including those with MS.\[116\] When this form of therapy is used, a plastic tube is placed over the penis and a pump is used to create a vacuum, drawing blood into the penis. A silicone or latex ring is then slipped over the base of the penis to maintain the erection (Fig. 38.10). Although results in some studies are promising, the attrition rate may be high in improperly selected patients. Many patients feel that use of vacuum erection devices makes their penis feel cold, is painful, and is less natural than other options. Patients may require assistance from their partner in operating the device, because some degree of dexterity is needed. Vacuum erection devices are, however, relatively inexpensive and have few associated risks.

The injection of vasoactive substances into the penis has been in use for nearly 20 years and may take one of two forms—intraurethral suppositories (prostaglandin E1) or injected suspensions (prostaglandin E1 or papavarine). These medications, though fairly reliable, carry with them a 0.5% risk of pain, priapism (a painful prolonged erection accompanied by corporal hypoxia), and chronic penile fibrosis.\[117\] Despite a better than 95% initial success rate with injection therapy, the attrition rate at 2 years in MS patients is between 39% and 80%.\[124,125\]

Penile prostheses in MS patients have been used for over 20 years.\[126–129\] They may take one of two forms—inflatable and semirigid prosthesis or malleable prostheses. Although the inflatable prosthesis provides a more natural esthetic erection, it does require manual dexterity by either the patient or his partner to activate its use. Infection
rates range from 1.2% to 1.8%, and the need for revision ranges from 4.5% to 7.7%. A 5-year comparison was made of patients undergoing penile prosthesis insertion with those undergoing injection therapy. Patients undergoing prosthesis insertion had sex twice as often as patients who used injection therapy. There also was significantly higher patient satisfaction (77% versus 70%) and partner satisfaction rates (88% versus 67%) with prostheses.

**Fig. 38.10** The vacuum erection device. When a vacuum erection device is used, a constriction ring is first placed on the base of the vacuum tube. The tube is then placed over the penis and the manual or battery-operated vacuum pump is activated, drawing blood into the penis. The elastic ring (arrow) is then slipped off the tube to constrict the base of the penis and prevent egress of blood. After intercourse, the constriction ring is removed, allowing detumescence.

**Female sexual dysfunction**

Although the majority of women with MS wish to remain sexually active, sexual dysfunction is a significant problem for 56–72%. The most common reasons for sexual dysfunction in women with MS are fatigue (68%), decreased sensation (48%),
decreased or absent orgasm (72%), difficulty with arousal (35%), and frequent urinary tract infections (21%). Vaginal dryness also is a frequently reported complaint and may be related to anticholinergic medications.

**Evaluation**

The evaluation of the female MS patient with sexual dysfunction should begin with a thorough sexual history. Patients should be questioned about their sexual activity and sexual satisfaction before MS as well as their present symptoms and current methods of coping. As the sexual response in females is less dependent on the mechanics of erection or sexual performance and more dependent on the dynamics of a loving relationship, sufficient time should be spent discussing the way the patient and her partner relate both sexually and non-sexually. Often a helpful way of assessing the female sexual response is with the use of a validated questionnaire. This may allow the practitioner to distinguish better the physiologic factors from the psychosocial factors involved in the sexual response. A complete medication history is of prime importance because a number of drugs (especially selective serotonin reuptake inhibitors) used in the MS population may have adverse effects on sexual functioning, especially on libido and orgasm.

The physical examination of the female patient with sexual dysfunction remains an integral part of the overall evaluation. As sexual dysfunction may be closely associated with bladder dysfunction, a careful vaginal and pelvic examination is important to rule out the coexistence of urogenital pathology, such as cystocele, enterocele, rectocele, or urethral diverticulum. Perineal and perianal sensation should also be assessed, because decreased sensation may be reported by up to half of patients.

The laboratory evaluation of these patients is limited. Although normal values for testosterone have been established for healthy women, the use of testosterone as an adjunct to diagnosis and treatment of sexual dysfunction is not established and unsupported.

**Treatment options**

Treatment for female sexual dysfunction may take many forms. As the presence of a loving and supportive partner is crucial to treatment for female sexual dysfunction, counseling may play a pivotal role in the treatment of women with sexual dysfunction. In nearly all relationships, sexual dysfunction can be a major stressor. For that reason, sexual counseling by a registered therapist can prove invaluable.

Symptomatic treatment is also of great benefit. Vaginal dryness can be effectively treated with water-soluble vaginal moisturizers or lubricants. For patients with orgasmic dysfunction, vibratory stimuli may aid in decreasing the orgasmic threshold. The use of oral sildenafil in females with sexual dysfunction, though not formally tested, may hold promise for patients with symptomatic sexual dysfunction, including anorgasmia, hypesthesia, and vaginal dryness. The basis for its use lies in the homologous nature of the male and female genitalia and the presence of type 5 phosphodiesterase activity in the genital tissues of both men and women.

In patients with decreased mobility, sexual positioning may be altered to aid in patient comfort. Involvement of the patient’s neurologist and careful attention to overall systemic
treatment can alleviate many somatic symptoms related to sexual dysfunction (e.g. fatigue, spasticity).

Historically, oral or parenteral testosterone has been used in an effort to improve libido and sexual response. However, as the female sex drive is not testosterone-dependent, few patients benefit from this type of therapy. Moreover, testosterone supplementation is not without risk and side effects. Patients may note mood swings and growth of facial or body hair. Systemic complications of testosterone therapy include hepatic or renal damage, increased risk of stroke, and suppression of the hypothalamic axis. In the majority of cases, loss of libido is more closely related to frustration and feelings of hopelessness over relationship issues and lack of sexual responsiveness than physiologically decreased sexual desire.

CONCLUSIONS

MS often is a devastating disease affecting 0.1% of both men and women in the prime years of their life. During the course of this disease, nearly all patients will manifest lower urinary tract symptoms or sexual dysfunction. Although these symptoms are rarely life-threatening, they nonetheless have a significant impact on quality of life. Consequently, the neurologist may be called upon to assist in the care of patients with these problems. To treat these problems effectively and intelligently, the neurologist must have a fundamental working knowledge of the disease process itself and its effects on the genitourinary system. Using this knowledge, a logical and individualized treatment plan can be formulated.

REFERENCES


Emotional disturbances are common in multiple sclerosis (MS).[1–9] They consist of disturbances of affect, in which emotional expression may be blunted, flat, inappropriate, or labile and disturbances of mood, such as depression, mania, and anxiety.[10] The terms ‘affect’ and ‘mood’ are often used interchangeably, but the differences between them are important and have etiological, diagnostic, and treatment implications. Mood refers to a sustained and pervasive emotion that influences perception of self, others, and the world. Affect refers to more fluctuating changes in the outward expression of inner feeling states. The disorders of affect—euphoria, pathological laughing and weeping, and other frontal lobe syndromes—are direct consequences of the pathological process in MS, are highly characteristic features of the disease, and follow the same course as the other signs and symptoms of MS. There are effective treatments for pathological laughing and weeping and, to some extent, for the apathy associated with frontal lobe and subcortical syndromes. By contrast, the relationship between MS and the disorders of mood—major depressive disorder, dysthymic disorder, bipolar disorder, panic disorder, and generalized anxiety disorder—is multifactorial and complex, and the extent to which mood disorders are direct consequences of the disease process or psychological reactions to it remains unclear. Whatever their cause, however, mood disorders in MS are phenomenologically no different from mood disorders more generally and respond similarly to standard treatments.

Untreated depression may be one of the most disabling aspects of MS. Indeed, the World Health Organization (WHO) estimated that, over the next 20 years, disability due to depression will be exceeded only by ischemic heart disease.[11] With highly effective and well-tolerated treatments now available, we can dramatically reduce the personal suffering, disrupted relationships, occupational impairment, and the number of deaths by suicide that result from depression. General health care providers have a particular opportunity to decrease depression-related morbidity and mortality since the majority of depressed patients are seen first in medical settings,[12,13] but unfortunately they too often fail to identify, diagnose, and treat mood disorders appropriately.[14–19] At the same time, patients and family members often have trouble acknowledging emotional difficulties, discussing them with health-care providers, and following recommendations for psychiatric consultation and treatment.[20,21] Given that suicide appears to be more
common among patients with MS than both the general population and patients with other neurological conditions, prompt diagnosis and successful treatment are particularly critical. The National Multiple Sclerosis Society has developed and sponsored educational materials and programs for physicians, other healthcare professionals, and patients and their families in an effort to enhance awareness, reduce stigma, and encourage treatment of mood and affect disorders in MS.

Identification and diagnosis of mood and affect disorders have been aided by major advances over the past 25 years in the classification of mental disorders and the acceptance of standardized terminology and diagnostic criteria. The current nomenclature, used in the USA and elsewhere and as outlined in the fourth edition of the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), is neutral with regard to etiology and is based on empirical evidence collected with reliable and valid diagnostic tools (i.e. semistructured interviews and symptom rating scales). A systematic approach to evaluation and use of accepted diagnostic criteria should help practitioners to identify and diagnose mood and affect disorders accurately; treatment then follows logically from the diagnosis.

The mental health field makes an important distinction between symptoms and disorders. Symptoms can be elicited through an unstructured clinical interview, a structured or semistructured research interview, or a symptom rating scale. Structured and semistructured interviews include the Structured Clinical Interview for DSM (SCID), National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS), Composite International Diagnostic Interview (CIDI), and Hamilton Rating Scale for Depression (HRSD); symptom rating scales include the Beck Depression Inventory (BDI), General Health Questionnaire (GHQ), Center for Epidemiologic Studies Depression Scale (CES-D), Zung Self-Rating Depression Scale, and Symptom Checklist (SCL-90). Both the interviews and the scales can be used to indicate the severity of the symptom(s). A mental disorder, on the other hand, can be diagnosed only if specified criteria are met with regard to the number, duration, and intensity of symptoms; their impact on functioning; and the absence of a physiological cause such as a substance or medical condition. Hence, a mental disorder is ‘a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and…is associated with present distress (e.g. a painful symptom) or disability (i.e. impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom…[which is not] merely an expectable and culturally sanctioned response to a particular event, for example, the death of a loved one’. A clinical interview or the structured and semistructured interviews cited above, but not the symptom severity rating scales, can be used to make criteria-based diagnoses.

Evaluation of a patient with an emotional disturbance, then, begins with identifying symptoms; determining their duration, intensity, and impact on functioning; and excluding alternative explanations such as physiological disturbances or life events. For people with MS, it is also necessary to distinguish between symptoms due to a mood disorder and symptoms due to MS, such as fatigue and diminished ability to think or concentrate. Clinically, this can usually be accomplished by careful questioning, but for research purposes it may be necessary to modify the administration and scoring of symptom severity rating scales and diagnostic interviews to avoid the confounding effects of MS symptoms. For example, Mohr et al. found that items measuring work
difficulty, fatigue, and concerns about health contributed significantly more to total BDI scores in patients with MS than in patients with major depression and normal controls, and they recommended eliminating these three confounding items from the scale.\[27\] Minden et al. reported psychological and somatic scores as well as total scores to differentiate items that could be confounded by physical symptoms from purely psychological ones.\[28\] These authors also recommended eliminating confounding items such as fatigue and slowed thinking from formal diagnostic criteria.\[28\] Others, however, believe that MS clinics can use symptom rating scales in the usual way to screen for depressed patients and simply raise the cut-off scores to reduce the number of false positive identifications.\[30,31\]

Systematic inquiry in the context of a supportive and empathic interview makes it possible to decide whether criteria have been met for a particular mood disorder, the symptoms do not meet those standards, or the patient is suffering from an MS-related disorder of affect. This diagnostic decision is critical since it determines treatment. Once the diagnostic decision has been made, evidence-based or consensus-based practice guidelines are available to recommend the most effective pharmacological and psychosocial interventions for virtually all mental disorders.\[26,32,33\] Therefore, this chapter describes the symptoms and diagnostic criteria for mood disorders and affect disturbances and focuses on diagnostic decision making since treatment is virtually the same for people with and without MS, except for the need to watch out for a few potential adverse effects. We expect that readers are familiar with accepted practices for treatment of mental disorders, and that they consult standard texts and the literature, as well as conferring with psychiatrists and other mental health professionals. Data from relevant epidemiological and pathophysiological studies of mood and affect disorders in MS are also presented, treatment options outlined, and implications for clinical practice and future research discussed. DSM-IV diagnostic criteria for all disorders mentioned in this chapter are summarized in the glossary below.

**MOOD DISORDERs**

The psychiatric disorders most common in MS are major depressive disorder, dysthymic disorder, and bipolar disorder. The literature also contains reports on generalized anxiety disorder, panic disorder, and psychotic disorders. Clinically, people with MS can develop any of the other mental conditions in the nomenclature.

**Major depressive disorder and dysthymic disorder**

There are no population-based estimates of the prevalence of depressive disorders in MS, but investigators have estimated their prevalence from clinical samples. As a result of differences in definitions, instruments, and samples, there is enormous variation. The prevalence rates for depression range from 6% to 57%, with rates of 10% to 54% for depression developing after the onset of MS.\[1\] Investigators who used more reliable and valid measurement techniques (i.e. semi-structured interviews) to determine whether patients met formal diagnostic criteria have estimated prevalence rates of major depressive disorder at 14%,\[34\] 22%,\[36\] 24%,\[37\] 34%,\[28\] 37%,\[38\] and 40%\[39\] and lifetime
prevalence rates at 23%, 42%, 50%, and 54%. The rate of major depression in one group of MS patients before the onset of their disease did not differ from the rate reported for a community sample with the same age distribution, but the rate after the onset of the MS was significantly higher than the age-adjusted lifetime rate for the community sample (20%). Lifetime rates of major depression or occurrence of depressive episodes have been shown to be higher in MS patients than in patients with general medical conditions, other chronic neurological conditions, and in some groups of patients, but not all, with chronic fatigue syndrome. The rate of depression among a group of MS patients discharged from hospital was significantly higher than for non-MS hospital users. Studies of the frequency of attempted and completed suicide suggest that rates are substantially higher for the MS population than for the general population.

Depression rating scales have been used by many investigators to determine the severity of depressive symptoms in MS. BDI mean scores were reported by different investigators to be 11.1±8.5, 12.7±8.4, and 22.03±11.4. These were significantly higher than scores found in samples of patients with general medical conditions or cancer and in normal controls. Scores were not higher than those of patients with chronic fatigue syndrome, spinal cord injury, or motor neuron disease. Investigators have hypothesized that if depression is more prevalent or severe in people with MS than in people with other medical conditions, particularly non-central nervous system disabling disorders, then it is less likely to be a psychological reaction to illness and more likely to be related to the disease process. To test this hypothesis, they examined the relationship between depression and various disease parameters, but their findings were inconclusive. In some studies, there were no observed correlations between depression and MS disease duration, severity and type of disability, cognitive impairment, various magnetic resonance imaging (MRI) measures, fatigue, disease activity, or course of illness. However, other investigators reported significant correlations between depression and MS disease duration, degree of neurological impairment, progressive MS, cognitive impairment, enlarged ventricles, lesions in the frontal and temporal lobes, paraventricular areas, left hemisphere, and left arcuate fasciculus region, and regional cerebral blood flow asymmetries in the limbic cortex. Associations have also been reported between depression and sleep disturbance, fatigue, relapses, sexual dysfunction, low melatonin secretion and circadian phase lability, lower CD8+ cell numbers and higher CD4:CD8 ratios, and higher CD4+ cell numbers and percentages. High plasma cortisol levels but normal responses to provocative tests of hypothalamic-pituitary-adrenal axis function, and failure to suppress cortisol release after dexamethasone challenge. Deuschle et al. reported finding antigens to human Borna disease virus only in cerebrospinal fluid from patients with recurrent major depression or MS but not in patients with other psychiatric or neurological disorders. Some studies found no higher risk of depression among first-degree relatives of depressed MS patients, arguing against a genetic susceptibility to unipolar depression. Suicide in male MS patients has been associated with age (40–49 years), previous suicidal behavior and mental disorder, recent worsening of MS, and moderate disability. Risk factors were less clear for women, but for all patients a more severe disease course was associated with higher risk.
The advent and now widespread use of the disease-modifying agents interferon beta-1b, interferon beta-1a, and glatiramer acetate have led to concerns about the impact on mood of these medications. Feinstein reviewed the data on this issue and found that while any of the interferons may be associated with depression, the literature shows conflicting results, probably because of differences in samples, treatments, and methods of assessment. Feinstein offers a thoughtful discussion of the methodological problems of these various studies. He concludes that we simply do not know the effects of the disease-modifying agents on mood since no study has adequately teased them apart from the complex array of genetic, disease, psychological, and social factors presumed to be involved in the etiology of depression in MS. Nevertheless, physicians should monitor all patients on these medications, particularly those with previous depressive illness and a family history of depression, and initiate treatment as indicated.

**Bipolar disorder**

The literature contains several case reports of mania in patients with MS, and three studies found the rate of bipolar disorder to be significantly higher than general population rates. Some investigators have suggested a genetic relationship between these disorders based on findings of familial clustering of MS and bipolar disorder and certain major histocompatibility class II markers. Hypomania and mania may be precipitated by corticotropin or corticosteroids, primarily with higher doses, and particularly in patients with a previous history of mood disorder and a family history of depression or alcoholism.

**Anxiety disorders**

There are fewer studies of anxiety than depression in MS. Noy et al. found that the rate of anxiety was higher than the rate of depression (90% versus 50%) among 20 patients with relapsing-remitting MS. Anxiety was associated with disease activity but not with disease duration or severity. Feinstein et al. found clinically significant anxiety, either with or without depression, in 25% of a group of 152 patients, a rate that was three times higher than the rate of depression. Stenager et al. reported elevated scores on measures of both state anxiety (i.e. anxiety at the time of assessment) and trait anxiety (i.e. anxiety as an enduring characteristic) in a sample of MS patients. Anxiety correlated significantly with neurological disability but not with disease course or cognitive impairment. Indeed, this group and others observed that it is the moderately disabled patients who are the most anxious, most depressed, at highest risk of suicide, and most likely to have difficulty carrying out usual social roles and maintaining leisure activities. Panic attacks have also been reported in MS.
Adjustment disorders and quality of life

People with MS develop adjustment disorders with depressed or anxious mood, or both. There are no systematic studies of these disorders, but clinical experience suggests that they tend to occur at characteristic times, namely in association with diagnosis, exacerbations, and significant changes in clinical status such as those that require use of an assistive device. They also occur in response to MS-related life events such as withdrawal from the labor force, dissolution of a marriage, and entry into a long-term care facility. The role of stress in the onset, exacerbation, and course of MS remains a controversial issue whose study is complicated by a variety of methodological problems. Several studies have explored how people with MS adjust to and cope with their illness and have identified factors associated with successful or unsuccessful coping. In one study, patients hospitalized for an exacerbation reported that the most disturbing aspects were fatigue, inability to walk, and uncertainty about the future. They coped primarily by using self-reliance and humor and by trying to learn more about their disease. Optimistic coping was associated with less depression. In another study, people with MS used coping strategies that were similar in type and effectiveness to those used by normal controls, and they modified their coping strategies to deal with different types of stressors. Depression has been associated with perceived helplessness, illness representations, and perceived uncertainty and unsupportiveness of social network interactions. Past performance was the best predictor of ability to control mood and maintain social activity; self-efficacy and disability level also contributed.

As part of a growing interest in the quality of life of patients with various chronic illnesses, investigators have developed instruments specifically designed to study the quality of life of people with MS. Research in this area has shown a significant relationship between depression and poorer quality of life.

DISORDERS OF AFFECT

Pathological laughing and weeping

Estimates of the prevalence of pathological laughing and weeping in MS are highly variable—7%, 8%, 10%, 51%, 79%, 95%—as a result of different definitions, incommensurate samples, and variable evaluation methods. In their study of this issue, Feinstein et al. discuss the diagnostic problems that arise from the absence of a systematic definition: imprecise terminology (e.g. ‘pseudobulbar affect’, ‘emotional dyscontrol’, ‘emotional incontinence’, ‘excessive emotionality’, and ‘emotionalism’) and inappropriate grouping of patients with different problems (e.g. patients who have difficulty controlling facial musculature and cry without subjective feelings of sadness as opposed to depressed patients who have bouts of crying that appear excessive). Using explicit criteria—sudden loss of emotional control (crying or laughing, or both) on multiple occasions over 1 month that occurs in response to non-specific stimuli and lacks an associative, matching mood state—and a validated rating scale (the Pathological Laughing and Crying Scale), Feinstein et al. estimated a prevalence rate of 10%.
They also found that the disorder was related to chronic progressive MS, greater intellectual impairment and physical disability, and longer duration of illness, but not to the occurrence of a relapse, depression or anxiety scale scores, or premorbid or family history of mental illness. In a later study of 100 MS patients, Feinstein and Feinstein found that 73% of patients had difficulty controlling their emotions during the past month, most often reporting irritability, but also crying and sadness. Of these patients, 17% met diagnostic criteria for major depression and 8% for pathological laughing and crying. Both groups tended to have greater disability than patients who were emotionally stable or had self-perceived emotional difficulties without a formal syndromal diagnosis.

Pathological laughing and weeping has been associated with diffuse, bilateral cerebral disease, which is presumed to interrupt corticobulbar tracts involved in control of emotional expression; right hemisphere damage; prefrontal cortex dysfunction; and lesions in the pons or connections between the middle right cerebral hemispheres and pons.

**Euphoria**

Euphoria is different from both pathological laughing and mania. Whereas pathological laughing refers to outbursts of laughter without an underlying joyous mood state and mania describes an elated mood with hyperactivity, pressured speech, and racing thoughts, euphoria is a sustained “mental state of cheerfulness, happiness, [and] ease” in which patients appear “serene and cheerful”, report feeling physically fit and healthy, and display “an optimism as to the future and the prospects of ultimate recovery which is out of place and incongruous”. Euphoria is not an episodic emotional expression like pathological laughing or a reversible mood like mania. It is a persistent frame of mind or outlook, perhaps best characterized as a permanent change in personality. Patients with euphoria are different from how they had been, and there is an apparent disconnection between their intellectual understanding of their condition and the emotional response that would be expected to accompany it. Note, however, that investigators who explored underlying feeling states more closely did find significant unhappiness and depression in patients with euphoria.

Prevalence rates for euphoria are highly variable—0%, 5%, 7%, 10%, 13%, 26%, 48%, 54%, and 63%—again, owing to differences in assessment methods and in severity and duration of illness across samples.

Euphoria is a neurologically based emotional state, the result of pathological processes in the brain. Euphoric MS patients are more likely to have brain involvement, progressive MS, enlarged ventricles, and more cognitive impairment than non-euphoric MS patients. Relapsing-progressive patients with euphoria had significantly larger lesions in the parietal region and relatively smaller lesions in the temporal region compared with relapsing-remitting patients. Among patients with combined euphoria and depression, relapsing-progressive patients had larger lesions in parietal and occipital areas and relapsing-remitting patients had larger lesions temporally.
Psychotic and organic mental disorders

Psychiatric nomenclature clearly distinguishes mood from psychotic disorders (schizophrenia; schizoaffective disorder; delusional disorder; brief psychotic disorder; and psychotic disorders due to general medical conditions, medication, a drug of abuse, or toxin exposure). A distinction is also made between mood disorders and what formerly were called organic mental disorders, now classified under the rubric ‘delirium, dementia, and amnestic and other cognitive disorders’. \[10\] People with MS are at no higher risk of schizophrenia and schizoaffective disorder than the general population, but case reports describe delusions and other psychotic symptoms. It is sometimes difficult to determine from these reports whether patients were psychotic or had one of the disorders of affect, dementia, or delirium. \[107,174–178\] Clinically, these disorders should be distinguished with a careful mental status examination, since treatment approaches are different.

TREATMENT OPTIONS

There are three steps to successful management of disorders of mood and affect in MS: first, making the correct diagnosis; second, selecting the appropriate treatment; and, third, consulting with and referring to specialists.

Making the correct diagnosis

Effective treatment depends above all else on an accurate diagnosis. For people with MS, diagnostic decision-making should proceed as indicated in Fig. 39.1. Conflicting results from studies of depressive disorders in MS should not be discouraging. Rather, they support our current understanding of mood disorders as heterogeneous with regard to symptoms, course, outcomes, and etiologies. \[179,180\] With the wide array of efficacious treatment options now available, the clinical focus should be on identifying symptoms, making the correct diagnosis, providing appropriate treatment, and closely monitoring the patient’s response to therapy.

When clinicians talk empathically and listen carefully to their patients, it is not difficult to elicit symptoms of emotional distress. Open ended questions such as ‘How are things going?’ or ‘How are your spirits?’ provide patients the opportunity to talk about their distress. Depression often manifests itself through nonverbal clues. Recall the patient who walks and speaks slowly, sits slumped with downcast eyes, sighs and tears up, and evokes in you feelings of sadness or helplessness. Once the unhappiness is noted—‘You seem very sad’ or ‘It must be very difficult’—further conversation will determine precipitants, associated symptoms, and whether the duration, intensity, and impact of the symptoms meet criteria for a mental disorder. A review of systems, physical examination, and laboratory assessment will rule out medical conditions that mimic or are associated with abnormal mood states, such as thyroid or other endocrine disorders, malignancy, autoimmune disease, and use of medications or substances (alcohol and drug intoxication or withdrawal) that could produce these symptoms.
Distinction must be made between mood disorders and normal or expected responses to life experiences. Grief over the loss of a loved person, the ability to carry out desired activities or a sense of oneself as whole and one’s life as meaningful makes people sad and anxious and affects their appetite, sleep, and concentration. Major depression and dysthymia can be distinguished from grief by the intensity of the symptoms and their failure to diminish over time. While grief always has a precipitant, major depression and dysthymia may or may not be related to life events. Loss of interest in formerly pleasurable activities and diminished capacity for enjoyment occur in both grief and depression, but they are far more characteristic of depressive states. Grief does not involve loss of self-esteem, pessimism, self-reproach or suicidal thoughts, unlike depression.

In all patients, but particularly the elderly and those with neurological conditions such as MS, care must be taken to assess the true import of ‘diminished ability to think or concentrate or indecisiveness’. Pseudodementia of depression (i.e. reversible cognitive deficits secondary to depressive illness) has been well described, but it must be

**Fig. 39.1 Decision-tree for diagnosing disorders of mood and affect**
distinguished from the irreversible cognitive deficits commonly found in people with MS. Ultimately, the only reliable ‘test’ is that depression-related cognitive deficits will resolve with effective treatment of the depression whereas MS-related deficits will not.

The presence of various risk factors makes a diagnosis of mood disorder more likely than not: family history of the disorder, including alcoholism for major depressive disorder, and previous episodes of mood disorder. Disorders of affect, by contrast, are associated with longer duration of illness, progressive course, and high lesion load, particularly in frontal areas.

Feinstein and Feinstein have suggested that many patients with MS have subsyndromal depression (i.e. depressive symptoms that are too few or too mild to meet the diagnostic criteria for major depression) and that this can contribute to poor psychosocial outcomes and the occurrence of a major depressive episode. Minden et al. found that, although 34% of their sample of 50 patients met criteria for major depression, many more reported depressive symptoms, including depression (64%), anger (64%), irritability (56%), worry (48%), and discouragement (42%). Relatively fewer patients reported self-criticism, withdrawal, and loss of interest. The study by Feinstein and Feinstein supports the common clinical observation that many depressed patients present with irritability rather than sadness.

As noted earlier, screening instruments like the BDI or the SCL-90 are useful, as are the Brief Carroll Depression Scale and the Zung Self-Rating Depression Scale, but the overlap between MS and certain depressive symptoms may falsely inflate the scores. In a clinical setting, however, where it is important to identify and treat as many patients as possible, ‘high-scoring patients should be given a more thorough clinical assessment to ascertain whether they are true or false positives for depression’. Indeed, it has been suggested that two questions from the Primary Care Evaluation of Mental Disorders (PRIME-MD) produce sensitivities of 89–96% and specificities of 51–72% for diagnosing depression—‘During the past month, have you often been bothered by feeling down, depressed or hopeless?’ and ‘During the past month, have you often been bothered by little interest or pleasure in doing things?’ Given the low rate of identification of mood disorders in medical settings, it is prudent to err on the side of over-identification and to be aware of and follow patients with elevated scores on screening tests. Randolph et al. argued that certain neurovegetative symptoms, particularly disinterest in sex and sleep disturbance, are reliably associated with depression and should not simply be discounted as overlapping with the physical symptoms of MS.

It is particularly important to inquire about suicidal thoughts and behaviors. Clinicians often fear that asking about suicide will put such ideas into patients’ heads. Not only is there no evidence for this, but most people feel enormous relief when asked to talk about their suicidal feelings. Knowing that someone will help, whether by treating the depression as an outpatient or by providing the safety of a psychiatric unit or hospital, is reassuring and comforting. With the increased rate of suicide among people with MS, frank discussion of self-destructive impulses is critical.
Selecting the appropriate treatment

**Major depressive disorder and dysthymia**

In general, the combination of psychotherapy and pharmacotherapy is more effective than either modality alone for treatment of depressive disorders (or, in fact, for any mental disorder). Antidepressants provide effective treatment for both major depressive disorder and dysthymia. Individual and group psychotherapy are particularly useful in helping patients adjust to MS and to minimize the sequelae of depressive disorders. They are also effective treatments for problems in living and personality issues unrelated to MS. Mohr et al. compared outcomes for 63 depressed MS patients randomly assigned to individual cognitive-behavior therapy, supportive-expressive group therapy, and sertraline (average dose for patients completing the study was 139 mg/day [range, 50–200 mg/day]). They found that all treatments were effective at reducing depressive symptoms during treatment and for 6 months after treatment, and that improvement was significantly greater with both cognitive-behavioral therapy and sertraline than with the group therapy. As Mohr and Goodkin state in their meta-analysis of studies of treatment of depression in MS: ‘both psychotherapy and antidepressant medication are very effective at reducing levels of depression in patients with MS…and MS patients who receive no treatment are likely to become more depressed over time’. Mohr et al. also reported that both pharmacological and non-pharmacological treatment of depression resulted in decreases in elevated pre-treatment levels of interferon-γ production.

There are few systematic studies of pharmacological treatment of depression in MS. Schiffer and Wineman conducted a double-blind, placebo-controlled trial of desipramine in 28 patients with MS and major depressive disorder and found significantly greater improvement in the active treatment group. Unfortunately, almost 40% of patients experienced side effects with doses of 125 mg/day or higher. Scott et al. conducted a retrospective review of mood disorders in 238 MS patients seen over a 6-month period. They found that 22% received pharmacological treatment for depressive symptoms during the 6 months or within 4 years and that 7% received treatment for rapid mood swings. Therapeutic response to medication was high and side effects were tolerable; the relapse rate after discontinuing the antidepressant was 59%. The same group conducted an open label trial of sertraline 100 mg/day in 11 patients with MS. One patient discontinued treatment because of perceived lack of efficacy; the remainder continued for at least 3 months, showed significant improvement, and had no side effects. There are also anecdotal reports of positive responses to fluoxetine and valproate.

Depression occurs in many other neurological disorders, and pharmacological treatments have proven safe and efficacious. Clinical experience suggests that any of the currently available antidepressants are effective in treating depressive disorders in people with MS. Side effects are the same for people with MS as for other patients, although they may occur at lower doses and anticholinergic effects (urinary retention, blurred vision, and dry mouth) may be more problematic.Clinicians should assume, even without systematic study, that people with MS will be more vulnerable to such symptoms and that the consequences (urinary infection and tremor) may be more profound.
Selective serotonin reuptake inhibitors (SSRIs), unlike tricyclic antidepressants (TCAs), tend not to have these problems. Given their equivalent efficacy, they are probably safer for people with MS at standard doses. The dietary restrictions, potential drug interactions, and wide range of serious and discomforting adverse effects of monoamine oxidase inhibitors (MAOIs) make them poor candidates for use in MS. Readers should refer to standard psychopharmacology texts and the literature for discussions of available medications, dosages, and adverse effects. Table 39.1 provides clinically relevant information for several of the more commonly used antidepressants.\{184,196\}

A general approach to the pharmacological treatment of depression in a person with MS is outlined in Table 39.2. The basic elements of this approach—careful evaluation and diagnosis, thoughtful patient-specific selection of medication, careful monitoring, and a strong patient-doctor relationship—apply as well to treatment of other mood and anxiety disorders and will not be repeated in those sections. Table 39.2 addresses two issues of particular importance to patients with MS: sexual side effects of SSRIs and drug interactions of psychotropic agents.

Psychotherapy is an important component of treatment.\{186,188\} Minden discussed the psychological issues that arise in psychotherapy with people with MS,\{187\} and Schiffer described four interpersonal management strategies that nonpsychiatric physicians can use in treating depressed MS patients.\{197\} Crawford and McIvor found that patients in insight-oriented group psychotherapy were significantly less depressed than patients in a current events group and patients who had no treatment. Participation in the structured current events group alone resulted in an improvement in emotional state compared to no treatment.\{198\} Other kinds of group therapies,\{199,200\} and individual and group cognitive-behavioral, coping, and stress management therapies are also helpful.\{201–204\} Mohr et al. found that an 8-week structured program of cognitive-behavioral therapy administered by telephone and using homework assignments resulted in significant reduction in scores on a depression symptom rating scale.\{205\}

Whether the physician who treats the MS should also manage the psychotropic medication or provide the psychotherapy depends on several factors: the physician’s interest, experience, and skill; the severity and complexity of the patient’s problems; and the patient’s preference.\{187\} Regardless of who provides psychotherapy or who manages antidepressant medication, a strong and consistent relationship between the patient and family and the MS physician is key to successful management of mood disorders. Patients and family members should feel comfortable and secure enough with their MS physician to talk openly about the stresses associated with the MS and to seek help for painful and disruptive emotional symptoms. Physicians should know their patients well enough to detect subtle changes in mood and to offer counsel and assistance. They should talk frankly with their patients about referrals to mental health professionals for consultation and treatment, being sensitive to concerns people have that they are being ‘got rid of’ or considered ‘crazy’. Physicians can help patients recognize that referral to a mental health provider is intended to provide them with the best possible care by being clear about the reasons for the referral, addressing patients’ concerns directly, and telling patients what they may expect at the initial visit and over the long term. When mental health professionals become involved in a patient’s care, close communication with the primary physician is essential.\{186,206\}
<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Pros</th>
<th>Cons</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine Initial: 10–20 mg Therapeutic: 20–40 mg Maximum: 80–100 mg May use 90 mg Prozac weekly after stable on 20 mg</td>
<td>FDA-approved for depression, bulimia, obsessive-compulsive disorder</td>
<td>May cause agitation, akathisia, restless legs syndrome and by 2D6</td>
<td>Potent 2D6 inhibitor Metabolized by 2D6</td>
<td></td>
</tr>
</tbody>
</table>
|                    | Initial: 10–20 mg Therapeutic: 20–40 mg Maximum: 80–100 mg May use 90 mg Prozac weekly after stable on 20 mg | for atypical depressions, anxiety | Fewer drug interactions than TCAs (as with all SSRIs) | |}
| Sertraline Initial: 25–50 mg Therapeutic: 50–100 mg Maximum: 200 mg | FDA-approved for depression, obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder Fewer drug interactions than other SSRIs | May cause agitation, insomnia Discontinuation effects Gastrointestinal side effects | Modest 2D6, 2C inhibitor Metabolized by 2D6 | |
* Most Selective Serotonin Reuptake Inhibitors have low anticholinergic and sedation effects compared to the tricyclic antidepressants.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Pros</th>
<th>Cons</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (continued)</strong></td>
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</tr>
<tr>
<td><strong>Paroxetine</strong></td>
<td>Initial: 10–20 mg</td>
<td>FDA-approved for depression, generalized anxiety disorder, social anxiety disorder, and panic</td>
<td>May be more sedating</td>
<td>Potent 2D6 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Therapeutic: 20–40 mg</td>
<td></td>
<td>Possibly more weight gain</td>
<td>Metabolized by 2D6</td>
</tr>
<tr>
<td></td>
<td>Maximum: 60–80 mg</td>
<td></td>
<td>Mild anticholinergic effects</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Discontinuation effects</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Drug interactions</td>
<td></td>
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</tr>
<tr>
<td><strong>Fluvoxamine</strong></td>
<td>Initial: 25–50 mg</td>
<td>FDA-approved for obsessive-compulsive disorder</td>
<td>Twice daily dosing usually necessary</td>
<td>Potent 3A4, 1A2, 2C19 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Therapeutic: 75–150 mg</td>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum: 300 mg</td>
<td></td>
<td>Drug interactions</td>
<td></td>
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</tr>
<tr>
<td><strong>Citalopram</strong></td>
<td>Initial: 10–20 mg</td>
<td>FDA-approved for depression</td>
<td>Sedating</td>
<td>Mild 2D6 inhibition with high doses</td>
</tr>
<tr>
<td></td>
<td>Therapeutic: 20–40 mg</td>
<td></td>
<td>Usually less agitating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum: 60 mg</td>
<td></td>
<td>Possibly less disruptive to sleep</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Fewer drug interaction</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Well-tolerated by elderly patients</td>
<td></td>
</tr>
</tbody>
</table>

**Other antidepressants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Pros</th>
<th>Cons</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trazodone</strong></td>
<td>Initial: 25–50 mg</td>
<td>FDA-approved for depression</td>
<td>Antidepressant efficacy requires high dosing and at least twice-daily dosing</td>
<td>Metabolized by 2D6</td>
</tr>
<tr>
<td></td>
<td>Therapeutic: 300–600 mg</td>
<td>Very helpful for sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum: 600 mg in divided doses</td>
<td>Low rate of sexual side effects (except priapism)</td>
<td>Sedating</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Priapism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Orthostasis</td>
<td></td>
</tr>
</tbody>
</table>
Very low anticholinergic effects compared to TCAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial:</th>
<th>FDA-approved</th>
<th>Therapeutic:</th>
<th>Maximum:</th>
<th>Other antidepressants (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>100 mg SR or 75 mg IR</td>
<td>for depression</td>
<td>150 mg in divided doses</td>
<td>450 mg in divided doses</td>
<td>Most stimulating (SR form may be safer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effective in attention-deficit hyperactivity disorder and restless legs syndrome</td>
<td></td>
<td></td>
<td>Very low risk of sexual side effects Least likely to induce rapid-cycling and mixed states No weight gain No cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice- or three-times daily dosing above 200 mg</td>
<td></td>
<td></td>
<td>Potent 2D6 inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated in epilepsy and eating disorders, owing to increased risk of seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg IR or XR</td>
<td>Probably more effective at high doses than SSRIs in severe depression</td>
<td>No drug interactions</td>
<td>No drug form requires divided dosing Sexual side effects</td>
<td>Tachycardia and hypertension above 200 mg daily</td>
</tr>
<tr>
<td></td>
<td>75–225 mg</td>
<td></td>
<td>Effective for anxiety and, at higher doses, concentration and attention</td>
<td></td>
<td>No significant inhibition</td>
</tr>
<tr>
<td></td>
<td>375 mg</td>
<td>No weight gain</td>
<td></td>
<td></td>
<td>Metabolized by 2D6 and 3A4 (minor)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 mg</td>
<td>Little nausea or diarrhea</td>
<td>May be too sedating</td>
<td>No drug</td>
<td>No significant inhibition</td>
</tr>
<tr>
<td></td>
<td>15–30 mg</td>
<td>Little agitation</td>
<td>Weight gain</td>
<td>No weight gain</td>
<td>Metabolized by 2D6, 1A2</td>
</tr>
<tr>
<td></td>
<td>60 mg</td>
<td>May help sleep</td>
<td>Rare cases of reversible agranulocytosis (1.1 per 1000)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
interactions
Fewer sexual side effects
No cardiotoxicity
Safe in overdose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Pros</th>
<th>Cons</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nefazodone</td>
<td>Initial: 50 mg</td>
<td>Particularly calming</td>
<td>Twice-daily dosing necessary for some patients Metabolized by 2D6 (m-CPP) and 3A4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Therapeutic: 200–400 mg in divided doses</td>
<td>Good for panic disorder</td>
<td>Difficult to titrate Discontinuation effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum: 600 mg in divided doses</td>
<td>Effective for insomnia</td>
<td>Sedating, cognitively dulling drug interactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No sexual side effects</td>
<td>No weight gain</td>
<td></td>
</tr>
</tbody>
</table>

**Tricyclic antidepressants (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Pros</th>
<th>Cons</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline</td>
<td>Initial: 10–25 mg</td>
<td>FDA-approved for depression</td>
<td>Sedating No significant P450 inhibition (as with all TCAs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Therapeutic: 75–150 mg</td>
<td>Effective for severe deprivations, chronic pain, anxiety</td>
<td>Weight gain (as with all TCAs) ECG monitoring required (as with all TCAs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum: 200 mg</td>
<td>Causes less orthostasis than other TCAs May help sleep Established therapeutic blood level window of 50–150 ng/ml</td>
<td>Lethal in overdose (as with all TCAs) Induction of rapid-cycling or mixed states (as with all TCAs) Moderate anticholinergic and moderate sedating effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causes less orthostasis than other TCAs May help sleep Established therapeutic blood level window of 50–150 ng/ml</td>
<td>Lethal in overdose (as with all TCAs) Induction of rapid-cycling or mixed states (as with all TCAs) Moderate anticholinergic and moderate sedating effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causes less orthostasis than other TCAs May help sleep Established therapeutic blood level window of 50–150 ng/ml</td>
<td>Lethal in overdose (as with all TCAs) Induction of rapid-cycling or mixed states (as with all TCAs) Moderate anticholinergic and moderate sedating effects</td>
<td></td>
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<td></td>
<td></td>
<td>Causes less orthostasis than other TCAs May help sleep Established therapeutic blood level window of 50–150 ng/ml</td>
<td>Lethal in overdose (as with all TCAs) Induction of rapid-cycling or mixed states (as with all TCAs) Moderate anticholinergic and moderate sedating effects</td>
<td></td>
</tr>
</tbody>
</table>

**Tricyclic antidepressants (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Pros</th>
<th>Cons</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>Initial: 25 mg</td>
<td>FDA-approved for depression More orthostasis Can be</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Therapeutic: Effective for Can be Metabolized by 2D6</td>
<td>Effective for Can be Metabolized by 2D6</td>
<td>Effective for Can be Metabolized by 2D6</td>
<td>Effective for Can be Metabolized by 2D6</td>
</tr>
<tr>
<td>Dose</td>
<td>Condition(s)</td>
<td>Stimulating (might need morning dosing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>--------------</td>
<td>----------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150–250 mg</td>
<td>severe depression, chronic pain, anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum: 300 mg</td>
<td>Slightly less sedating and anticholinergic than other TCAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Established therapeutic blood levels of &gt;125 ng/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial: 25 mg</th>
<th>Therapeutic: 150–250 mg</th>
<th>Maximum: 250 mg</th>
<th>Metabolized by 3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomipramine</td>
<td>FDA-approved for depression, obsessive-compulsive disorder</td>
<td>Many side effects</td>
<td>Blood levels not useful clinically</td>
<td>Slightly higher seizure risk</td>
</tr>
</tbody>
</table>

Adapted from Levy and Walker\cite{184} and Gelenberg and Delgado\cite{196}

FDA, Food and Drug Administration (in the USA); SSRI, Selective Serotonin Reuptake Inhibitor; TCA, tricyclic antidepressant; EGG, electrocardiographic

### Table 39.2 Approach to the pharmacologic treatment of depression

1. Perform a thorough medical (including cardiac) history and examination, review organ systems and current medications, and take a psychiatric history regarding past episodes, treatments, and responses (including adverse reactions)

2. Determine whether the patient can be treated as an outpatient or requires hospitalization because of suicidal or homicidal ideas or behavior; severe symptoms including psychosis, significant weight loss, poor self-care, agitation, insomnia, etc; failure of optimal outpatient treatment; or lack of adequate care and supervision at home

3. Initiate treatment with an SSRI or atypical antidepressant (see Table 39.1) because they have fewer side effects, are better tolerated by patients with age-related or medical conditions, and are relatively safer in overdose than the TCAs or MAOIs\cite{234}

4. Choose a drug based on the following considerations: least problematic adverse effects and interactions given the patient’s age, medical history, clinical status, and other medications (i.e. cardiovascular, anticholinergic, sedation); desirable effects such as sedation for an agitated patient; previously effective for the patient or a family member

5. Talk with patients (and possibly family members) about the recommended treatment and rationale, risks and benefits, alternatives, and possible adverse effects; establish rapport and engage patient (and possibly family) in a collaborative treatment process. Talk explicitly with patients (and possibly family) about drug interactions and the
possibility of sexual side effects (see point 9 below)

6. Develop a plan to monitor effects closely and to provide support and reassurance (e.g. access to physician by telephone to answer questions about effects; weekly visits for the first several weeks, monthly until stabilized, then visits every second month after that. With TCAs, steady state blood levels are recommended after dosage changes

7. Begin with the lowest possible dose (except with mirtazapine) and increase very slowly to minimize adverse effects. Advise patients that it may take several weeks to achieve a therapeutic level and several weeks after that to achieve full antidepressant effect. Tailor the dosage to each patient: there is considerable variation among patients in their sensitivity and responsiveness to antidepressants, with some requiring doses lower and others requiring doses higher than standard regimens. (For patients who are apprehensive about medication or at risk for adverse effects, it may be helpful to break lowest dosage tablets in half)

8. Monitor for adverse effects due to drug interactions. Table 39.4 shows the potential interactions between antidepressants and other medications caused by hepatic metabolism via P450 isoenzymes. Interactions should be avoided if possible by selecting a different antidepressant; alternatively, very close monitoring to detect changes in concentrations of either medication is essential

9. Monitor for adverse effects including nausea, overstimulation or insomnia, oversedation, weight gain, and sexual disturbances. MS patients may be particularly prone to SSRI-related sexual disturbances because of the loss of sensation and impaired sexual functioning resulting from the disease process. Rates of sexual dysfunction may be as high as 70% in the non-MS population and include diminished desire and impaired or absent arousal and orgasm. Patients tend not to report these problems and should be asked directly. Sexual dysfunction appears to be less common with nefazodone, mirtazapine, and bupropion. Various medications have been tried with variable success and side effects, including the following, all of which are taken 1–2 hours before intercourse: amantadine, bupropion, buspirone, cyproheptadine, yohimbine, and methylphenidate

10. Assess patient regularly for suicidal ideas and take precautions regarding availability of medications, particularly those that are life-threatening when taken in an overdose, by prescribing only small amounts at a time (and possibly asking a family member to keep the medication)

11. Monitor patient for response to treatment. Talk with patient (and possibly family) about treatment with any antidepressant being a ‘trial’: if one does not work, another should, but all of them usually take several weeks to be effective. Specifically, tell patients that it usually takes two to four weeks after reaching a therapeutic level to achieve a full antidepressant effect (i.e. typically 6–8 weeks or even longer after starting treatment)

12. Talk with patient about what to expect and not to expect from an antidepressant. Medication can improve mood and vegetative symptoms within a matter of months, but improvement in depression-
related interpersonal, occupational, and social functioning may take much longer. Life problems that are unrelated to depression are not likely to change and should be addressed through psychotherapy.

13. The goal should be complete remission of depressive symptoms: if the dose has been gradually increased to the maximum (perhaps higher in consultation with a psychopharmacologist) and there has been no response after 4–5 weeks, incomplete response after 6–8 weeks, or intolerable side effects, then another drug should be tried. Sometimes combinations of antidepressants or augmentation with stimulants, lithium or tri-iodothyronine are used, but this should be tried only after consultation with a psychiatrist.

14. Once the depression has resolved, the patient should be monitored and the treatment continued at the dose that allowed the remission for about 6–12 months and then re-evaluated. Some patients may remain free of depression if the drug is gradually tapered and discontinued, but others may need ongoing treatment at the same dose. With SSRIs, some patients reach a plateau and need an increase in dose. For patients who do not continue an antidepressant for 4–6 months after remission, the risk of relapse is nearly 50%.[236] Between 70% and 85% of patients with depression have a recurrent course and may need to reinstate treatment; if recurrences are frequent, ongoing treatment may be indicated. Indeed, research indicates that there is a 70% risk of recurrence for patients with a history of one previous depressive episode, an 80% risk of recurrence for patients with two previous episodes, and a 90% or greater risk of recurrence for patients with three previous episodes. Therefore, it is prudent to maintain treatment indefinitely for patients with two previous episodes or when depression has been associated with suicidal ideas, psychosis, or other severe symptoms.

15. When discontinuing an antidepressant, taper gradually since flu-like serotonin withdrawal symptoms have been reported with rapid discontinuation.

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor

Bipolar disorder

There have been no systematic studies of treatment of bipolar disorder in MS. Lithium carbonate was found to be as effective in treating mania in MS patients as it is in non-MS patients in two reports, but it failed to produce improvement in a third study.[106,108,112] Lithium has also been used successfully to prevent psychiatric reactions to corticotropin.[207] There is no reason to believe that other mood-stabilizing agents, including carbamezapine, valproic acid, and lamotrigine, would not be effective in people with MS. MS physicians are advised to consult and to work closely with a psychiatrist for assessment, diagnosis, and long-term management of patients with bipolar disorder.
Anxiety disorders

There are no studies of treatment of anxiety disorders in MS. In one case report, an MS patient with panic attacks during a depressive episode was treated effectively with clonazepam and clomipramine.\textsuperscript{[123]} There are, however, reports of MS symptoms becoming worse with psychotropic medications.\textsuperscript{[123,193,208]} As with depression, MS patients with generalized anxiety disorder or panic disorder have been treated effectively with a combination of psychotherapy and medication. For generalized anxiety disorder, the many available benzodiazepines, buspirone, and the SSRIs are effective (see Table 39.3).\textsuperscript{[205,210]} Barbiturates (e.g. phenobarbital) and propanediols (e.g. meprobamate) are no longer indicated for the treatment of anxiety. With the SSRIs now available, the antihistamines (e.g. hydroxyzine) with their anticholinergic side effects are no longer needed for persons at risk of addiction (i.e. with a history of alcohol, sedative-hypnotic, opiate or cocaine dependence). When used in therapeutic doses for short-term treatment (less than a few weeks), the benzodiazepines provide significant relief from troublesome symptoms and are not associated with dependence. They are of particular value in helping people to cope with a life crisis such as the diagnosis of MS, although they rarely cause a paradoxical disinhibition in patients with brain disease. Long-term treatment (more than a few months) produces tolerance, dependence, and withdrawal symptoms upon discontinuation, but may be necessary for some patients. Withdrawal generally occurs after high doses have been taken for long periods of time but it can occur after a relatively brief period of use with the short-acting agents.

Management of generalized anxiety disorder, panic disorder, and the phobic disorders over the long term is best accomplished with an SSRI, an atypical antidepressant, buspirone, or a TCA.\textsuperscript{[211]} The major advantage of the antidepressants is that they can treat coexisting depression, are taken once per day, have no addictive or abuse potential, and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.25–0.5 mg three times daily</td>
<td>Short</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 mg two or three times daily</td>
<td>Long (18–50 hours)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2–10 mg two to four times daily</td>
<td>Long (30–200 hours)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 mg two or three times daily</td>
<td>Short (10–20 hours)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>10–15 mg three or four times daily</td>
<td>Short</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5–20 mg three times daily</td>
<td>N/A</td>
</tr>
<tr>
<td>Selective Serotonin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reuptake Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(see Table 39.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Minden et al.\textsuperscript{[210]}
do not produce dependence and withdrawal. The antidepressants are prescribed at the same starting doses and increased to the same maintenance doses as for depression (see Table 39.1). In some patients, antidepressants may cause a paradoxical activation, increasing anxiety, panic, and sleeplessness. Buspirone is minimally sedating, does not affect arousal, attention, or reaction time, and does not lead to abuse, tolerance, or withdrawal. It may, however, take 2–4 weeks to work and many patients discontinue use before it becomes effective. Medications used to treat generalized anxiety disorder are described in Table 39.3. Panic disorder in people with MS as in other patients responds to the SSRIs and atypical antidepressants as well as to some TCAs and the MAOIs. It has also been treated effectively with alprazolam, clonazepam, and lorazepam.

As with all mood disorders, physiological causes of anxiety should be ruled out, including endocrine, metabolic, cardiovascular, and respiratory disorders, and intoxication with or withdrawal from medications and other substances.

**Pathological laughing and weeping**

Schiffer et al. conducted a double-blind, cross-over study comparing amitriptyline and placebo in 12 patients with pathological laughing and weeping. Eight patients improved dramatically on an average dose of 57.8 mg/day (maximum dose 75 mg/day). Improvement was unrelated to change in concurrent measurements of mood. There are reports of levodopa being effective as well as desipramine and fluoxetine in other patient groups. Fluvoxamine 100mg at bedtime was used successfully to treat emotional lability and emotional incontinence in 10 patients with amyotrophic lateral sclerosis, MS, or stroke. Within 2–6 days the number of emotional outbursts dropped from more than 30 per day to 0–5 per day. In addition to medication, it is important to explain the nature of this syndrome to patients and families to help them to cope with it.

**Euphoria**

There is no known treatment for euphoria. However, explaining the condition to family members and caregivers can enhance their understanding and their capacity for empathy and support for the person with MS.

**Apathy**

For the treatment of apathy associated with frontal lobe and subcortical syndromes, stimulants and dopamine agonists have been tried with varying success

**Other treatments**

Sandyk reported that extracerebral applications of pulsed electromagnetic fields in the pico tesla range improved depression and suicidal behavior in three patients, presumably mediated by augmentation of 5-hydroxytryptamine neurotrans-mission and resynchronization of circadian melatonin secretion. Lithium or bright light therapy
may also be effective through mechanisms related to melatonin secretion and circadian phase lability.\textsuperscript{[82]}

Garland and Zis reported two cases to illustrate the difficulties in distinguishing organic illness from functional illness and suggested that anti-inflammatory agents may be required to manage acute psychiatric symptoms, in spite of the risk of precipitating psychosis.\textsuperscript{[221]}

**Consulting with and referring to specialists**

Consultation with a psychiatrist is advisable for patients whose diagnoses are not clear-cut; those whose symptoms are severe, disruptive, or lifethreatening, and for those who do not respond to standard treatments in the usual doses. The psychiatrist may evaluate the patient and make recommendations for treatment that is then carried out by the primary care physician or neurologist. Alternatively, the psychiatrist may assume responsibility for treating the mental disorder, either alone or in combination with a non-physician mental health practitioner (e.g. a psychologist, a social worker, a psychiatric nurse). Many MS centers and clinics now include a range of mental health professionals among their staff to facilitate consultation and referral and help patients to recognize that attention to emotional issues is part of good MS care. As discussed above, patients and family members should be active participants in the entire treatment process. They should be made aware of the reasons for a consultation or referral, informed about what will happen, and advised of the results. They should participate fully in decision making about what treatment will entail and who will provide care. The better the communication among the referring physician, the mental health professional, and the patient and family, the better the results in treating disorders of mood and affect in MS.

**IMPLICATIONS FOR PRACTICE**

The literature suggests that people with MS are not adequately treated for their mood disorders. Minden et al. found that although 40 out of a sample of 50 patients met diagnostic criteria for major depression in the preceding year, only 24 received some sort of psychiatric treatment.\textsuperscript{[28]} Moreover, many of the treatments were not appropriate for the disorder.

Research has shown that depression has a significant adverse effect on patients’ work, family functioning, and leisure activities. Even with successful treatment, these areas of life may continue to be impaired for at least 1 year after the depressive symptoms resolve. Many studies have shown that treatment of mental disorders improves functional status, ‘how patients feel about themselves, their lives, and the efficacy of their health care’\textsuperscript{[222]} Indeed, Mohr et al. found that treatment of depression improved adherence to interferon therapy.\textsuperscript{[223]}

It is clear, then, that early detection and effective treatment of mood disorders relieves pain and suffering, enhances patients’ levels of functioning and quality of life, and contributes to the effectiveness of medical care. Given the high rate of mood disorders in MS and the morbidity and mortality associated with them, the quality of care of people
with MS depends on physicians being able to identify, diagnose, and treat these conditions.

Many decision-making aids are now available

**Table 39.4 Drug interactions with antidepressants caused by cytochrome P450 isoenzymes**

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6</td>
<td>Secondary TCAs</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>Phenothiazines, haloperidol</td>
<td>Norfluoxetine</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>Risperidone, olanzapine, clozapine</td>
<td>Quinidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trazodone, nefazodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine, mirtazapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoxetine, sertraline, paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-blockers (timolol, metoprolol, propranolol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 1C antiarrhythmics (encainide, flecainide, propafenone)</td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Codeine, hydrocodone</td>
<td>sertraline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td>citalopram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpheniramine</td>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>TCAs</td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>Ibuprofen, Naproxen, Warfarin, Phenytoin, Methadone</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2C9)</td>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td>1A2</td>
<td>Tertiary TCAs</td>
<td>Fluvoxamine</td>
<td>Cabbage</td>
</tr>
<tr>
<td>-----</td>
<td>---------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>Fluoxetine</td>
<td>Charbroiled foods</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>Sertraline</td>
<td>Brussel sprouts</td>
</tr>
<tr>
<td></td>
<td>Barbiturates</td>
<td></td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mephenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(2C19)
### Isoenzyme Substrate

<table>
<thead>
<tr>
<th>Isoenzyme Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A3/4 Tertiary TCAs</td>
<td>Sertraline, nefazodone</td>
<td>Nefazodone, ketoconazole, erythromycin (very strong)</td>
</tr>
<tr>
<td>Sertraline, nefazodone</td>
<td>Ziprasidone, quetiapine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ziprasidone, quetiapine</td>
<td>Buspirone</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Buspirone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tiagabine, lamotrigine, carbamazepine</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td></td>
<td>Triazolobenzodiazepines (alprazolam, triazolam, midazolam)†</td>
<td>Fluvoxamine, protease inhibitors</td>
</tr>
<tr>
<td></td>
<td>Diazepam, clonazepam, estazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zolpidem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-sedating antihistamines (terfendaine, astemizole)‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine, paroxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers (nifedipine, diltiazem, verapamil)</td>
<td>Flavoxamine, protease inhibitors</td>
</tr>
<tr>
<td></td>
<td>Quinidine, lidocaine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Steroids (corticosteroids, estrogens, testosterone, progesterone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macrolide antibiotics (erythromycin, clarithromycin, troleandomycin) and ketoconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

Potent inhibitors and inducers are shown in **bold** type, weak in *italic* type

* Ritonavir>saquinavir>indinavir>nelfinavir
† To avoid increased blood levels, use benzodiazepines metabolized by conjugation (lorazepam, oxazepam)
‡ Loratadine, cetirizine, and fexofenadine blood levels may also rise, but not associated with QT interval prolongation, therefore considered safe TCA, tricyclic antidepressant

to non-psychiatric physicians to assist in identification, diagnosis, and treatment, including screening instruments for detecting mental disorders in medical settings\cite{224} and clinical practice guidelines for primary care physicians\cite{32,33}. Psychiatric and psychopharmacological specialists are widely available for consultation\cite{225}. The SSRIs and atypical antidepressants are so safe, efficacious, and well tolerated that physicians should have a low threshold for initiating pharmacological treatment of depression in their MS patients; however, since low doses and short trials are major causes of treatment failure, they should have an equally low threshold for consultation with and referral to a psychiatrist. Similarly, since mood disturbances associated with high-dose corticosteroids are preventable with lithium carbonate, clinicians should not hesitate to use it prophylactically in patients at risk.

While this chapter has emphasized underdiagnosis and under-treatment of mood disorders in MS, the opposite problem also occurs when only the mental disorder is diagnosed and the MS goes unrecognized and untreated\cite{226,227}. This may be particularly difficult when MS presents with depression, as has been reported to occur\cite{42,228}. In some cases, missing the MS is simply an error; in other cases, physical signs and symptoms are apparently absent\cite{229} or the cognitive and affective impairments overshadow mild and intermittent evidence of neurological disease\cite{230}.

**IMPLICATIONS FOR FUTURE RESEARCH**

Our understanding of disorders of mood and affect in MS has advanced considerably over the past 20 years. Areas for future research include instrument development, population-based prevalence studies, randomized clinical trials of the relative effectiveness of different treatments, and clinical-pathological correlations.

Reliable and valid instruments for diagnosis of euphoria and pathological laughing and weeping are prerequisites for prevalence studies and clinical trials. The Pathological Laughing and Crying Scale\cite{162} is now available, but we need a standardized definition and tool to measure euphoria. The semistructured interviews and rating scales used in psychiatric research are adequate for detecting symptoms and diagnosing mood disorders in people with MS, although the extent to which they should be modified to account for overlapping symptoms remains unclear.

To date, we have made inferences on the prevalence of disorders of mood and affect in MS and on the adequacy of their treatment based on clinical studies of small samples\cite{1} and on the mental health service utilization of respondents in population surveys such as the National Health Interview Survey and the National Ambulatory Medical Care Survey\cite{231}. The National Multiple Sclerosis Society’s Sonya Slifka Longitudinal Multiple Sclerosis Study will provide data on the prevalence and severity of depressive symptoms among a non-clinical representative sample of over 2000 people with MS drawn from across the USA. This study will re-assess depressive symptoms and examine use of mental health services and pharmacological and psychotherapeutic interventions annually. Large clinical samples are available through various MS databases such as COSTAR, EDMUS, and the NARCOMS and New York State Registries, but disorders of mood and affect are not systematically evaluated. Medical claims files and other administrative databases (e.g. the Veterans Administration and Medicare) can be
searched for persons with MS and diagnostic and procedure codes that indicate mental disorders and the use of mental health services, although the limitations of administrative databases will apply.\cite{232,233}

It appears that standard pharmacological treatments are as efficacious for mood disorders in people with MS as they are for others. With the SSRIs and atypical antidepressants, adverse effects are uncommon and less likely to interfere with effective treatment. Still, with the ongoing development of pharmacological agents and with increasing understanding of the neurotransmitters associated with mood disorders and the pathophysiology of MS, more specific and targeted treatments may be possible. Much more work is needed to clarify the mechanisms underlying disorders of affect in MS and to explore different treatment options.

Health services researchers should study the economic and social consequences of disorders of mood and affect, particularly their impact on employment, income, and quality of life. Given the prevalence of mood and other mental disorders in MS, people with MS are doubly vulnerable to issues such as denial of health insurance because of pre-existing illness, lack of parity for medical and mental illnesses, and limited mental health benefits under managed care. People with MS encounter the same obstacles to high-quality health and mental health care as people with other chronic medical conditions and people with serious mental illness. Policy analyses are needed to examine these obstacles and identify solutions. Advocates for all these groups have much in common and can learn from each other; working together, they can enhance access to high-quality care for persons with a wide variety of chronic and disabling conditions.

**GLOSSARY**

The information in this glossary has been adapted from DSM-IV.\cite{10}

*Adjustment disorder*

Development of emotional or behavioral symptoms (i.e. anxiety and depression) in response to and within 3 months of an identifiable stressor; symptoms are clinically significant as evidenced by marked distress and/or impairment in social or occupational functioning; criteria for another mood disorder are not met; the symptoms resolve within six months after the stress ends; and the symptoms do not represent grief or bereavement.

*Affect*

Fluctuating changes in the outward expression of inner feeling states. Affect may be *blunted* (significant reduction in the intensity of emotional expression), *flat* (absence of emotional expression), *inappropriate* (mismatch between what is felt, said, and/or thought), or *labile* (rapid and sudden shifts in emotional expression).
**Bipolar disorder**

History of one or more hypomanic or manic episodes in addition to one or more major depressive episodes (see below).

**Cyclothymic disorder**

Numerous periods of both hypomanic and depressive symptoms over a period of at least 2 years and no period without symptoms greater than 2 months; symptoms cause clinically significant impairment and are not due to another mental disorder or the physiological effects of a substance or medical condition.

**Delirium**

Developing over a short period of time (hours to days) with a tendency to fluctuate over the course of the day; the following symptoms: a disturbance of consciousness (i.e. reduced clarity of awareness of the environment), reduced ability to focus, sustain or shift attention; a change in cognition (i.e. memory deficit, disorientation, language disturbance) or development of a perceptual disturbance; and evidence of a direct physiological cause.

**Dementia**

Gradual onset and continuing worsening of the following symptoms: memory impairment (impaired ability to learn new information or recall previously learned information) and one or more of aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), or disturbance in executive functioning (planning, organization, sequencing, abstracting); and evidence of a direct physiological cause.

**Dysthymic disorder**

At least 2 years of depressed mood for more days than not, accompanied by at least two of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, feelings of hopelessness. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct physiological effects of a substance or a medical condition.

**Generalized anxiety disorder**

Anxiety and worry are associated with at least three of the following symptoms for at least 6 months and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning: restlessness or feeling keyed up or
on edge; easy fatigability; difficulty concentrating or mind going blank; irritability; muscle tension; trouble falling or staying asleep or restless unsatisfying sleep. The symptoms are not due to the direct physiological effects of a substance or medical condition.

**Grief (bereavement)**

Expected reaction to loss (e.g. of a person, functional capacity, or life style); unlike major depressive episode, grief is not associated with feelings of worthlessness, psychomotor retardation, suicidal ideas, or marked impairment in occupational or social functioning.

**Major depressive disorder**

One or more major depressive episodes involving at least 2 weeks of depressed mood or loss of interest accompanied nearly every day by at least four of the following: significant weight loss or weight gain or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate or indecisiveness; recurrent thoughts of death, suicidal ideas, or a suicide attempt. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct physiological effects of a substance, a medical condition, or to bereavement.

**Manic episode**

A distinct period of abnormally and persistently elevated, expansive, or irritable mood for at least one week in association with three or more of the following symptoms: inflated self-esteem or grandiosity; decreased need for sleep; more talkative than usual or pressure to keep talking; flight of ideas or racing thoughts; distractibility; increase in goal-directed activity or psychomotor agitation; excessive involvement in pleasurable activities that have a high potential for painful consequences. Symptoms cause marked impairment in social or occupational functioning, necessitate hospitalization, or have psychotic features; and are not due to the direct physiological effects of a substance or a medical condition.

**Mood disorder**

A sustained and pervasive emotion that influences perception of self, others, and the world.

**Panic attack**

A discrete period of intense fear or discomfort with abrupt and rapid development (i.e. within 10 minutes) of at least four of the following symptoms: palpitations, pounding heart, accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, light-headed, or faint; feelings of unreality or being
detached from oneself; fear of losing control or going crazy; fear of dying; numbness or tingling sensations; chills or hot flashes.

**Panic disorder**

Recurrent and unexpected panic attacks, and at least one attack that has been followed by 1 or more months of persistent concern about having additional attacks, and/or worry that the attack signifies losing control, having a heart attack, or ‘going crazy’, and/or leads to significant change in behavior. Attacks are not due to the direct physiological effects of a substance or medical condition. Agoraphobia (i.e. anxiety about being in places or situations from which escape might be difficult or embarrassing, as in a crowd or tunnel or on a bridge, and which are avoided or endured only with marked distress or a companion) may or may not be present.

**REFERENCES**


Human survival necessitates pain sensation. It protects us from imminent danger by triggering reflexes and aversive responses. If tissue has been damaged, a series of adaptive changes occurs rapidly in the sensory system in and around the injury. Such ‘normal’ pain pathways are well understood in terms of the receptor types, neuroanatomy, and neurochemicals involved in transmitting and carefully modulating this information. Paroxysmal and chronic persistent, maladaptive pains and paresthesias resulting from nerve or spinal cord injury or inflammation are also common but are poorly understood. These sensations follow distinctly separate anatomical pathways or subvert short circuits, adopt a different neurochemical repertoire, and are poorly modulated; they are thus dubbed neuropathic pain. These maladaptive pain syndromes seem to be the price we pay for damage to our otherwise exquisite sensory pathways.

One or more forms of neuropathic pain or uncomfortable paresthesias are experienced by >80% of multiple sclerosis (MS) patients (Table 40.1). Regional, segmental, or radicular pain syndromes can be intermittently lancinating or static and may have the character of sharpness, burning, stabbing, or deep ache. Uncomfortable paresthesias are protean and may include buzzing, tingling, formication, itch, and so on. Pain and other paresthesias can be spontaneous or stimulus-evoked, episodic or persistent.

Why two patients with similar patterns of cervical myelitis should have two completely different paresthetic syndromes, or none at all, remains mysterious. Likewise, two different mechanisms of spinal injury may lead to identical symptoms. It is apparent that in all cases, a myriad of neurochemical changes, changes in growth and maintenance factors, and neural cross-wiring all participate. It was hypothesized by Woolf and Mannion that genetic factors play a role in how an individual’s nervous system responds to a given injury (e.g. specific DNA polymorphisms that could lead to inappropriate up-regulation of non-NMDA glutamate receptors). Unfortunately, whether an MS patient’s myelitis will lead to paresthesias, pain, and disability cannot be predicted.

During the development of the pain survey by the North American Research Consortium on Multiple Sclerosis (NARCOMS), one of the author’s MS patients, a particularly well-spoken woman in her mid-30s who had been treated for painful paresthesias of the torso, took a ‘test drive’ of the survey to see if it was reasonably simple and sensible. She indicated that ‘the problem with this survey is that on Monday I feel tingling in the legs, on Wednesday I have painful spasms in the legs that are gone on Thursday but I am left with burning sensation in the chest most of the time’. This
illustrates that the survey needed to clarify whether an abnormal sensation was being experienced at the time that the survey was being completed, and also whether the patient had ever experienced a given symptom at any time. Thus, the columns in Table 40.1 are parsed out as ‘ever experienced’ symptoms and ‘experiencing now’ symptoms. Reference to severity was only asked of the ‘experiencing now’ symptoms.

The proper treatment of chronic pain requires a multidisciplinary approach that includes behavioral and psychological therapies, non-pharmacological treatments, social services, exercise, and diet. Nevertheless, the emphasis of this chapter is on the neurochemical underpinnings and pharmacotherapies of neuropathic pain and paresthesias resulting from inflammatory demyelinating disease. To that end, a discussion of what is currently understood of the molecular changes that lead to pain is reviewed, providing in part a rationale for choices of medication.

**BACKGROUND**

Symptomatic management of patients with MS is a complex and varied problem that must take into consideration the many dimensions of quality of life. Pain and paresthesias can be disabling to patients with MS. Many physicians underestimate the importance of these symptoms and are challenged to devise a rational treatment plan. As a result, the problem is under-recognized, poorly understood, and under-treated. Excluding headache, Moulin et al. found, in a retrospective chart survey, that 48% of MS patients (76 of 159) suffered a form of chronic pain, including dysesthetic limb pain (29%), back pain (14%), painful leg spasms (13%), or visceral pain (2%).[3] Patients with chronic dysesthetic limb pain had relatively lower scores on the

<table>
<thead>
<tr>
<th>Table 40.1 NARCOMS pain survey</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Aching leg pain</td>
</tr>
<tr>
<td>Painful spasms</td>
</tr>
<tr>
<td>Burning pain</td>
</tr>
<tr>
<td>Facial pain or neuralgia</td>
</tr>
<tr>
<td>Uncomfortable squeezing</td>
</tr>
<tr>
<td>Uncomfortable tingling</td>
</tr>
<tr>
<td>Uncomfortable itch</td>
</tr>
</tbody>
</table>

Patients with MS (n=7940) answered questions concerning pain and uncomfortable paresthesias. Women comprised 69.9% of the respondents. Mean age was 48.3±10.7 years with mean disease duration of 19.9±10.6 years. The duration of disease bore no relationship to the frequency of any of the symptoms. The percentages reporting mild, moderate, or severe refers to those who reported
expanded disability status scale (EDSS) (average, 3.3) than those with back pain (5.3) or painful leg spasms (6.0). There was no positive correlation between the EDSS score and pain intensity. Chronic pain did correlate with disease duration and increasing age. Women were about twice as likely as men to suffer pain (3:1 in the survey, in which the ratio of women to men was 2.1:1). Virtually all cases had an associated myelopathy, although myelopathy per se did not predict the presence of chronic pain.

Overall, the study by Moulin et al. revealed a prevalence of chronic pain that was comparable to that reported by Archibald et al. (53%),[^4] but about twice as high as estimated by Clifford and Trotter (28.8%),[^5] whose estimate also excluded headache.

Using a 36-item health survey, Brunet et al. evaluated eight health domains in MS patients, including physical functioning, role limitations due to physical and emotional problems, social functioning, energy and vitality, general health perceptions, and body pain.[^6] The survey was illuminating with respect to MS patients’ poor health perceptions as well as their decreased role functioning in several domains, both of which correlated with the EDSS. The ‘body pain and headache’ portion of the questionnaire demonstrated that pain and headache in a general sense are moderately disabling symptoms. Interestingly, the degree of disability from pain bore no correlation with the EDSS, as reported by Moulin et al.[^3] and the NARCOMS studies (see below). Thus, it may be interpreted that chronic pain is an issue for MS patients across all EDSS scores and is not confined to the most disabled.

All forms of paresthesia (e.g. cold, warmth, tingling, crawling, pressure, itching) taken together are extremely common in MS—84% in one survey of 127 patients.[^7] Paresthesias were a presenting symptom in 40%. Interestingly, abnormal neurological examinations and somatosensory evoked responses did not correlate with the presence of paresthesias.[^7]

### NARCOMS patient registry

The NARCOMS patient registry currently has over 18000 participants diagnosed with MS. The purpose of the registry is to facilitate clinical and epidemiological research as well as research on health-care services, symptomatology, disability, treatments, and outcomes. Registry participants are followed over time with annual updates, and newly diagnosed patients will be a cohort for prospective and longitudinal studies.

Selected results from the pain survey portion of the NARCOMS questionnaire are shown in Table 40.1. These results have previously been reported in preliminary form.[^8] The symptom choices were determined empirically by the clinical experiences at the author’s center and based on input from a number of patient support groups. Surprisingly, a majority of patients were actively experiencing what was described as ‘aching leg pain’ at the time the survey was completed. Of those, 47% indicated that it was at least moderate in severity (i.e. they had to alter lifestyle or treat it with medication). The pain was described as severe (i.e. they were unable to perform routine tasks or activities of daily living as a result of the pain) by 21.3%. About half of the population had experienced burning pain or painful spasms at some point. These symptoms were active
in about one-third of all patients. A minority of patients indicated that they suffered only a single pain syndrome. For example, out of a total of 7940 patients, 4629 complained of aching leg pain. Of those, 465 gave that as the only pain syndrome. Similarly, of 2969 patients actively experiencing burning pain at the time the survey was completed, 112 reported that as the only pain syndrome.

The incidence of trigeminal neuralgia in the general population has been estimated at 4.5 per 100000 with a female: male ratio of 3:2.\(^9\) If only 10% of the respondents in the NARCOMS survey who reported facial pain or neuralgia actually fulfilled the International Headache Society criteria for trigeminal neuralgia,\(^10\) the prevalence would be 10-fold or more higher in MS patients than in the population at large. The syndrome is usually easily recognizable as triggerable lancinating pain lasting seconds to minutes separated by pain-free intervals. Typically, treatment with sodium channel blockers is effective. In refractory cases, adjunctive therapies with other broad-spectrum anticonvulsants or tricyclic antidepressants may be useful.

### TREATMENT

Treatment of neuropathic pain and paresthesias is difficult. The study by Archibald et al. indicated that 65% of patients with MS pain took medication, but in virtually all cases pharmacological therapy was only partially effective.\(^4\) In this study, 17% of patients reported continuous pain in spite of treatment, which in turn led to poor social functioning and disability.

The usual first-line therapy involves tricyclic antidepressants alone or in combination with carbamazepine or phenytoin. The most common antidepressants used in the treatment of neuropathic pain are amitriptyline, other tricyclics, and doxepin. Several new-generation anticonvulsants, including gabapentin, tiagabine, lamictal, topiramate, zonisamide, and levetiracetam, have not been systematically studied or surveyed in this cohort of MS patients with pain. Tizanidine, an α-receptor agonist (α-2 receptor agonism is much greater than α-1 receptor agonism), has been approved in the USA by the Food and Drug Administration to treat spasticity. It can be used adjunctively to treat various neuropathic pain syndromes. The use of non-tricyclic antidepressants, such as bupropion and venlafaxine, has only been preliminarily demonstrated.\(^{11,12}\)

#### Pathophysiology and rationale for neuropathic pain treatments

There are no animal models of pain or hyperalgesia resulting from inflammatory central nervous system (CNS) disease, an area that deserves exploration in light of the frequency of pain associated with myelitis and spinal trauma. Therefore, much of the text that follows in this section—an effort to justify empirical treatment choices for MS-related pain and paresthesias—depends heavily on research involving animal models of traumatic nerve and spinal injury, clinical reports of treatment successes, and the hypothesis that at least some molecular mechanisms leading to neuropathic pain following peripheral nerve injury and inflammation occur in CNS injury as well. Our current understanding of the molecular pathopharmacology of neuropathic pain, in fact, derives mostly from experiments involving peripheral nerve injury. For example, while
central sensitization occurs following persistent C-fiber sensory neuronal firing in the dorsal horn,\textsuperscript{[13]} it is unknown if the consequences of central sensitization such as Aβ-mediated hyperalgesia occur following a central insult. Nevertheless, identical manifestations may be seen in MS patients. Nerve injury potentially disrupts normal sensory pathways, neurotransmitters, and modulatory mechanisms in a number of ways (Figure 41.1). Perhaps hundreds of neuronal or axonal membrane components undergo altered synthesis and deportation following injury, as demonstrated in a variety of animal models.

The systems or membrane components identified as being affected by injury offer clues as to how pharmacotherapies may offset symptoms associated with nerve injury. In the following sections, each system or membrane component is discussed individually along with the desirable pharmacotherapeutic mechanism thus needed to offset the pathologic derangement. The medications and their respective putative mechanisms for treating paresthesias are listed in Table 40.2. The logic behind treating an individual patient involves prescribing drugs with complementary mechanisms. Patients need to be educated as to the appropriate expectation in terms of benefit and side effects. A period of time before the patient improves should be anticipated as medication dosages are titrated; only partial relief should be anticipated at first.

\textbf{Sodium channel blockers}

\textit{Pathophysiology}

The studies of Black et al.\textsuperscript{[14]} revealed that nerve injury leads to concomitant up-regulation of axonal type, fast, TTX-sensitive sodium channels deployed to demyelinated axons in a rat model,
Fig. 40.1 Schematic diagram of spinal cord depicting main sensory pathways into the dorsal horn, ascending sensory systems. Several neurochemical systems and anatomic pathways are disrupted following spinal injury. The diagram depicts those systems that may be pharmacologically targeted, e.g. interrupted descending modulation by norepinephrine and serotonin (tricyclics, venlafaxine indicated), altered Na+ channel regulation (Na+ channel blockers), decreased GABA (compensatorily, GABA agonists), and possibly glutamate or Ca++ antagonists.
Table 40.2 Pharmacological actions of drugs used for neuropathic pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>GABA receptor agonism</th>
<th>Sodium channel blockage</th>
<th>Serotonin receptor agonism</th>
<th>Potassium channel antagonism</th>
<th>Calcium channel antagonism</th>
<th>Glutamate NMDA AMPA-kainate antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td>Baclofen (+type B receptor)</td>
<td></td>
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<tr>
<td>Clonazepam (+type A receptor)</td>
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</tr>
<tr>
<td>Carbamazepine</td>
<td>+</td>
<td></td>
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<tr>
<td>Gabapentin</td>
<td>↑+ (non-vesicular GABA receptor)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lamotrigine</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Levetiracetam</td>
<td>+ (negative internal modulators)</td>
<td></td>
<td>+ (HV-rectifier)</td>
<td></td>
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</tr>
<tr>
<td>Oxcarbazpine</td>
<td>+</td>
<td></td>
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<tr>
<td>Phenobarbital</td>
<td>+ (sensitizes)</td>
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<tr>
<td>Tiagabine</td>
<td>+(uptake inhibitor)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tizanidine</td>
<td>+(type 2 specific)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+(antagonizes)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>+(potentiates)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>+</td>
<td></td>
<td></td>
<td>+(non-type specific)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+, the drug performs the ‘desired’ therapeutic action

while the Rt-PCR for sodium channel type III RNA is quantitatively increased.[15] Such adaptive mechanisms, while in principle improving axonal conduction, have been posited to bring about simultaneously the maladaptive development of paresthesias.[16] Each of
three laboratory models of nerve injury, inflammation, crush, ligation-cleavage, is followed by a unique sodium channel RNA response repertoire. Thus, while the ligation-cleavage model was shown to up-regulate TTX-sensitive fast sodium channels, an inflammatory model using subcutaneous carrageenan injection in the rat hindlimb demonstrated selective increase in TTX-resistant, kinetically slow sodium currents. These observations are pertinent to our usage of sodium channel blockers in the treatment of painful paresthesias in MS. A variety of regional painful paresthesias and spinal segmental paresthesias that are common in MS respond (albeit partially) to use-dependent sodium channel blockers.

Interestingly, patients with MS suffer neuralgic pain (shock-like triggerable pain), which probably results from sodium channel deployment (e.g. in the trigeminal ganglion) and hyperexcitability. The many potential contributors to trigeminal neuralgia are reviewed by Devor et al. It seems counterintuitive that a central disease process can lead to paresthesias in a sensory territory subtended by a peripheral nerve or root. In addition, many or most cases of trigeminal neuralgia in MS are not associated with evidence on magnetic resonance imaging of demyelination in the appropriate anatomic territory (i.e. the lateral basis pontis). In such cases, barring the presence of an unrelated structural abnormality such as an over-riding vein, it is possible that the environment alone, enriched with cytokines or neuroactive amino acids, irritates the nerve roots, leading to altered sodium channel complement and hyperexcitability. The subject of central pain resulting from sodium channel plasticity was recently reviewed.

**Treatment**

Although phenytoin was among the first medications found to be beneficial for patients with trigeminal neuralgia, it has largely been replaced as a first-line therapy by carbamazepine, and more recently, arguably, by lamotrigine. Most pain and paresthesias in MS patients, including neuralgic pain, segmental paresthesias, spasms, burning, and itch, should be treated by one or another of the sodium channel blockers. McCleane reported a 38-year-old woman with burning paresthesias in the legs associated with allodynia whose symptoms were completely ameliorated by 200 mg of lamotrigine only. As outlined in Table 40.2, physicians have substantial flexibility in prescribing sodium channel blockers. Associated symptoms may be taken into consideration when choosing treatment. For example, the presence of migraine can lead one to choose a broader-spectrum sodium channel blocker, such as topiramate or zonisamide. Side effects and concerns as indicated in Table 40.3 should be weighed against the patient’s gender and lifestyle and the cost of the drug. Initial therapy for painful paresthesias could include, for example, amitriptyline (demonstrated in vitro to have sodium channel blocking capability) 10 mg at bedtime combined with lamotrigine 25 mg in the morning with food. Lamotrigine can be slowly titrated up to 75 mg or more per day in divided doses, sometimes up to 500 mg/day. If lamotrigine or carbamazepine with or without a tricyclic antidepressant is ineffective, the sodium channel blocker can be replaced with zonisamide or topiramate, again beginning at very low dosages.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages, side effects, concerns</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Effective at low doses; once nightly dosing; broad spectrum and excellent adjunct; sleep aid; inexpensive</td>
<td>Anticholinergic side effects can be prohibitive; vigilance for urinary retention or constipation; weight gain</td>
<td>10 mg at bedtime; increase as tolerated to 75 mg at bedtime</td>
</tr>
<tr>
<td>Baclofen (oral)</td>
<td>Generally well tolerated; used to treat both paresthetic symptoms and spasticity; adjunct for trigeminal neuralgia</td>
<td>Sedation, generally mild but caution at higher doses (&gt;80 mg/day)</td>
<td>10 mg three times daily, titrate as needed or tolerated to 20 mg four times daily; some patients may need and tolerate doses up to 120 mg/day</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Very long acting (0.5–36 hours) and well tolerated; acts centrally and on primary afferents; adjunct for vertigo and/or tremor</td>
<td>Sedation; abrupt withdrawal can lead to seizure; tendency for abuse (has ‘street value’); vigilance for depression</td>
<td>0.5 mg at bedtime or twice daily; increase up to 1 mg three times; daily; compliant patient may need up to 6 mg/day</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tried and true for lancinating or radicular pain and trigeminal neuralgia; new long-acting formulations easier to dose</td>
<td>Difficult to titrate up to therapeutic dose range owing to gastrointestinal and mental status side effects; watch for aplastic anemia, hyponatremia</td>
<td>100 mg twice daily to 200 mg four times daily or higher as tolerated; extented-release formulations allow twice-daily dosing</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Its popularity derives mainly from how well tolerated it is, even at high doses; used for wide variety of symptoms; no drug interactions</td>
<td>Mechanism of action remains unknown and therefore rational choice is difficult; memory disturbance, weight gain</td>
<td>Can begin at 300 mg three times daily, although doses as low as 100mg four times daily may be effective; titrate up to 4800</td>
</tr>
<tr>
<td>Drug</td>
<td>Advantages</td>
<td>Disadvantages, side effects, concerns</td>
<td>Dosing</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------</td>
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<td>---------------------------------------------</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Probably the best tolerated of the pure sodium channel blockers; good for lancinating pain and burning paresthesias</td>
<td>Gastrointestinal side effects; rash is dose-titration dependent</td>
<td>mg/day or more 25 mg daily, twice daily, then three times daily; increase as needed or tolerated to 100 mg four times daily; higher doses not likely to add benefit</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Novel mechanisms mean flexible adjunctive applications; well tolerated; no known drug interactions; mainly renal elimination</td>
<td>Mild sedation; irritability has been reported in children</td>
<td>As low as 500 mg twice daily can be effective; well tolerated up to 2000 mg twice daily</td>
</tr>
<tr>
<td>Oxcarbazine</td>
<td>No 10,11-epoxide metabolite and thus better tolerated than carbamazepine; slight interaction with other antiepileptics</td>
<td>Sedation, gastrointestinal side effects</td>
<td>100 mg three times daily to 400 mg four times daily; higher may be tolerated</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Easy once daily dosing; long half-life; inexpensive</td>
<td>Sedation, mood changes, abuse potential</td>
<td>30–120 mg at bedtime</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Novel GABA uptake inhibitor; complements other GABAergic drugs; no influence on metabolism of other antiepileptics</td>
<td>Requires slow upward titration owing to gastrointestinal and cognitive side effects</td>
<td>2 mg at bedtime increased, to 4 mg; then increase to 4–8 mg three times daily,</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>α-agonist with minor effects on blood pressure; adjunct in many forms of pain, spasticity; bedtime dosing may be adequate</td>
<td>Sedation allows for bedtime dosing only in many patients; vigilance needed if combined with antihypertensive medication</td>
<td>2 mg at bedtime; increase to 8–12 mg at bedtime; if tolerated can try adding 2–4 mg in the morning; some patients experience little sedation</td>
</tr>
</tbody>
</table>
Topiramate

- Broad spectrum; non-NMDA receptor inhibition is important for neuropathic pain mechanisms; weight loss seems to be a plus
- Cognitive difficulties may limit dosing; paresthesias at higher doses; kidney stones
- 25 mg at bedtime and then three times daily; increase to 100 mg three times daily as tolerated; many patients respond to 50–75 mg/day

Valproate

- New extended-release formulation well tolerated; effective for comorbid migraine prophylaxis
- Weight gain; idiosyncratic liver toxicity
- 250 mg at bedtime then twice daily; increase to 500 mg (extended release) twice daily

Zonisamide

- Broad spectrum; mixed sodium and calcium channel effects is unique
- Sedation; cognitive changes
- 100 mg at bedtime then twice daily; increase to 400 mg/day as tolerated

Baclofen (intrathecal)

- Delivery system minimizes side effects and maximizes efficacy
- Complications of surgery or implanted pump—infected, bleeding, etc.; needs to be refilled in the office every 3 months
- 75–100 mcg/day continuous infusion; increased as tolerated

Clonidine (intrathecal)

- Delivery system minimizes systemic side effects
- Broad spectrum, multiple mechanisms of action; non-NMDA receptor inhibition is important for pain

Dosing presented here is merely a guideline; effective doses can be highly variable from patient to patient. Upward titration beginning with the lowest dose is highly recommended since the therapeutic range is wide and generally overlaps significantly with toxicity.

Topical lidocaine now is commercially available. It is applied as a patch over the skin in which painful paresthesias or allodynia is present. It is generally placed for 12–18 hours and then removed for 12 hours before being placed again. It is hypothesized that lidocaine is transported retrogradely to the dorsal root ganglion and possibly to the dorsal horn termini, which may explain why the treatment requires several weeks to be effective. This intervention is appropriate for MS patients suffering dermatomal or segmental paresthesias, in which the territory involved is focal and well defined.

Mexilitine, although demonstrated to be effective in diabetic neuropathy, may not have adequate CNS penetration to be effective for central pain. Generic phenytoin can be a consideration if cost is an issue, although the side effects may be prohibitive, especially hirsutism and gum disease in young women.
γ-aminobutyric acid

Pathophysiology

γ-aminobutyric acid (GABA) is inhibitory to central neurons. Loss of spinal GABA ‘tone’ via receptor antagonists to GABA_A (bicuculline) or GABA_B (phaclofen) causes tactile allodynia and thermal hyperalgesia. In a ligation-cleavage model, GABA_A receptors were demonstrated to be dramatically up-regulated in dorsal root ganglion neurons such that GABA_A agonism produced currents on average two-fold greater following injury. On the other hand, spinal cord injury results in decreased available GABA. Thus, dorsal horn receptor upregulation following myelitis would hypothetically appear to be adaptive and is consistent with the clinical fact that GABA_A receptor agonism is an important treatment modality for paresthetic syndromes in MS.

Treatment

Many classes of medications influence GABA receptors (Table 40.2), either directly (e.g. benzodiazepines, barbiturates, baclofen) or indirectly via competition for intrinsic negative allosteric modulators of the receptor-channel complex (notably levetiracetam). GABA uptake is inhibited by tiagabine, leading to prolonged expected synaptic lifetime. Gabapentin appears not to influence GABA receptors directly. Instead, it has ill-defined effects on GABA metabolism. In hippocampal slices, gabapentin promoted non-vesicular release of GABA by potentiating currents induced by pulsed application of nipecotic acid (a GABA uptake inhibitor). Baclofen, a GABA_B agonist, can complement gabapentin or other direct GABA_A agonists for treatment of painful paresthesias.

Clonazepam has a long half-life and favorable side effect profile. Used alone or in conjunction with sodium channel blockers, it provides partial or even complete relief of painful spasms and aching leg pain. Clonazepam also can be used to treat comorbid tremor or positional vertigo. The effects of clonazepam and other benzodiazepines can be enhanced with addition of low-dose tiagabine or gabapentin. The side effect profile of gabapentin is more favorable, while the gabaergic effects of tiagabine are significantly more potent. The major drawback of these medications relates to their ability to potentiate major mood disorders. They should be used judiciously in patients with a history of depression, and any report of altered mood by patients on these medications should be taken seriously. Valproate is an excellent mood stabilizer and can be considered for therapy of mood disorders together with paresthesias.

The broad-spectrum anticonvulsant topiramate increases the opening probabilities of GABA_A receptors and provides a unique complement of activity, also possibly due in part to AMPA-kainate receptor antagonism.

Although phenobarbital carries the stigma of being a drug of abuse, it is very well tolerated in compliant patients and very inexpensive. It may be a favorable drug to use for pain syndromes in the elderly and is an excellent adjunct for paroxysmal tonic spasms, trigeminal neuralgia, or (as third-line therapy) for migraine.
**Glutamate**

**Pathophysiology**

Glutamate appears to be the principle excitatory synaptic neurotransmitter in the spinal cord and, in addition, it plays a role in metabolism at extrasynaptic sites. Glutamate receptors may be divided into metabotropic and ionotropic. The roles of glutamate and its ionotropic NMDA receptor, as they pertain to neuropathic pain, have been extensively studied in models of peripheral nerve injury leading to central sensitization. \(^2\) Studies in animal models of traumatic spinal injury also have demonstrated altered metabotropic glutamate receptor regulation, \(^3\) which, however, has not been clearly demonstrated to lead directly to allodynia. In a rodent model of spinal cord injury, intrathecal administration of both NMDA and non-NMDA receptor antagonists reduced mechanical allodynia. \(^32\) All told, glutamate receptor antagonism may contribute to treatment of pain and paresthesias in MS, although our current pharmacopeia is non-selective and toxic.

**Treatment**

Of the medications listed in Tables 40.2 and 40.3, topiramate and zonisamide are weak glutamate receptor antagonists. Thus, if stimulus-evoked allodynia is a major component of a patient’s symptoms one of these treatments should be considered. Other weak NMDA antagonists include dextromethorphan and memantine, both reported anecdotally to be of benefit in some cases of painful diabetic neuropathy. \(^33,34\) In the same studies, they were ineffective in postherpetic neuralgia. No experience with such therapies in MS patients has been reported.

**Norepinephrine (noradrenaline) and serotonin**

**Pathophysiology**

Inhibition of norepinephrine and serotonin reuptake by tricyclic antidepressants has long been a mainstay of therapy for the treatment of neuropathic pain (see Fig. 41.1). \(^35\) They participate in descending modulation of normal sensation. It is hypothesized that a spinal cord lesion will interrupt these descending pathways, leading to dyesthesias below or in the segment of an MS-related partial myelitis and that serotonin and norepinephrine uptake inhibitors would therefore be of benefit.

\(\alpha\)-adrenergic receptor plasticity within the dorsal horn following nerve injury \(^36\) suggests a role of \(\alpha\)-2 receptor agonists in the treatment of neuropathic pain. Both clonidine and tizanidine have been shown to inhibit release of substance P in rat spinal cord slices, \(^37\) which, again, derives from the physiological modulatory function of norepinephrine in intact sensory systems. \(^38\)
Treatment

As indicated in Table 40.2, amitriptyline has a critical role in the treatment of burning paresthesias, possibly resulting from interrupted descending modulatory pathways at a discrete level (e.g. from transverse myelitis). Experience tells us that low doses, of the order of 10 mg, sometimes can be very effective when used adjunctively with a sodium channel blocker or GABAergic therapy. Side effects from higher doses may be prohibitive, and caution must be exercised when using amitriptyline in patients predisposed to neurogenic bladder. Doxepin may be less toxic yet still very effective. Dosing either medication at more than 50–75 mg at bedtime is unlikely to add further benefit without introducing prohibitive sedation or anticholinergic side effects. Nortriptyline and other secondary amines may have significantly less effect on serotonergic than noradrenergic synapses, whereas amitriptyline and doxepin (both tertiary amines) inhibit the reuptake of both neurochemicals. There are preliminary reports that non-tricyclic compounds, such as venlafaxine and bupropion, are effective in neuropathic pain syndromes.\(^{[11,12]}\)

Tizanidine, used initially in low doses (about 2mg at bedtime) can have significant adjunctive effects on burning paresthesias in addition to large-fiber mediated spasms. Thus, for a patient with mixed paresthesias, such as the patient described earlier in this chapter, tizanidine combined with a tricyclic agent plus or minus clonazepam can significantly improve symptoms and quality of life. Clonidine can also be effective but it tends to have greater effects on blood pressure. Intrathecal clonidine is very well tolerated.

Potassium channel blockers

Pathophysiology

A large number of distinct potassium channels have been described (at last count more than 20 varieties in mammalian excitable membranes). Depending on their anatomical locus and their properties, each channel confers mixed metabolic, electrical, and other modulatory functions to the membrane. Abdulla and Smith demonstrated that, after axotomy, the delayed-rectifier type of non-inactivating current was reduced by about 60%.\(^{[39]}\) Calcium-activated potassium current was reduced in proportion to the loss of highvoltage calcium currents. Blockade of calciumactivated potassium channels could conceivably increase excitability by decreasing axonal interspike intervals. However, the delayed-rectifier potassium channel, although primarily axonal, may have a more important role in membrane repolarization following action potentials. Blockade of delayed-rectifier potassium channels may have unpredictable results in terms of maintaining or diminishing repetitive firing properties.

Treatment

Blocking the delayed-rectifier potassium channel could prolong the repolarization phase, delay sodium channel recovery from inactivation, and thus prolong the interspike
interval. In this context, the novel anticonvulsant levetiracetam may be considered as possibly decreasing axonal excitability. The agent 4-aminopyridine, a fast (IA) potassium channel blocker, induces axonal excitability and can cause troubling paresthesias. Yet, patients on compounded 4-aminopyridine have anecdotally reported improvements in painful spasms and paresthesias.\textsuperscript{[40]} Further studies of this uniquely multifaceted symptomatic therapy for MS patients are needed.

**Calcium channel blockers**

**Pathophysiology**
Calcium channels are emerging as crucial elements in neuropathic pain syndromes.\textsuperscript{[41]} Calcium-dependent processes control neuronal physiology at all levels, including synaptic release, receptor and channel sensitivity, and cell death. Moreover, central sensitization in part depends on the accumulation of intracellular calcium ion. N-type calcium channel blockade would be expected to inhibit synaptic transmission.

**Treatment**
Although some of the anticonvulsants listed in Table 40.2 cause calcium channel blockage, it may be difficult to single out this mechanism as contributing significantly to treatment decisions. Clinical studies in which carefully selected cohorts of patients, identified on the basis of mechanism of injury and symptomatology, must be undertaken before the effects of calcium channel blockade on paresthesias can be determined.

**Intrathecal preparations**
Implanted continuous infusion pumps can be programmed to deliver baclofen, clonidine, or morphine intrathecally, alone or in combination, to treat pain and spasticity in MS and other diseases.\textsuperscript{[42–44]} Much higher drug levels within the spinal cord tissue can be achieved with intrathecal administration than with oral administration. Baclofen alone may substantially reduce or eliminate paresthetic pain and spasms, while systemic side effects are spared. This avenue of therapy is probably under-used. The major adverse effect of intrathecal baclofen is weakness. This should be anticipated by the patient and physician. Since there can emerge a significant decrease in spastic co-contraction of antagonistic muscle groups, exercise for muscle strengthening becomes much more efficient.

**CONCLUSIONS**
Our current understanding of the roles that several pertinent neurochemicals, ionic channels, and membrane receptors play in the development of the symptoms of central neuropathic pain is limited. However, mechanisms that play a role in peripheral neuropathic pain may cause analogous chemical and structural changes in the spinal cord and result in central pain and paresthetic syndromes in MS. It appears that a multiplicity
of mechanisms can simultaneously contribute to pain and paresthesias in MS. Further studies are needed to determine the effect of CNS inflammation on the expression of neuronal membrane components, and thus to define better the rational pharmacotherapy necessary to treat MS patients.

To reiterate, therapy of chronic pain and paresthesias in MS may require concomitant non-pharmacological modalities, such as physical therapy and psychological counseling. Medications alone are not the answer. In addition, the patient’s expectations must be realistic, and this can only happen if the physician, nurse, or other practitioner takes the time to educate the patient.

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INTRODUCTION

Tremor is the most common movement disorder in multiple sclerosis (MS).\textsuperscript{[1]} It usually occurs in association with other symptoms of MS, and its severity usually correlates with the degree of dysarthria, dysmetria, and dysdiadochokinesia plus that of other neurologic manifestations of MS. However, at times tremor may be disabling out of proportion to other manifestations of ataxia and other MS symptoms. Lesions involving cerebellar white matter and nuclei can cause tremor. In addition, lesions in a variety of cerebellar afferent tracts (e.g. frontal and parietal cortex, corticocerebellar pathways through the ventral pons, the brachium pontis, restiform body) and cerebellar outflow tracts (e.g. brachium conjunctivum, red nucleus, thalamus) can also produce tremor. Medical and rehabilitative therapies for MS tremor are of limited efficacy. Stereotactic thalamotomy and deep brain stimulation (DBS) have been used with some success in carefully selected candidates.

The rapid advances in improving the natural history of MS have changed some of the therapeutic nihilism surrounding surgical treatments for MS tremor. Now patients may survive longer with less severely incapacitating symptoms, so there is greater impetus to treat tremor. The development of DBS with the ability to adjust the stimulation to the individual patient, especially as the underlying disease progresses, and the relatively low risks provide further justification for recommending surgical treatment for MS tremor.

DEFINITIONS

\textit{Tremor} is a rhythmic involuntary oscillating movement of an individual part or parts of the body.\textsuperscript{[2]} The incidence and prevalence of tremor in MS is difficult to establish, partly because the neurologic signs occurring during the relapsing and remitting phase of the disease are transient, which contributes to sampling error. Tremor in MS is usually identified as a cerebellar intention and postural tremor.\textsuperscript{[3,4]}

\textit{Action tremor} occurs during a targeted voluntary movement (e.g. during the finger-to-nose or heel-to-shin testing) with a frequency of 3–5 Hz.\textsuperscript{[5,6]}

\textit{Postural tremor} is observed when a limb is maintained in a fixed position against gravity, with proximal, large oscillations and/or distal, more rapid oscillations.\textsuperscript{[3]}
Axial tremor refers to titubation of the head and trunk.

Other cerebellar symptoms such as dysmetria may also be present. The term rubral tremor or Holmes’ tremor designates a combination of rest, postural, and action tremor due to midbrain lesions in the vicinity of the red nucleus. This type of tremor is irregular and slower in frequency (<4.5 Hz).

**PATHOPHYSIOLOGY**

The pathophysiology of MS tremor is not fully understood. Cerebellar, thalamic, and pyramidal lesions can all contribute to tremor. It is most likely related to demyelinating lesions in the cerebellar nuclei and cerebellar afferent pathways, particularly in the dentatorubrothalamic pathways. It is hypothesized that cerebellar tremor is the result of abnormal oscillations in sensorimotor loops. The ventralis intermedius (Vim) nucleus of the thalamus, which has been identified as the most effective target for relief of intention tremor, is considered as a proprioceptive relay for one or several of these feedback loops. The destruction or high-frequency stimulation of the Vim suppresses these oscillations, thus controlling the tremor.

**ASSESSMENT TOOLS**

Tremor in MS manifests itself on action, including posture (postural tremor) and during movement (kinetic tremor), or both. Tremor can be embedded in a complex ataxic movement disorder, making accurate grading of tremor difficult. It can be assessed in terms of impairments, disabilities, and handicaps, following the World Health Organization conceptual framework.

Qualitative assessment of tremor is based on standardized clinical examination, sometimes using videotapes to allow independent ratings by several observers and comparative assessment over time. Fahn’s Tremor Rating Scale is a widely used ordinal scale for the assessment of tremor severity, with a good inter-rater and intra-rater reliability. Quantitative measurement of tremor is commonly achieved with accelerometers.

Independent assessment of disability is at least equally important, since a satisfactory control of tremor does not automatically translate into functional improvement. Extensively validated generic or disease-specific disability scales are not very helpful in detecting modest changes secondary to reduction of tremor, especially in patients already severely disabled as a result of other impairments. Fahn’s Tremor Rating Scale includes a subjective assessment of disability by the patient. Most authors design their own scale for the purpose of the study or use non-standardized descriptive terms to reflect improvement. The global impact of antitremor treatments on handicap and quality of life is seldom evaluated, except for anecdotal reports.

The following tests have previously been shown to be reliable and valid ways of measuring tremor or of assessing the impact of tremor on activities of daily living in patients with MS:
• finger-tapping test, in which the patient is asked to press a key on a calculator as many times as possible in 10 seconds;
• nine-hole peg test, in which the time to transfer nine pegs from a receptacle to a peg board then back is determined;
• rating tremor from samples of handwriting or drawings of an Archimedes spiral on a 0–10 clinical rating scale; and
• tremor-related disability, using a Tremor-Activities of Daily Living Disability questionnaire.

TREATMENT OPTIONS

Medications

Several medications have been reported to be beneficial in some patients with MS tremor. However, in most cases, the action tremor of patients with MS responds poorly to medication.[16]

Isoniazid

Isoniazid has been studied in detail in a number of clinical trials. Two double-blind cross-over trials of isoniazid versus placebo showed improvement of postural tremor but no significant benefit on intention tremor.\(^8,18\) The dose of isoniazid used in published studies typically is between 800 and 1200 mg/day. Reported side effects are usually mild. Reversible perturbations of liver function tests have been reported in 0\(^8,18\) and 33% of patients.\(^25\) Other side effects included sleepiness, fever, rash, nausea, dysphagia, and increased bronchial secretions.\(^30–32\) Upper motor neuron weakness was also noted, probably unmasked by the reduction of tremor.\(^31\)

Ondansetron

Ondansetron is a 5-hydroxytryptamine-3 antagonist and can ameliorate vertigo in patients with acute brainstem disorders. A coincidental benefit is the improvement of cerebellar tremor caused by MS. In a placebo-controlled, double-blind, cross-over study, a single dose of intravenous ondansetron improved cerebellar tremor in 13 of 19 patients, including improvement on spiral copying.\(^33\) In contrast, in a recent small open-label, prospective and controlled study with 14 MS patients suffering predominantly from cerebellar tremor of the upper extremities caused by MS, there was no significant improvement noted in the upper extremity tests nor in the subjective response of the patients patients.\(^34\)

Other medications

Gluthetimide,\(^35\) oral tetrahydrocannabinol,\(^36\) primidone,\(^37\) carbamazepine,\(^6\) L-tryptophan,\(^38\) and clonazepam\(^39\) have been found to be at least partially effective against tremor in open label studies of small numbers of MS patients. Clonazepam,
oxazepam, and lorazepam are the drugs most likely to provide sufficient benefit to justify further trials. Propranolol is usually not effective for intention tremor. Intravenous injections of 50 ml of 10% solution of ethanol failed to produce any significant short-term improvement of MS tremor.

**Surgical treatment**

The surgical therapy for tremor in MS includes two surgical modalities, stereotactic ablative surgery (e.g. radiofrequency thalamotomy or radio-induced thalamotomy) and neurorestorative procedures (e.g. DBS).

**Ablative surgery**

Stereotactic thalamotomy has been used in the treatment of hyperkinetic movement disorders since the late 1940s, primarily in Parkinson’s disease and essential tremor. In 1967, Cooper reported that ventral thalamotomy was an effective therapy for tremor complicating MS. More than 30 years later, no consensus has been reached as to the role of this procedure in treating the action tremor associated with MS. Current knowledge of this form of surgery is based predominantly on retrospective studies and reports, which have shown highly variable results.

Immediate relief following thalamotomy is usually obtained in between 90% and 100% of cases. Long-term results are less satisfying, or are unknown, owing to the lack of follow-up. Patients selected for thalamotomy are usually severely disabled from multiple impairments before surgery, which limits the potential for significant functional improvement. Ambulatory patients appear to have a better functional outcome.

The literature reports alleviation of contralateral limb tremor in 30–96% MS patients, although tremor recurrence occurs in approximately 20% of patients within 12 months. This wide range of results probably relates to the varied origins of tremor, which depend on the location of the MS lesions. Wester and Hauglie-Hanssen, in a series of nine patients, reported a moderate or good long-term result of the surgery in only 45% of cases, based on ratings by the patient’s treating neurologist. Functional rehabilitation of the relevant arm is estimated to occur in 25–70% of MS patients after thalamotomy.

The adverse effects caused by thalamotomy have not been measured and quantified accurately. The reported incidence varies from 0 to 45%. The most common complications are gait deterioration, hemiparesis, and dysarthria. Epilepsy, sensory disturbances, dysphagia, bladder disturbance, confusion, depression, lethargy, and somnolence also have been described. Mortality can occur in the postoperative period, although its relationship to the surgery has not always been established.

A recent prospective case-controlled study highlighted a significant improvement in contralateral upper limb postural and kinetic tremors. Tremor-related disability and finger tapping speed were also significantly better 12 months after surgery.

Another modality of ablative surgery for tremor in MS patients is radiosurgery. Stereotactic radiofrequency thalamotomy is the most commonly performed destructive neurosurgical procedure for tremor relief. However, the effects of radio-induced thalamotomy may lessen over time (as occurs with other lesion modalities). The
effectiveness of radiosurgery in controlling tremor is lessened by the inability to confirm the target site with intraoperative physiologic tests. There also have been numerous reports of delayed complications such as paralysis. It is the consensus of most experts that radiosurgery does not have the accuracy of thalamotomy or thalamic DBS. Most recommend against radiosurgery except in rare patients who cannot undergo surgical thalamotomy or DBS.

**Deep brain stimulation**

Recently, the neurosurgical community has witnessed a renaissance in the use of therapeutic brain stimulation for the treatment of movement disorders and in other emerging areas. This technique, considered today as one of the most technologically advanced in the neurosurgical armamentarium, has its roots in more than 100 years of diagnostic human brain stimulation and in 50 years of neurosurgical experience with therapeutic stimulation of the human brain. Improvements in stimulation equipment, advances in imaging and computer-assisted navigation devices, breakthroughs in anatomic and physiologic brain mapping, and the realization of the limitations of medical therapies have all contributed to the renaissance of brain stimulation techniques.

The excellent results obtained with DBS of the Vim nucleus for parkinsonian and essential tremor encouraged the same groups and others to explore the use of DBS for the relief of MS tremor (Figs 41.1 and 41.2). Besides reversibility, DBS also offers an adjustable therapy for a progressive disease. Nevertheless, published series have been small, and objective data have not been reported consistently.

Since the report of Brice and McLellan[^48] 20 years ago, intention tremor related to MS has been a constant yet elusive treatment target for
Fig. 41.1 Axial magnetic resonance image (inversion recovery) showing the position of the quadripolar DBS electrode in the left motor thalamus (Vim). The tip of the electrode is located at 9 mm anterior to the posterior commissure.
thalamic stimulation. Geny et al. reported significant improvement in tremor in 69% of patients undergoing Vim stimulation for MS-related tremor, although the degree of functional improvement was variable.[12] Koller et al. were the first American group to report their results in this indication and did not observe the tendency for late tolerance to stimulation reported by other groups.[49] Montgomery et al. reported their series of 15 patients who underwent Vim stimulation for the treatment of MS-related tremor of the upper extremity (Fig. 41.3).[13] Although patients needed frequent reprogramming of the stimulator, all patients had significantly reduced tremor, with a greater improvement noted in postural tremor than in action tremor. Taha et al. reported improvement in limb tremor in two of two patients with MS.[50] Although Tasker et al. noted improvement in tremor in four patients undergoing unilateral procedures,[51] Benabid et al. did not detect a consistent long-lasting functional benefit in these patients owing to the continuing evolution of the disease.[10]
The most common complication of thalamic DBS is a worsening in dysarthria, which is usually mild, it is reversible when the stimulation is reduced or eliminated.\textsuperscript{[10]}

Continuous DBS is a reasonable alternative to ablative surgery. Its reversibility and the capability to modulate the amount of stimulation according to the patient’s symptoms make it an attractive alternative for MS patients. Thalamic stimulation has been adopted by many centers, and clinical studies suggest that this approach is as effective as thalamotomy with fewer complications, allowing bilateral treatment.\textsuperscript{[9,14]} In a recent randomized study, Schuurman et al. compared continuous thalamic stimulation and thalamotomy in patients with severe tremor.\textsuperscript{[52]} Thalamic stimulation and thalamotomy were equally effective for the suppression of drug-resistant tremor, but stimulation had fewer adverse effects and resulted in a greater improvement in function. This latter point is particularly important for patients with MS who often have numerous lesions and disabilities. Consequently, the authors rarely, if ever, recommend ablative thalamotomy. Only 10 of the 68 patients reported by Schuurman et al. had MS.\textsuperscript{[52]}

MS patients with severe tremor frequently have numerous other functional disabilities, particularly ambulation. This poses a significant problem in interpreting results of published studies. For example, the Expanded Disability Status Scale for measuring MS disability is heavily weighted for ambulation. Therefore, significant improvement in tremor control can be obscured when the total disability score is considered and can lead to erroneous conclusions that thalamic DBS was only minimally effective.\textsuperscript{[52]} However, if the expectations are modest and realistic (i.e. increased functional use of a single upper extremity), then the results can be gratifying and justifiable.\textsuperscript{[13]} We do not recommend bilateral DBS because of the greatly increased risks of worsened speech and swallowing.

\textbf{Fig. 41.3 Best response on postural and action tremor following DBS in 14 MS patients. From Montgomery et al.\textsuperscript{[13]}}
However, if a patient, after careful consideration of the risks, still wishes to proceed with bilateral thalamic stimulation, this is done as a staged procedure. If there are any complications with the first procedure, the recommendation is not to perform the second procedure.

The authors’ criteria of patient selection are:

• the patient has tremor secondary to precerebellar, cerebellar, or postcerebellar lesions, identified clinically or by imaging. The tremor is not associated with significant sensory loss or motor weakness in the upper extremity;
• there is no significant speech or swallowing abnormalities (there is a significant risk of worsening with thalamotomy or thalamic DBS);
• the tremor must be a significant factor in the patient’s disability—if tremor were reduced, then there should be a significant improvement in the patient’s quality of life. This could include increased independence for example, by being able to eat ‘finger foods’ or to dial a telephone; and
• there has not been any significant exacerbation of the MS in the previous 6 months. In the authors’ experience, there is a 20% risk of an exacerbation following surgery.

Deciding which side to place the thalamic stimulating lead can be problematic. Generally, the authors recommend that the stimulation lead should be placed in the dominant hemisphere even if the non-dominant limb has greater tremor. There is a greater improvement in function with tremor reduction in the dominant limb.

Critical to the success of thalamic DBS surgery are the methods used for localization. Virtually every surgeon uses neuroimaging, whether magnetic resonance imaging, computed tomography, ventriculography, or some combination of these plus clinical testing through the implanted therapeutic lead. Unfortunately, some surgeons stop there. Microelectrode recording from individual neurons is critical to the success of thalamic DBS surgery. It is critical to identify the anterior border of the ventral caudal thalamus (sensory relay nuclei) in order to place the therapeutic DBS lead sufficiently anteriorly so that stimulation-evoked paresthesias do not limit subsequent treatment. Furthermore, tremor in MS tends to involve more proximal joints than distal joints, as is the case in essential tremor. Therefore, the shoulder region is neurophysiologically mapped using microelectrode recording. Because there is no consensus governing how thalamic DBS surgery is to be done, it is incumbent on the physician to recommend patients to those centers that use appropriate techniques, including microelectrode recordings.

Another issue unique to MS patients is the remarkable degree of tolerance to the stimulation. Patients can do well for periods of time, only later for it to lose efficacy. In the vast majority of such cases, reprogramming can regain control. It is not that patients become more resistant to the stimulation and need progressively greater stimulation. Often reducing the stimulation can regain control. Perhaps the single most important factor in the long-term efficacy is the availability of physicians and nurses expert in stimulator adjustments.

Rehabilitative therapies

Intention tremor in association with cerebellar ataxia is one of the disabling neurologic sequelae of MS. MS tremor limits or precludes completion of activities of daily living.
(e.g. writing, feeding, dressing) and may significantly reduce social participation. Its impact on self-esteem and quality of life should not be underestimated. Referral to physical or occupational therapists and the development of a comprehensive rehabilitation program, focusing on compensation strategies, stabilization of the joints, and co-ordination exercises, aims at maximizing functional performances for a given level of impairment, but is of limited efficacy.\cite{39} Hewer et al. reported objective reduction of tremor in four of 10 MS patients after applying weights (480–600 g) to the wrist.\cite{53} However, the use of weights is limited by weakness and fatigability, and sometimes results in increased tremor.\cite{52,53} There is no linear relationship between the amount of weight applied and the clinical benefit, and viscous loads appear to be more effective than weights.\cite{22} Weighted eating utensils can be helpful. Techniques, such as training to use the less affected hand for feeding, writing, and performing other daily activities can improve function. A collar or neck brace can minimize neck tremor. Javidan et al. studied the efficacy of functional electrical stimulation—the use of neuromuscular electrical stimulation for functional purposes—on different types of tremor.\cite{54} They used concomitant flexor and extensor surface stimulation at the wrist or elbow, with a closed-loop control system. Attenuation of tremor in five MS patients ranged from 0 to 68%.

**IMPLICATIONS FOR PRACTICE**

The use of level 1 evidence-based medicine in the treatment of MS tremor (i.e. placebo-controlled, randomized and blinded studies) is limited. The complexity, cost, and ethical issues involved may make such studies unfeasible. In any event, physicians are confronted each day with patients who need help. In the authors’ opinion, there is sufficient level 2 and 3 data to justify the use of thalamic DBS for the treatment of tremor due to MS. Immune-modulating therapies affecting the disease process may be indirectly helpful for tremor reduction as well. There are few controlled trials, and in most cases the assessment of functional results is not standardized or carried out with validated tools. The dynamic nature of disease and the presence of multiple associated impairments, limits our ability to compare results from different studies and to predict results of treatments. Owing to the inherent risks of surgery and the risks of MS exacerbations, medication remains the first line of treatment. However, when this approach is inadequate in controlling the tremor, it is appropriate to discuss the DBS in the Vim thalamus to try to attenuate tremor in the affected limb. DBS is effective and has the advantages over thalamotomy of being reversible and adaptable and of having a lower rate of complications and the possibility of bilateral stimulation.\cite{3,10,12,13} DBS is more costly than thalamotomy, requires highly skilled personnel, and necessitates follow-up visits for adjustment of parameters.\cite{14} The indications for DBS could possibly be extended to less severely disabled patients, in whom the potential for functional improvement may be greater. However, careful selection of patients is still required. In particular, associated motor and proprioceptive deficits in the targeted limb must be carefully assessed. A comprehensive rehabilitative program is an important complement to other therapies, in an effort to optimize functional gain after reduction of impairment.
IMPLICATIONS FOR FUTURE RESEARCH

Better understanding of the pathophysiology of MS tremor is certainly necessary to enhance the effectiveness of therapeutic approaches and to develop new therapies. Microelectrode recordings and stimulation during surgery for DBS has provided better insight into the pattern of neuronal activity in thalamic nuclei in MS patients. The area of interest for future research includes the long-term effect of chronic stimulation and the best target for MS tremor.

Well-designed clinical trials, involving multiple centers to achieve larger sample sizes, would be helpful to refine further the indications of antitremor medications and surgery. For this purpose, valid, reliable, and sensitive assessment tools are needed, particularly for disability. With the increasing use of surgical treatments, criteria for patient selection will be refined, and new anatomical targets may be identified. Finally, adjunctive therapies such as rehabilitation would benefit from a more scientific evaluation, in order to optimize their use in a comprehensive care model.

REFERENCES


INTRODUCTION

As discussed in Chapter 3, impairment of one or more cognitive domains has been reported in 54–65% of MS patients in clinic-based studies and in 43–46% of patients in community-based samples. The full spectrum of deficits that can occur includes impairment of attention, speed of information processing, learning, memory, executive function, and visual information processing. Basic language skills and verbal intelligence are relatively spared. Cognitive impairment is a significant determinant of quality of life for patients with MS, who have higher rates of unemployment and greater social isolation and who require greater personal assistance at home than cognitively intact MS patients, even after controlling for the degree of physical disability. Cognitive impairment can also affect safety, including child care and driving ability. In this chapter, the practical management of cognitive impairment is discussed, including methods of identifying cognitive impairment in routine practice and potential treatment strategies.

IDENTIFICATION OF PATIENTS WITH COGNITIVE IMPAIRMENT

In the course of a routine office visit, patients often complain of difficulty with short-term memory, concentration, and word retrieval. Unfortunately, self-reported impressions are notoriously unreliable. Often, patients with minimal impairment exaggerate their symptoms because of depression and diminished self-worth. Conversely, patients with substantial impairment often underestimate their problems because of denial and lack of insight, which can be viewed as a form of anosagnosia. Patients reporting moderate levels of impairment tend to be more accurate in their assessments, but all self-reports must be interpreted cautiously.

On the other hand, reports from an informant who sees the patient regularly can provide a more accurate assessment of cognitive abilities. In patients with possible Alzheimer’s disease, informants were able to categorize 92% of people with dementia and 86% of the cognitively intact correctly. Informants are also better able to judge changes in the severity of cognitive impairment. Although these observations come from patients with Alzheimer’s disease, they are likely to apply to cognitive impairment in general, regardless of the etiology.
In addition to specific historical information about cognitive impairment obtained from the patient and informant, astute clinicians can identify patients who deserve further attention on the basis of indirect clues during the neurological evaluation. Even before examining the patient, clinicians should suspect those who are frequently late or miss appointments. Patients who have difficulty relating a coherent history, providing detailed information about their symptoms, or making treatment decisions also may be demonstrating cognitive impairment. Patients who report difficulty in their work and social roles out of proportion to their physical deficits should raise concern, although depression and fatigue are also common contributors to such discrepancies. Patients with secondary progressive MS, prominent cerebellar signs on examination, substantial brain atrophy, or extensive T2-hyper-intense or T1-hypointense lesions on cerebral magnetic resonance imaging are also more likely to have cognitive impairment.[13]

The clinician may choose to perform a cursory cognitive examination in all patients or a more detailed examination in the subset of patients in which cognitive impairment seems more likely. Either way, these examinations tend to be quite brief and rarely address all of the most commonly affected cognitive domains, such as learning and memory, attention and concentration, information processing speed, executive function, visuospatial function, and verbal fluency. Screening tools that have been developed for this purpose are generally too insensitive to deficits that are likely to occur in MS (e.g. the MiniMental State)[14,15] or are too long to be practical for routine practice (e.g. the Screening Examination for Cognitive Impairment).[16] While many clinicians develop their own brief testing strategies incorporating variations of standardized tests (e.g. remembering a list of five words and listing as many animals as possible in 1 minute), responses may be difficult to interpret without normative data. Furthermore, depression, anxiety, and other psychological symptoms can easily confound these partial evaluations. Because of these limitations in bedside testing, clinicians correctly identify a small minority of MS patients with cognitive impairment.[17]

Formal neuropsychological testing, using standardized tests addressing a wide range of cognitive domains, is considered the ‘gold standard’ for characterizing cognitive status in patients with MS. Ideally, all patients with MS would have such testing at the time of diagnosis to serve as a baseline for future evaluation. Repeat testing would be performed whenever symptoms or signs appeared to be worsening, or perhaps even on a routine basis (e.g. every 5 years), at the transition from relapsing to secondary progressive MS, or when assistance is required with ambulation. Unfortunately, such testing is expensive and timeconsuming and has limited availability in many areas. As a result, it is not practical to perform formal testing on all patients, or even on all patients in whom the clinician suspects cognitive impairment. Nevertheless, there are several situations in which formal neuropsychological testing is clearly needed to enhance clinical care (Table 42.1).

A complete neuropsychological evaluation should include an interview with the patient and an informant and detailed testing of the cognitive domains most commonly affected in MS as well as any additional domains appropriate to the patient’s complaints. Briefer testing of domains less commonly affected also may be appropriate, especially when alternative explanations for cognitive symptoms are suspected. Self-report questionnaires about affective symptoms and fatigue
Table 42.1 Indications for neuropsychological testing

<table>
<thead>
<tr>
<th>Ideal</th>
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<tr>
<td>To obtain a routine baseline evaluation</td>
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<tr>
<td>To assess change at routine intervals</td>
</tr>
<tr>
<td>To assess change at important milestones</td>
</tr>
<tr>
<td>To monitor the effects of treatment for cognitive impairment</td>
</tr>
<tr>
<td>Clinically necessary</td>
</tr>
<tr>
<td>To document cognitive status when symptoms are interfering with employment, education, child care, driving, or other important social roles</td>
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<tr>
<td>To differentiate cognitive symptoms from psychological symptoms (depression, anxiety) and fatigue</td>
</tr>
<tr>
<td>To determine the role of cognitive impairment in patients with functional impairment out of proportion to their physical impairment</td>
</tr>
<tr>
<td>To help the patient and significant others understand functional limitations</td>
</tr>
<tr>
<td>To determine the ability of the patient to participate in rehabilitation</td>
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</table>

should be administered. Personality inventories should be included when other psychiatric disorders are suspected. After formulating test results into a diagnostic impression, the neuropsychologist or referring clinician should present the results to the patient and significant others, making practical suggestions for ways to compensate for any documented deficits. In some cases, this will be the first step in developing a treatment plan to ameliorate cognitive symptoms and minimize further worsening.

NON-PHARMACOLOGICAL THERAPY

The first step in the management of patients with cognitive impairment should begin with a search for factors other than MS that might be contributing. Depression, anxiety, and fatigue are very common symptoms in MS, and they can interfere considerably with both cognitive and non-cognitive activities, especially those that require substantial effort. As described above, however, separating the effects of affective disorders and fatigue from primary cognitive impairment is often difficult. For most patients with a combination of these symptoms, the most logical approach is to treat all of their symptoms simultaneously. The management of affective disorders and fatigue are discussed in detail in Chapters 36 and 39.

Medications can also contribute to cognitive impairment in patients with MS, especially medications that cause sedation or have anticholinergic properties. These include agents commonly used for spasticity (baclofen, tizanidine, and benzodiazepines), dysesthesias (tricyclic antidepressants and anticonvulsants), urinary symptoms (oxybutynin and tolterodine), and tremor (benzodiazepines and myoline). In some cases, there may be alternative treatments that are less likely to affect cognitive function. Selective serotonin reuptake inhibitors, for example, cause less sedation and cholinergic inhibition than tricyclic antidepressants. Tolterodine is less likely to have central nervous system effects than oxybutynin, and long-acting forms of these urological medications
tend to have fewer side effects in general. Patients requiring large dosages of antispasticity medications may be better able to tolerate intrathecal baclofen. If alternatives are not available or are not effective, the lowest possible dosages of these medications should be used.

The next step in helping patients with cognitive impairment is the development of compensatory strategies. A wide variety of approaches have been used, including external aids (e.g. memory note-books, calendars, pill cases, personal digital assistants) and internal aids (e.g. instruction in the use of mnemonics and visual associations). These strategies are relatively simple and can be used by all patients. Ideally, the neuropsychologist or clinician would instruct patients and significant others about these techniques while explaining the results of the patients’ neuropsychological testing. In many cases, further sessions to review the use of these techniques and their effectiveness would be appropriate.

Cognitive rehabilitation can be viewed as an extension of this approach, providing more formalized, intensive instruction in compensatory strategies. In general, the same neuropsychological rehabilitation principles established in the care of patients with stroke, brain injury, and other neurological insults also apply to MS. Following thorough evaluation of the deficits present, an individualized plan for restitution of function, compensation with relatively spared cognitive functions, and adaptation using external aids may significantly improve functional ability. Psychiatrists or neuropsychologists with experience in cognitive therapy are generally best equipped to develop appropriately comprehensive plans.

While these approaches have a strong appeal, there have been only a few studies attempting to determine whether they promote meaningful improvements in function. Freeman et al. performed a randomized, wait-list-controlled study evaluating the effects of a comprehensive, individualized, inpatient rehabilitation program on disability and handicap in 66 patients with progressive MS. They demonstrated that impairment did not change in patients receiving rehabilitation, but disability and handicap improved significantly. Although the rehabilitation program included interventions by neuropsychologists and by speech, occupational and physical therapists, specific effects on cognitive impairment were not evaluated. DiFabio et al. performed a similar wait-list-controlled study of outpatient rehabilitation in 46 patients with progressive MS, except that patients were not randomly assigned to the treatment groups. Improvements in a symptom checklist composite score occurred in patients receiving rehabilitation compared with controls, but, again, specific effects on cognitive impairment were not evaluated. Several other uncontrolled studies have reported similar generalized benefits without providing evidence of specific cognitive effects.

Jonsson et al. performed the first controlled study specifically assessing the effects of cognitive rehabilitation in MS, randomly assigning 40 patients to individualized cognitive therapy or diffuse mental stimulation. The patients assigned to cognitive therapy received direct training in concentration, memory, and visuospatial function, as well as psychotherapy to help integrate these techniques into daily activities. After treatment averaging 46 days in duration, visual perception was improved in treated patients compared with controls, but none of the other tests demonstrated treatment effects. Six months after completing the rehabilitation program, treated patients had improved visuospatial memory compared with controls, and there were trends toward improvement.
in visual perception and a composite of the entire neuropsychological test battery. Interestingly, there also was significant improvement in self-reported depressive symptoms in patients receiving the rehabilitation intervention, which was detected at both time points. As with all rehabilitation studies, the lack of patient blinding may have confounded the results of this study, and the sample size was too small to rule out modest treatment effects. Furthermore, baseline differences in cognitive status raised the possibility that some of the apparent treatment effects in this study may actually have reflected regression to the mean.

Rodgers et al. performed a non-randomized, wait-list-controlled study in 27 patients with MS, in which treated patients received group psychotherapy, expressive therapy (art and music), mind-body approaches using training in self-regulation, visualization techniques, guided imagery, meditation, relaxation, and mental and physical exercises.[24] Although this may not be considered classic cognitive therapy, patients had improvement in verbal learning and memory, verbal abstraction, and depression compared with controls. As with the study by Jonsson et al.,[23] baseline differences complicated the interpretation of results, especially because patients in the study by Rodgers et al.[24] were allowed to choose whether they would participate in the intervention or wait.

Plohmann et al. performed an uncontrolled study in 22 patients, focusing primarily on deficits in attention.[25] Each patient’s worst attentional deficit (separated into components of alertness, vigilance, selective attention, and divided attention) was identified and specifically addressed by a different module of a computer-based training intervention. The targeted attentional component improved with training, while non-specific effects on untargeted domains were minimal. When patients underwent a second round of training aimed at their next most severe attentional deficit, however, no improvement was detected. This may reflect a ceiling effect or limited capacity of MS patients to learn. Because of the unblinded, uncontrolled, short-term design of this study, the lasting functional benefits of this intervention could not be adequately assessed. Nevertheless, the results of this study support the hypothesis that specific interventions can improve specific aspects of cognitive impairment.

Together these studies suggest that cognitive rehabilitation may improve cognitive impairment and disability in MS patients, but they all have significant limitations. The sample sizes have been small, making it difficult to assess the magnitude of treatment effects accurately. The outcome measures generally have uncertain ecological validity and are assessed relatively soon after completing therapy, making it difficult to determine whether benefits of therapy are clinically meaningful and sustained. The study designs have had inadequate controls and blinding, making it difficult to determine whether treatment effects are truly related to the intervention received. Patient blinding is particularly difficult to achieve in rehabilitation studies, but blinding of the examiners should be considered a required step toward minimizing potential sources of bias. Future studies should address these limitations, determine which patients are most likely to benefit, and which interventions are most successful.
PHARMACOLOGICAL THERAPY

At the same time, studies examining the effects of rehabilitation have been initiated in patients with cognitive impairment from MS, pharmacological interventions have been studied as well. Ideally, these would be hypothesis-driven studies based on a clear understanding of the mechanisms responsible for cognitive impairment in MS patients, but current evidence only allows us to speculate. Early imaging studies suggested that brain lesions play a major role, because various indices of damage, including semiquantitative lesion scores, third ventricle size, corpus callosum size, and ventricle-brain ratios, were moderate predictors of impairment.\cite{26,27} More recently, even better correlations were demonstrated using more precise quantification of lesion volumes.\cite{28} These studies suggested that the severity of damage within lesions and normal-appearing brain were important determinants of cognitive impairment.\cite{29,30} In fact, longitudinal changes in cognitive impairment correlated better with changes in whole brain atrophy than with changes in lesion burden.\cite{31}

The specific location of MS lesions is another important factor. Studies suggest, for example, that juxtacortical lesions and those near the hippocampi are associated with memory deficits,\cite{32-34} and that frontal lobe lesions are associated with executive dysfunction.\cite{35,36} Similarly, corpus callosum size is a strong predictor of impairment of information processing speed and tasks requiring interhemispheric transfer, while anterior corpus callosum atrophy is specifically associated with decreased verbal fluency.\cite{37-39}

At the cellular level, much of the effect of MS lesions presumably would be caused by structural disconnection, occurring when critical pathways are damaged enough that signals can no longer be transmitted. This probably involves substantial axonal transection as pathways traverse more severe brain lesions.\cite{40} There may be additional contributions to impairment by functional disconnection, occurring when critical pathways are inflamed or demyelinated enough to disrupt but not permanently preclude signaling and axonal transport. At present, potential treatments for structural disconnection are rather limited, but prevention of further damage using course-modifying immunotherapy or compensatory strategies fostered by rehabilitation would be rational. Potential treatments for functional disconnection are more varied (Table 42.2). In practice these can be divided into course-modifying and symptomatic approaches, similar to the overall therapeutics of MS. Although the effects of these potential approaches have not been thoroughly evaluated, several relevant clinical trials have been performed.

Course-modifying treatments

The pivotal trials for the course-modifying agents (glatiramer acetate, interferon beta-1a, and interferon beta-1b) in relapsing MS have all included a neuropsychological component. In the glatiramer acetate study, 248 of 251 participants underwent neuropsychological testing with the Brief Repeatable Battery of Neuropsychological Tests\cite{2} (BRBNT) at baseline and after 1 year and 2 years of double-blind, placebo-controlled treatment.\cite{41} The BRBNT, which includes tests of verbal and visuospatial
learning and memory, information processing speed and sustained attention, and verbal fluency, was selected based on published recommendations from a National MS Society Task Force. Patients had mild to moderate disability at baseline, with expanded disability status scores between 0 and 5.0, but baseline neuropsychological test scores were within the normal range except for the test of verbal fluency. During 2 years of follow-up, mean test scores improved in both the glatiramer acetate and placebo groups, even though alternative test forms were used to minimize practice effects. There were no significant differences between groups at any time point. These results should be considered uninformative rather than negative. The study was designed with the assumption that patients receiving placebo would have worsening cognition over time. The hypothesis being tested was that patients receiving course-modifying therapy would have less decline in cognitive function than patients receiving placebo. Because there was no measurable decline in cognitive function in the placebo group during the study period, there was no opportunity to determine whether glatiramer acetate affected that decline. There are three features of this study that led to this result: patient selection, study duration, and neuropsychological test selection. Because the evaluation of cognitive effects was a secondary goal of this study, enrollment criteria were not established with cognitive outcomes in mind. Natural history studies suggest that worsening cognitive function is most likely to occur in patients who already have measurable deficits, so it should not be surprising that the participants in this study had no worsening. Furthermore, natural history studies suggest that relatively long periods of follow-up are needed to detect worsening cognition in a broad group of MS patients, so it should not be surprising that no worsening was detected over 2 years. Finally, it is possible that other neuropsychological tests would be better able to detect worsening over time. The tests comprising the BRBNT were selected because they were able to distinguish MS patients with and without cognitive impairment. These would not necessarily be the same tests that are most responsive to change over time. If the eligibility criteria, treatment duration, and neuropsychological test battery selected for

### Table 42.2 Potential pharmacological approaches for cognitive impairment from MS

<table>
<thead>
<tr>
<th>Pathogenic mechanism</th>
<th>Intervention</th>
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<tr>
<td>Structural disconnection</td>
<td>Prevent further damage using course-modifying immunotherapy</td>
</tr>
<tr>
<td>Signals blocked</td>
<td>Foster compensation through rehabilitation</td>
</tr>
<tr>
<td>Functional disconnection</td>
<td></td>
</tr>
<tr>
<td>Signals disrupted by demyelination</td>
<td>Enhance signaling (e.g. potassium channel blockers or cooling therapy)</td>
</tr>
<tr>
<td>Signals disrupted by inflammatory mediators</td>
<td>Reduce inflammation (e.g. immunotherapy)</td>
</tr>
<tr>
<td>Neurotransmitter transport disrupted</td>
<td>Augment neurotransmitter function (e.g. cholinesterase inhibitors)</td>
</tr>
<tr>
<td></td>
<td>Bypass endogenous neurotransmitters (e.g. nicotinic agonists)</td>
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</table>
this study led to a measurable decline in cognition in the placebo-treated patients, then the effects of glatiramer acetate could have been evaluated more definitively.

The interferon beta-1a study had similar eligibility criteria and treatment duration, but it used a much more extensive neuropsychological test battery. In this study, 166 of 266 participants underwent neuropsychological testing at baseline and after 2 years of double-blind, placebo-controlled treatment. The baseline level of cognitive function was not reported, making comparisons to the glatiramer acetate study difficult. Improvement in cognitive function was noted in both the interferon beta-1a and the placebo groups, but patients receiving interferon beta-1a had more improvement in a composite of tests of memory and information processing speed compared with patients receiving placebo. Patients receiving interferon beta-1a also had a trend towards more improvement in a composite of tests of visuospatial and executive function compared with those receiving placebo.

Although these results indicate that interferon beta-1a had a therapeutic effect, the mechanism of that effect is somewhat unclear. As with the glatiramer acetate study, there was no measurable decline in mean test scores in the placebo group during the study period, so there was no opportunity to determine whether interferon beta-1a affected that decline. Presumably practice effects were responsible for improving test scores, but it is difficult to determine whether the difference between groups reflects symptomatic improvement in function, less worsening over time, an alteration of the practice effect itself, or a combination of these factors. A secondary analysis partially addressed this issue by demonstrating that the time to a 0.5 standard deviation worsening in performance on one of the tests of attention and information processing speed (the Paced Auditory Serial Addition Test) was delayed in patients receiving interferon beta-1a compared with those receiving placebo. Only a minority of patients reached this endpoint during the 2-year study (37% in the placebo group and 20% in the interferon beta-1a group), however, and the reproducibility and clinical significance of this change has not been established.

The interferon beta-1b study did not include neuropsychological tests at its beginning, but one of the study sites administered a test battery to 30 of 372 participants after 2 years and 4 years of double-blind, placebo-controlled treatment. As with the glatiramer acetate study and the interferon beta-1a study, patients were not selected for cognitive impairment. The baseline level of cognitive function was not formally compared with normative values, but scores were generally within the normal range. Most of the tests on the neuropsychological battery did not change significantly over 2 years of evaluation. The main exception was delayed visual recall. Although the patients receiving placebo demonstrated little change in delayed visual recall, patients receiving high-dose interferon beta-1b had significant improvement over 2 years. Conclusions from this study are limited because it had a small sample size (only eight to 13 patients per group), the initial assessments were performed 2 years after beginning the study, and no correction was made for the many statistical comparisons made. Nevertheless, results seem to parallel those from the interferon beta-1a study, demonstrating improvements in memory during course-modifying treatment.

Results from studies of interferon beta-1a and interferon beta-1b in secondary progressive MS may help to clarify the effects of course-modifying treatment on cognitive impairment, because these patients are more likely to be cognitively impaired at
baseline and to worsen during the study period. However, these results have not yet appeared in peer-reviewed publications.

Symptomatic treatments

Studies exploring the effects of course-modifying therapy on cognition began with the premise that treatment would delay worsening of cognitive function in MS patients by preventing further structural disconnection. The interferon studies raise the possibility that anti-inflammatory treatments might also have a symptomatic benefit, improving cognitive function by reducing functional disconnection related to inflammatory mediators. If so, then cognitive function might be expected to worsen during acute exacerbations and to improve with anti-inflammatory treatment of exacerbations. There is little evidence that cognition worsens during acute exacerbations, however. Furthermore, one study has demonstrated that high-dose methylprednisolone, which is commonly administered to reduce acute inflammation during MS exacerbations, may actually cause temporary worsening of cognitive function. Fourteen patients experiencing an acute exacerbation were administered a battery of neuropsychological tests before treatment and 7 and 60 days after 5–7 days of treatment with methylprednisolone. Seven days after treatment, verbal learning and recall were worse than baseline, and other domains were unchanged. Sixty days after treatment, performance on all tests was back to baseline levels.

This study should not be considered definitive because of the small sample size and unusual lack of practice effects, but it does not support the hypothesis that general immunosuppression will improve cognitive function. It is still possible that this concept is correct, but that methylprednisolone has deleterious effects on cognitive function that interfered with the detection of beneficial anti-inflammatory effects. Moreover, if specific cytokines are interfering with conduction through pathways involved in cognitive function, it is possible that immunotherapy directed more specifically against them would be more effective.

Several other symptomatic approaches have also been studied in clinical trials. Cholinesterase inhibition, for example, is based on the hypothesis that cholinergic function is critical to memory and other cognitive functions. This hypothesis is particularly appealing in Alzheimer’s disease, in which a cholinergic deficit exists as a result of degeneration of basal forebrain neurons that are responsible for synthesizing and distributing acetylcholine throughout the brain. Although there is no evidence that this area is prone to damage from MS, axonal projections from the basal forebrain pass through the periventricular regions that are most likely to be damaged in MS (Fig. 42.1). Demyelination of these pathways might disrupt axonal transport necessary for acetylcholine distribution, and transection would block distribution altogether. Consistent with this hypothesis, cerebrospinal fluid levels of
acetylcholinesterase, which correlate with the number of active cholinergic terminals, are lower in MS patients than in healthy controls or patients with Alzheimer’s disease.\textsuperscript{[48]} Even if MS patients do not have a cholinergic deficit, cholinesterase inhibitors may have broad therapeutic effects, improving neuropsychological function in patients with cognitive impairment from conditions that are not necessarily associated with cholinergic deficits, including traumatic brain injury and vascular dementia.\textsuperscript{[49–51]}

The earliest studies of cholinesterase inhibition in MS patients were difficult to interpret because of very small sample sizes and mixed results.\textsuperscript{[52,53]} This approach has received increased attention in the past few years, however, owing to the availability of several well-tolerated treatment alternatives. To date, only one study has been published. This was a relatively small, unblinded, open-label pilot study in which 17 patients were treated with donepezil for 12 weeks.\textsuperscript{[54]} Unlike most other studies, the participants in this trial had relatively severe cognitive impairment at baseline. During treatment, there were significant improvements in tests of attention, memory, executive function, and verbal fluency. Concomitant improvements in apathy, disinhibition, agitation, depression, and euphoria were noted on the Neuropsychiatric Inventory,\textsuperscript{[55]} and a Clinical Global Impression demonstrated significant improvement in overall cognition. Conclusions from this study must be tempered by the small sample size and the unblinded, uncontrolled

\textbf{Fig. 42.1 Relationship of cholinergic projections from the basal forebrain to periventricular lesions.}
design, but treatment was well tolerated and sufficiently promising to warrant further controlled studies.

Another symptomatic approach involves the use of aminopyridines (potassium channel blockers), which may enhance conduction through demyelinated pathways. The first study examining the effects of aminopyridines on cognition was a double-blind, placebo-controlled, crossover study of 4-aminopyridine in 20 patients with MS. Patients did not need to demonstrate cognitive impairment to enroll, and mean scores on the BRBNT were generally within the normal range at baseline. There was a trend toward improvement in delayed visual recall and speed of information processing during active treatment, but these changes did not reach statistical significance. These results are difficult to interpret because practice effects complicated the cross-over design, and because there was carryover of treatment effects from the first period into the second on some of the tests. In a similar study of 3,4-diaminopyridine performed in 36 patients with motor deficits from MS, no treatment-related changes were detected using the BRBNT. Both of these studies may have had different results if they focused on cognitively impaired patients.

Because many investigators have suggested that fatigue may affect cognition, there have also been studies examining the effects of fatigue treatments on cognitive impairment. The first of these was a double-blind, placebo-controlled, cross-over study of amantadine in 29 patients. There were significant improvements on the Stroop Interference Test, a measure of executive function, during treatment with amantadine, but practice effects overshadowed the improvement, and none of the other cognitive tests showed treatment-related benefits. The cognitive effects of amantadine and pemoline were assessed in a double-blind, placebo-controlled, parallel group study in 45 patients. Patients were required to have severe self-reported fatigue at baseline, but their neuropsychological test scores were normal on average. There was significant improvement on the written version of the Symbol-Digit Modalities Test, a measure of attention and visuomotor search, in patients treated with amantadine, but none of the other tests demonstrated treatment effects. There was no correlation between fatigue and any of the neuropsychological variables at baseline or between changes in fatigue and changes in cognition during fatigue treatment. As with the studies of aminopyridines, these studies may have demonstrated different effects if they required patients to have cognitive impairment at baseline.

CONCLUSIONS AND FUTURE DIRECTIONS

There is a growing appreciation for the prevalence and importance of cognitive impairment as a symptom of MS. Assessing cognitive function in routine practice can be difficult; formal neuropsychological testing is required to characterize deficits fully. Clinical trials evaluating therapeutic interventions for cognitive impairment have had mixed results, leaving uncertainty about the value of these approaches. Compensatory rehabilitative strategies may be helpful in improving cognitive function, but further studies are needed to determine whether there are meaningful long-term benefits. Course-modifying therapies may have a positive effect on cognition, but further studies are needed to determine whether cognitive worsening is significantly delayed and which
patients are most likely to benefit. Symptomatic pharmacotherapies have not yet demonstrated convincing effects, but ongoing studies of cholinesterase inhibitors may establish the value of this approach. All of these studies have been based on very rudimentary information about the mechanisms of cognitive impairment in MS patients. As our understanding of these mechanisms grows, more successful preventive and symptomatic strategies should emerge.

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<tr>
<th>No.</th>
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<th>Journal</th>
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<td>1997</td>
<td>120:15–26</td>
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Management of cognitive impairment in multiple sclerosis

Rehabilitation has been defined as ‘the process of helping a person to reach the fullest physical, psychological, social, vocational, avocational, and educational potential consistent with his or her physiologic or anatomic impairment, environmental limitations, and desires and life plans.’ As illustrated by this definition, the philosophy on which the concept of rehabilitation is based goes beyond the traditional biomedical model of care, to seek a broader, more comprehensive approach of the person in relation to the environment. To target these ambitious goals, rehabilitation programs usually involve a multidisciplinary team, which can comprise physiatrists, physical therapists, occupational therapists, recreation therapists, rehabilitation nurses, speech-language pathologists, psychologists, social workers, and other rehabilitation professionals. It is commonly acknowledged that rehabilitative interventions, particularly in neurorehabilitation, do not affect the underlying disease process. However, these interventions can have a significant impact on the consequences of central nervous system (CNS) damage caused by multiple sclerosis (MS).

Although rehabilitation is acknowledged as a component of the management of MS, its exact role and modalities are not as clearly defined as in other CNS pathologies, such as spinal cord injury, stroke, and traumatic brain injury. The relatively low incidence of MS, the progression of disability over time observed in many patients, and the generally low tolerance of MS patients for exertion may explain this situation. Additionally, the attention of patients, families, and health professionals has been focused on recently introduced disease-modifying therapies, which aim to prevent the development of disability. Therefore, it is important to re-examine the available evidence supporting the use of rehabilitation in MS, and to define more precisely the areas in which it is likely to be helpful. A more provocative way of presenting the problem could be to ask whether, beyond focused interventions such as the teaching of a stretching program or the adaptation of an ankle-foot orthosis, rehabilitation is more than a placebo intervention destined to make the patient and caregivers feel that ‘they are doing something’.

MEASURING THE RESULTS OF REHABILITATION IN MS

To understand better the rehabilitation literature, it is necessary to possess a minimal knowledge of the language and tools used in rehabilitation practice and research. The
application of evidence-based medicine to the field of physical medicine and rehabilitation is relatively recent. Rehabilitation professionals traditionally relied on empirical evidence. Both the difficulty of applying biomedical concepts to rehabilitative interventions and certain methodological limitations (e.g. defining a placebo intervention) are among the factors contributing to this situation. However, methodological standards for physical medicine and rehabilitation have now been published and the development of specific concepts and derived assessment tools has set the basis for the development of methodologically sound clinical research.

Conceptual framework

The most widely used theoretical framework for rehabilitation was introduced by the World Health Organization (WHO) in 1980, with the publication of the International Classification of Impairments, Disabilities, and Handicaps (ICIDH), recently updated with the publication of the International Classification of Functioning, Disability, and Health (ICIDH-2). Definitions of basic ICIDH and ICIDH-2 concepts are presented in Table 43.1. In addition, there is an increasing interest in perceived health status and quality-of-life assessment (see chapter 4). Although there is no consensus on the definition of concepts and on the interpretation of ‘subjective’ data, patient-reported outcomes are increasingly integrated into clinical care and research. The WHO definition of quality of life reflects the

<table>
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<th>ICIDH</th>
<th>ICIDH-2</th>
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<tbody>
<tr>
<td><strong>Impairment</strong> Any loss or abnormality of a psychological, or anatomical structure or function</td>
<td><strong>Impairment</strong> Loss or abnormality of body structure or of a physiological or psychological function</td>
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<tr>
<td><strong>Disability</strong> Any restriction or inability (resulting from an impairment) to perform an activity in the manner or within the range considered normal for a human being</td>
<td><strong>Activity</strong> Nature and extent of functioning at the level of the person. Activities may be limited in nature, duration, or quality</td>
</tr>
<tr>
<td><strong>Handicap</strong> Any disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfillment of a role that is normal for that individual</td>
<td><strong>Participation</strong> Nature and extent of a person’s involvement in life situations in relation to impairment, activities, health conditions, and contextual factors. Participation may be limited in nature, duration, or quality</td>
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complexity of this concept, and its relevance to rehabilitative interventions: ‘...an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’.

[6]
Outcomes measures

Valid and reliable outcomes scales were developed based on the WHO theoretical frameworks. It is beyond the scope of this chapter to present all outcomes measures available for MS. Detailed information can be obtained elsewhere in this book (see chapters 2 and 4) or in other publications. This chapter discusses a few instruments that have been used in publications on MS rehabilitation. These instruments can be divided into those that are specific for MS and generic outcome measures.

The Minimal Record of Disabilities (MRD) for MS, developed under the auspices of the International Federation of Multiple Sclerosis Societies, includes the Expanded Disability Status Scale (EDSS), the Incapacity Status Scale (ISS), and the Environmental Status Scale (ESS).[8] Each scale is designed to cover one dimension of the ICIDH. In fact, the EDSS combines an evaluation of neurologic impairments (functional systems) and disability (walking, transfers, etc.). Despite well-known limitations,[7,9] the EDSS remains widely used in the MS field. In rehabilitation research, the EDSS is often used as a measure of neurologic status at baseline or as an indicator of clinical disease progression.[10–12] In most cases, EDSS mean scores either remain stable or worsen slightly during the course of prospective rehabilitation studies, which seems to support the absence of effect of rehabilitation on impairments and disease process. The ISS associates traditional assessment of disability (ambulation, self-care, and sphincter control) with observed or reported severity of common MS symptoms (e.g. visual symptoms, fatigue). Although validated and potentially more informative than generic measures of disability, the ISS has been seldom used by rehabilitation professionals. This is also true of the ESS, which is a measure of the social consequences of MS. A self-administered version of the MRD was developed and validated.[13] The Multiple Sclerosis Functional Composite (MSFC) was proposed to address the relative insensitivity of the EDSS to change.[14] It appears to be a promising tool for clinical trials in MS. Its relevance to MS rehabilitation remains to be evaluated.

The EDSS gives a global picture of neurologic impairments in a given individual patient, but it is not very useful for the evaluation of treatments focused on a specific impairment. Validated generic scales are usually preferred, such as the Ashworth scale for spasticity. The Functional Independence Measure (FIM™) has been established as the ‘gold standard’ for the evaluation of disability in rehabilitation settings, at least in North America. More precisely, the FIM™ is a measure of dependence, which correlates well with burden of care in MS patients.[15] In general, the FIM™ is sensitive to change for in-patient rehabilitation, and this appears to be true in particular for the MS population.[10–12,16] Its performance in an out-patient setting is not well established. Since MS patients receive most of their care in out-patient clinics or offices, this potentially is a significant issue. The Rehabilitation Institute of Chicago Functional Assessment Scale (RIC-FAS) has been used in a prospective study of out-patient rehabilitation in MS.[17] The Functional Assessment Measure (FAM) is composed of 12 items added to the 18 items of the FIM™, in an effort to improve the performance of the FIM™ in patients with traumatic brain injury and stroke. Hobart et al. recently evaluated the performance of the ‘FIM+FAM’ in 149 neurorehabilitation in-patients (including 64 MS patients) and found no significant difference with the psychometric performance of the FIM™ alone.[16]

Several authors have used either the Short-Form-36 (SF-36)[18,19] or the Sickness Impact Profile (SIP)[20] to evaluate the results of rehabilitative interventions in MS.
Freeman et al. reported that the SF-36 may not be the most sensitive measure of subjective health status in a rehabilitation setting, owing to marked floor effect in several subscales. More recently, the same team questioned the validity and usefulness of adding disease-specific items to the SF-36 after observing no change in measurement properties between the SF-36 and the MSQOL-54 in 150 patients with MS (44 patients evaluated prospectively for responsiveness). Other MS-specific measures of perceived health status and quality of life are discussed in Chapter 4.

**POTENTIAL INDICATIONS FOR REHABILITATION IN MS**

**Education and prevention**

At any stage of the disease, rehabilitation professionals can teach the patient how to minimize the impact of neurologic impairments on the ability to perform daily activities and to fulfill expected roles. The goal is to prevent complications and progression of functional limitations and to empower a patient, who may often feel frustrated and anxious because of the unpredictable course of the disease. One area of particular interest is the role of exercise, which traditionally was not strongly recommended, or was even avoided, in MS out of fear of making symptoms worse or triggering a relapse. Results from a few studies have helped in the understanding of the role of physical deconditioning in functional limitations and of the potential benefits of exercise. A controlled study of aerobic exercise in 46 MS patients showed improvement in fitness, psychological status (Profile of Mood States), perceived health status (SIP), and fatigue (Fatigue Severity Scale) in the exercise group compared with the non-exercise group.

**Symptom management**

The management of MS symptoms has become an increasingly complex matter. The necessity of monitoring disease activity and managing disease-modifying therapies decreases the time that neurologists can devote to the planning and adjustment of symptomatic therapies. The multiplicity of factors contributing to symptoms, the interaction of consequences from different symptoms, and the frequent necessity of combining medications and interventions make the rehabilitation approach particularly relevant to this matter when simple first-line treatments fail to provide adequate relief. For example, a comprehensive fatigue management program should include aerobic exercise and education on energy effectiveness strategies.

**Reduction or stabilization of chronic activity limitations**

A basic example of this type of indication is a referral to physical therapy to improve gait performance, through exercises and use of technical aids. Recent controlled studies suggest that more comprehensive interventions are also effective. Di Fabio et al. reported a significant decrease in symptom frequency (MS-Related Symptom Checklist) and level of fatigue at 1 year in 20 patients receiving weekly outpatient rehabilitation, compared with 26 patients on a waiting list. There also was a slower decline of disability (RIC-
FAS) in the treatment group (all patients were diagnosed with progressive MS). In a randomized, single-blind, controlled study of a 3-week inpatient rehabilitation program (treatment group, n=27) versus home exercises (control group, n=23), Solari et al. observed that disability (FIM™) improved in the treatment group and worsened in the control group on average. There also was greater improvement of perceived health status (SF-36) in the treatment group. Approximately 20% of patients in each group were diagnosed with relapsing-remitting MS. Freeman et al. compared the outcome at 6 weeks in 32 patients receiving in-patient rehabilitation and 34 patients on a waiting list (all patients had progressive MS). Changes in FIM™ motor domain scores and London Handicap Scale scores were significantly greater in the treatment group. A 1-year uncontrolled longitudinal study in the same institution suggested that improvement of disability, handicap, psychological status, and perceived physical health status achieved after in-patient rehabilitation in 50 patients with progressive MS was sustained for at least 6 months despite worsening of impairments. Another uncontrolled outcomes study in an in-patient setting (n=28) showed that improvement was most dramatic for ambulation.

Recovery after acute worsening of disability

Acute loss of function can occur secondary to disease activity (i.e. a relapse) or an intercurrent health event (e.g. infection, surgery). A common conception of rehabilitation, reinforced by the reimbursement guidelines of third-party payers in some countries, favors the concentration of interventions on a relatively short period of time, in response to an acute injury or disease process. MS relapses fit into this category, but, for reasons outlined above, rest was recommended in most cases. Some degree of recovery is usually expected after acute worsening, possibly enhanced or accelerated by the use of intravenous corticosteroids. However, a recent uncontrolled prospective study of 24 patients treated with intravenous methylprednisolone for a relapse of MS showed that significant improvement of activity limitations may not be associated with improvement of perceived health status or frequency of occurrence of symptoms. On the basis of these findings, a randomized trial of outpatient rehabilitation after MS relapses was initiated and is currently in progress.

IMPLICATIONS FOR CLINICAL PRACTICE

Many questions remain to be answered about the use of rehabilitation in MS. As is usual in health care, there may not be a single ‘good answer’ to any of these questions. Cultural preferences, the structure of the health-care system, the availability of services, and the experience and beliefs of health-care professionals will inevitably and diversely influence the way in which rehabilitation is utilized. It is not possible to present here a catalog of available interventions and indications. Nevertheless, a few general recommendations can be formulated, based on the information presented above.

Rehabilitation, as any other treatment, is not likely to be successful if it is used as a ‘last resort’, after all other interventions have failed, or without a precise strategy. Instead, rehabilitation should be integrated into the plan of care, particularly for symptom
management and when the patient reports limitation in his or her ability to carry out daily activities. The patient is more likely to be motivated and compliant with rehabilitative interventions if he or she feels that the prescribing physician is supportive and inquires about outcomes.

It is important to educate patients early in the course of the disease about the importance of exercising at home to avoid deconditioning. When the patient finds it difficult to initiate an exercise routine (e.g. because of worsening of symptoms with exertion), a referral to physical therapy should be considered.

Single evaluations or short-term interventions by a rehabilitation professional to address a focused problem are often useful (e.g. to adapt and teach how to use a walking aid, to design an orthosis for an upper extremity). When focused intervention fails, it is necessary to analyse the reasons for failure before ‘giving up’ on rehabilitation, based on information given by the patient and on feedback from the therapist. For example, if it is very difficult to fit an ankle-foot orthosis on a very spastic lower extremity, increasing antispasticity medications or performing botulinum toxin injections may solve the problem.

When the presenting problem is complex or when rapid and severe loss of function has occurred, more intensive multidisciplinary outpatient or even in-patient rehabilitative interventions are usually indicated, although the exact timing, duration, and content are not clearly defined.

Studies discussed above support the use of rehabilitation in the progressive phase of the disease, although the level of evidence is not as strong as for drug therapies. However, one should not wait until disability is severe to initiate rehabilitative interventions (as is true for disease-modifying therapies).

**CONCLUSIONS**

There is an increasing body of evidence suggesting that rehabilitative interventions are indeed effective in MS. Disease-modifying therapies (e.g. interferon beta, glatiramer acetate) do not improve existing symptoms and functional limitations and, unfortunately, do not stop all disease activity. Thus, these therapies have not obviated the need for rehabilitative interventions. Instead, the underlying philosophy supporting early interventions to prevent progression of disability over time can be applied to rehabilitation, allowing a more comprehensive approach to the disease and its consequences from the time of the diagnosis. Further research work is needed to determine or develop appropriate outcomes measures, gather scientific evidence of the efficacy (and cost-effectiveness) of rehabilitation protocols, compare different types of interventions, determine subgroups of patients most likely to benefit from intensive rehabilitation, and define the best timing of interventions.
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