Emerging Trends in Diagnosis and Treatment of Rheumatoid Arthritis

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KEYWORDS
- Rheumatoid arthritis  
- Juvenile rheumatoid arthritis  
- Disease-modifying antirheumatic drugs  
- Synovitis  
- Elderly onset rheumatoid arthritis

EPIDEMIOLOGY

Rheumatoid arthritis (RA) is a chronic inflammatory disease with multiple comorbidities and is a cause of disability for many children and adults worldwide. The role of primary care is essential in early diagnosis and treatment of this debilitating disease. The prevalence of RA is estimated to be 0.8% globally, with women 2 to 4 times as likely as men to develop the disease. The incidence of RA in the United States is estimated at 25 per 100,000 men and 54 per 100,000 women, affecting approximately 2.1 million people.1,2 Age at onset is usually between 30 and 50 years of age; however, juvenile RA and elderly onset RA (over age 65) also occur.1,2

In the United States, arthritis and other rheumatic conditions are the leading cause of disability. Approximately 39% of adults with arthritis report limitations in their physical activities because of their condition. Patients with RA are more than 7 times as likely to have greater than moderate disability as their sex- or age-matched counterparts. In addition, RA disability is linked with increased mortality. The Health Assessment Questionnaire (HAQ) disability index used to follow RA patients found that a change of 1 standard deviation in the HAQ correlates to an odds ratio for mortality of 2.3.2 After 10 to 20 years of having the disease, as many as 80% show a compromise of their activities of daily living. Beginning early treatment can reduce the potential for disability by more than 60%.3

In economic terms, RA accounts for an estimated 250,000 hospitalizations and 9 million physician office visits annually. Within 2 to 3 years of diagnosis, 20% to 30%
of those with RA become permanently disabled from work because of pain, impaired physical function, and transportation difficulties.\textsuperscript{1,2} The total costs of arthritis and other rheumatologic conditions in the United States in 2003 was $128 billion ($80.8 billion from direct medical costs and $47 billion from indirect costs such as lost earnings). In addition, a reduced life expectancy of 5 to 15 years can occur.\textsuperscript{3}

**RISK FACTORS**

Several environmental and genetic factors that potentially contribute to increased risk of developing RA have been identified. There are no definitive risk factors.

Environmental factors include hormonal exposure, tobacco use, microbial exposure, smoking, and consumption of more than 3 cups of decaffeinated coffee daily.\textsuperscript{1,4} Among these, tobacco use has the most consistent evidence for an association.\textsuperscript{4}

Genetic factors include female gender, positive family history, older age, and the HLA genotype.\textsuperscript{1,4} In monozygotic twins, the concordance rate for the development of RA is more than 30%.\textsuperscript{1} Siblings of patients with the disease are 2 to 4 times more likely to develop the disease than persons who are not related.\textsuperscript{3} Among whites who have RA, 80% express the HLA-DR1 or HLA-DR4 subtypes.\textsuperscript{1}

Risk of RA is reduced through high vitamin D intake, tea consumption, use of oral contraceptives, and with breast-feeding.\textsuperscript{1} Women who have never given birth seem to have a slight to moderate risk of developing RA, and the evidence is mixed regarding an association between RA and hormone replacement therapy.\textsuperscript{1}

**PATHOPHYSIOLOGY**

The pathophysiology of RA essentially remains only partially understood. A complicated interaction between environmental and genetic factors eventually results in the onset of disease. A viral infection or other biologic factor can initiate an abnormal autoimmune inflammatory response in persons who are genetically predisposed to RA. Where chronic inflammation exists in these cases of RA, there is an imbalance among the mediators controlling the system’s response, resulting in eventual damage to cartilage and bone.\textsuperscript{5} The pathophysiology of RA originates with inflammation of the synovium at any joint location, possibly triggered by the presentation of an antigen, autoantigen, or athrogenic peptide to the immune system. It appears that the subsequent cascade of inflammatory responses leads to proliferation of synovial macrophages, fibroblasts, and chondrocytes in the articular cartilage. These cells secrete enzymes that degrade proteoglycans and collagen, which eventually precipitate synovial tissue destruction.\textsuperscript{5} Further infiltration by lymphocytes and other inflammatory cells occurs and is accompanied by angiogenesis in the synovium, causing irregular regrowth of the synovial tissue and eventually forming invasive pannus tissue. This process stimulates the increased activity of osteoclasts, resulting in further inflammation, leading to more cartilage destruction and the characteristic bony erosion of RA (Fig. 1).\textsuperscript{1} Continued ongoing release of inflammatory mediators along with interleukins, tumor necrosis factor $\alpha$ (TNF$\alpha$), cytokines, and proteinases, also contributes to the development of systemic symptoms and the extra-articular manifestations of RA.\textsuperscript{1,5} There is suspected to be a “shared epitope,” possibly derived from the disease-associated HLA-DR4/1 allele that is initially presented by an antigen-presenting cell to the T cell as a self-antigen.\textsuperscript{6} Later in life, these T cells could be activated by cross-reactive antigens that display the shared epitope, leading to the inflammatory cascade.\textsuperscript{6} Multiple infectious agents are known to possess potentially cross-reactive peptides so that possible reactivation of RA by these common and ubiquitous organisms might occur.\textsuperscript{6}
Research continues to elucidate the role of macrophages and their cytokines in the synovitis of RA and to decipher the mechanisms of the apparent autonomous and aggressive behavior of fibroblast-like synoviocytes. Greater understanding of these elusive issues could have a significant impact on the therapeutic approach to RA.
DIAGNOSIS

No single test confirms the diagnosis of RA. Diagnosis is largely based on clinical findings and patient history, which is challenging because the symptoms are similar to many other potential causes of joint inflammation and pain. There are several tests that can be used to increase diagnostic probability and monitor disease progression. It is imperative that a diagnosis be established as early as possible, because a delay as much as 4 to 6 months in initiation of treatment could result in long-term joint injury.

In 1987, the American College of Rheumatology (ACR), in conjunction with the American Rheumatism Association, established 7 diagnostic criteria to aid in the clinical diagnosis of RA. These criteria are also used to define RA in epidemiologic studies. Any patient who presents with at least 4 of the listed criteria for 6 weeks or longer is considered to have RA (Table 1). Early RA is the classification of disease that is diagnosed within 6 months of symptom onset. There is considerable focus in this area because early treatment has been demonstrated to have a positive impact on disease progression and prognosis.

Efficient diagnosis of RA requires vigilant attention to the patient’s medical history. Signs of early synovitis in the absence of obvious joint deformity might be uncovered by the squeeze test of the metacarpophalangeal (MCP) joints or the metatarsophalangeal (MTP) joints. A key sign of RA at the time of the onset is symmetric joint swelling.

### Table 1
1987 Criteria for the classification of acute arthritis of RA

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 h before maximal improvement</td>
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<tr>
<td>Arthritis of 3 or more joint areas</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints</td>
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<tr>
<td>Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint</td>
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<tr>
<td>Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)</td>
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<tr>
<td>Rheumatoid nodules</td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician</td>
</tr>
<tr>
<td>Serum RF</td>
<td>Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in &lt;5% of normal control subjects</td>
</tr>
<tr>
<td>Radiographic changes</td>
<td>Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (ostearthritis changes alone do not qualify)</td>
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</table>

For classification purposes, a patient shall be said to have RA if he or she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made.

**Abbreviations:** MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; RF, rheumatoid factor.

with local heat and erythema. In the early phase there is usually no clinical evidence of joint disease and no evidence of cartilage or bone loss on plain radiographs. The physician or diagnostic clinician also needs to evaluate the patient for extra-articular features of RA, which will determine the potential course of the disease and guide treatment options.3

SYMPTOMS

Patients with RA typically present with pain and stiffness in multiple joints. However, one-third of patients have initial symptoms at a solitary location. The most common presentation of RA is that of an insidious onset of morning stiffness or diffuse aching that lasts for at least 1 hour or longer, followed by involvement of the small peripheral joints such as the MCP, MTP, and proximal interphalangeal (PIP).5 It is not unusual for the larger joints to be affected first. Symptoms usually occur over weeks to months, yet in 15% of patients onset can occur more rapidly over days to weeks. Most patients have accompanying prodromal symptoms of weakness, fatigue, or anorexia. In 8% to 15% of patients, symptoms begin soon after a trigger event, such as a viral illness.1 Characterizing the pain often helps distinguish RA from other forms of arthritis, as does a positive family history for RA. Determination of disability and ability to perform activities of daily living facilitates monitoring the effects of treatment.

The joints that are usually affected are those with the highest ratio of synovium to articular cartilage, such as the wrist, PIP, and MCP joints. The distal interphalangeal and sacroiliac joints are usually not affected. Affected joints are usually warm, tender to palpation, and boggy. There might be increased blood flow to the inflamed area with subsequent symptoms of puffy hands by patients.1 Joint swelling is usually symmetric and, with tenderness on palpation, is one of the key signs of RA.2 Beyond the joints, axillary, cervical, or epitrochlear lymphadenopathy may be noted. Muscles in close proximity to the inflamed joints often atrophy. Weakness is commonly out of proportion to the pain on examination. Joints are often held in flexion by patients to minimize painful distension of the joint capsules. Clinically, one may also appreciate decreased grip strength from tendon damage, tendon rupture in the wrist and fingers, decreased range of motion in the shoulders from synovitis and anterior effusions, and heel pain with antalgia from talus involvement. The hip is usually affected later, and hip involvement is usually rare.3

LABORATORY TESTS

Indications for testing include a history of persistent joint pain with early morning stiffness. Baseline laboratory tests are recommended and include a complete blood cell count with differential, rheumatoid factor (RF), and erythrocyte sedimentation rate (ESR) greater than 30 mm/h or C-reactive protein (CRP) greater than 0.7 pg/mL. Renal and hepatic function parameters are also recommended because findings guide medication choices, and monitoring should continue throughout the course of treatment.1 RF is an immune complex consisting of an autoantibody and IgG. A positive RF is not diagnostic of RA. Incidence of positivity increases with duration of disease (ie, 6–12 months), and with age. Of patients with RA, 20% may never have a positive RF, approximately 5% to 10% of healthy individuals are RF positive, and RF might also be positive in many other disease processes.1,8 Other laboratory tests that aid in the diagnosis of RA are as follows.
**Anticyclic Citrullinated Peptide IgG Antibody**

When positive, this test supports the diagnosis of RA. It is produced in the first stage of RA pathogenesis at the site of joint inflammation. During this process, citrullination of synovial antigens occurs, involving several synovial proteins. The antibody, anticyclic citrullinated peptide (anti-CCP), is secreted by B cells, which are present in the synovium and bone marrow of anti-CCP–positive patients. Anti-CCP is more than 98% specific, and sensitivity increases when used in combination with RF. It might be negative during the course of early disease. One study found the anti-CCP antibody to be associated with some parameters of disease activity and severity, being more specific in patients with advanced RA with a mean duration of 9.8 years.

**Arthrocentesis (Joint Aspiration)**

This option is a useful one if the diagnosis is uncertain. Arthrocentesis helps to differentiate crystal-induced arthropathies and septic arthritis. In RA, fluid is usually straw-colored, and fibrin flecks are often seen; clotting may occur at room temperature; a white blood cell count of 5 to 25,000 per mm$^3$ is common, with a differential count of 85% polymorphonuclear leukocytes. Findings also include no crystals, low glucose levels, and negative cultures. Synovial fluid evaluation for anti-CCP has been suggested by a study to be a useful tool to assist with diagnosis of RA in cases of undifferentiated arthritis. The presence of anti-CCP in synovial fluid is a high risk factor for progression to RA. Some patients may have negative serum levels when the joint fluid is positive.

**Plain Film Radiography**

Plain film radiography remains the preferred method for initial examination to evaluate bone and soft tissue changes. Although a definite diagnosis might not be possible, even subtle findings and evaluation of soft tissue changes can facilitate a differential diagnosis. Depending on the severity of the disease, radiography can reveal soft tissue swelling and joint space narrowing as a consequence of cartilage thinning, or joint space widening as an indication of joint effusion. Juxta-articular osteoporosis is also one of the nonspecific changes that can confirm the clinical impression of an inflammatory process.

**EXTRA-ARTICULAR SIGNS AND SYMPTOMS**

Although well described, the prevalence and incidence of many extra-articular features of RA are not accurately known. It is also difficult to separate these findings into those that arise as a complication of the disease, its treatment, or an immunologic disease associated with RA but occurring in isolation. Pathogenesis of extra-articular signs varies between patients and anatomic location of the findings, but it is reasonable to conclude that any component in the autoimmune pathogenesis of RA is associated. Extra-articular disease has a significant influence on mortality from RA. Infection is the leading cause of death (25%), followed by cardiac and pulmonary disease (18%), with renal and gastrointestinal disease being equal but lower in frequency (10%). Other manifestations of extra-articular disease are outlined in Box 1.

**JUVENILE RA**

Children are not exempt from the disease of RA. The true incidence is unknown. A 2007 study by the Centers for Disease Control and Prevention estimates that
294,000 children in the United States younger than of 18 years (1 in 250) have been diagnosed with arthritis or another rheumatologic condition.\textsuperscript{13} The most common form of childhood arthritis is juvenile rheumatoid arthritis (JRA).\textsuperscript{13} The American Rheumatism Association acknowledges 3 clinical classifications of JRA: systemic-onset disease (10%–20%), polyarticular disease (20%–40%), and pauciarticular disease (30%–40%).\textsuperscript{12} Clinical symptoms are varied in each category and each type has its own unique presentation, clinical course, and immunogenetic association. The polyarticular and pauciarticular forms contain more than 1 subgroup (Polyarticular: RF-negative and RF-positive disease; Pauciarticular: early childhood onset and late childhood onset).\textsuperscript{12} Recognition of the subgroups is important for the appropriate diagnosis and treatment of the younger JRA patient.\textsuperscript{12} One feature that all JRA patients have in common is the presence of chronic synovitis.

Once treatment is initiated, children should be encouraged to lead full lives as much as possible. Occasionally, some may be disabled or too ill to be self-sufficient and require inpatient rehabilitation. Support and counseling is necessary to prevent educational deficits, provide support of career plans, and in general to prevent children from thinking of themselves as people with disability.\textsuperscript{12}

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**Box 1**

**Extra-articular manifestations of RA**

- Rheumatoid nodules of varying size and consistency are found in up to 25% of patients. Location: extensor area of the forearm (common), internal organs (rare). Complications: gangrene and ulcer formation.
- Hematologic: normocytic, normochromic anemia; thrombocytosis or thrombocytopenia; lymphadenopathy.
- Felty syndrome: the association of RA with leukopenia and splenomegaly
- Vasculitis: may involve eyes, brain, skin, renal, cardiovascular, and gastrointestinal (GI) tract
- Pulmonary: pleural effusions, pulmonary nodules, interstitial lung disease, bronchiolitis obliterans with organizing pneumonia; complications of treatment with disease-modifying antirheumatic drugs (DMARDs)
- Cardiac: pericardial effusions; valvular lesions; cardiac manifestations from systemic influences of RA such as serositis, amyloidosis, vasculitis, conduction abnormalities secondary to nodule formation
- Renal: microalbuminuria (correlates with disease activity); mesangial glomerulonephritis; (nephritic syndrome); nephrotoxicity secondary to DMARDs
- Ophthalmologic: keratoconjunctivitis sicca or secondary Sjögren syndrome; episcleritis and scleritis (prompt treatment necessary to avert vision loss); effect of drug therapy—risk of retinopathy with hydroxychloroquine requires ongoing surveillance
- Neurologic: mononeuritis multiplex and central nervous system features including seizures, aseptic meningitis, and stroke secondary to vasculitis. Entrapment neuropathies via nerve impingement associated with subluxation of the atlantoaxial joint, amyloid deposits, or nodules
- Musculoskeletal: osteoporosis and fractures caused by disease process and corticosteroid treatment. Muscular weakness of varying etiology
- Amyloidosis: found in 21% of patients in postmortem studies of patients with RA

Currently 75% to 80% of children with JRA are expected to survive the disease without disability.12 Those at greatest risk for joint destruction are those with systemic-onset JRA and RF-positive polyarthritis. Careful follow-up is necessary for all JRA patients throughout the course of active disease, and there is always the possibility of unexpected recurrences even after years of remission.12 However, the future remains positive for most affected children.

ELDERLY ONSET RA

Elderly onset rheumatoid arthritis (EORA) includes patients who develop RA between the age of 60 and 65 years. The prevalence is approximately 2% in this age group.14 Symptoms of EORA are different from those in younger patients, and 3 subsets have been identified14:

1. Patients who have classic RA signs and symptoms with clinical onset similar to that in patients who develop seropositive RA at an earlier age. These patients have high levels of disease activity, and aggressive treatment is required.14
2. Patients presenting with symmetric arthritis associated with Sjögren syndrome. The synovitis is less severe and more readily controlled than in the first subset.14
3. Patients have a clinical picture that mimics polymyalgia rheumatica. RF is negative in the vast majority of cases but high levels of acute phase reactants are present. Arthritis in this subset of patients is usually well controlled with low-dose corticosteroid treatment; joint damage and radiological changes are less severe than in the other forms.14

EORA occurs in a balanced female to male ratio of about 1.5:1 to 2:1.14 Poorer functional outcomes have been noted in patients who score high on the HAQ and who have RF seropositivity.14 However, overall, EORA patients are more likely to experience clinical remission (odds ratio [OR] = 2.99) with a much higher remission rate in the seronegative EORA group than all other groups (including the younger seronegative RA group). It should also be noted that continuous use of corticosteroids for more than 3 months in EORA patients has been associated with joint erosion (OR = 4.09).

Diagnosis of EORA requires early and appropriate initiation of DMARD therapy no different from that given to younger RA patients. The higher remission rate in seronegative EORA patients implies that therapy might be given for a shorter duration than for seropositive patients. Awareness should be heightened regarding the increased risk of adverse events associated with RA treatments in the elderly patient. Careful follow-up and prudent use of the appropriate medications is extremely important.14

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RA is extensive. Most patients present with symptoms in common with RA. A careful clinical history, followed by a meticulous physical examination, and acquisition of prudent laboratory and imaging studies is mandatory to initiate the diagnostic process.14 Differential diagnoses include but are not limited to the conditions listed in Table 2.1,8,14 Potential causes of infectious arthritis include hepatitis B and C, human immunodeficiency virus, and other bacterial infections.

Included in the differential diagnosis for EORA is remitting seronegative symmetric synovitis with pitting edema syndrome (also known as RS3PE syndrome).14 This condition historically develops abruptly in elderly patients with the finding of edematous symmetric arthritis involving the distal extremities, specifically hands and wrists and/or feet and ankles. The edema on the dorsal aspect of the involved areas is
caused by extensor tenosynovitis. There is no development of bony erosions and RF is negative. Patients with the condition demonstrate a satisfactory response to corticosteroids, and the prognosis is excellent. It is still debatable as to whether this syndrome is part of the spectrum of RA or a completely different medical condition. Many of the same findings can occur in patients with polymyalgia rheumatica, other inflammatory arthropathies, and malignancies involving the hematologic system as well as solid tumors.14

**TREATMENT**

Early treatment reduces the rate of disease progression and is therefore recommended to be initiated during the early phase of the disease.1 Many patients experience RA symptoms for an average of 9 to 12 months before a diagnosis is made.2 The American College of Rheumatology Subcommittee on Rheumatoid Arthritis (ACRSRA) recommends that patients with suspected RA be referred to a rheumatologist within 3 months of presentation to confirm the diagnosis and initiate treatment. The National Guideline Clearinghouse also supports specialist referral and recommends urgent referral if the small joints of the hands or feet are affected, more than 1 joint is affected, or there has been a delay of 3 months or more between the onset of symptoms and seeking of medical advice.15 Therapeutic goals must be discussed with the patient and should include preservation of quality of life, reducing pain, minimizing inflammation, protecting the joints, and reducing RA complications.1

Patients with mild disease and normal radiograph joint findings can begin treatment with hydroxychloroquine, sulfasalazine, minocycline, or methotrexate.1,16 Fig. 2 contains an algorithm that simplifies the approach to treatment.1 Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used alone, as they do not change the disease course. Precautions should be observed with NSAID use, as RA patients are almost twice as likely as osteoarthritis patients to have serious complications from NSAID use.

Cyclooxygenase-2 (COX-2) selective NSAIDs are equally as effective as nonselective NSAIDs for reducing pain and inflammation as well as improving joint function. These agents should be used with caution in renal and geriatric patients.1 There is also ongoing concern of the cardiovascular safety of COX-2 NSAIDs. Therefore, careful patient selection is imperative. There have been long-term studies, such as the CLASS study (Celecoxib Long-term Arthritis Safety Study), which showed a reduction in adverse upper GI events in patients taking celecoxib alone without low-dose aspirin versus NSAIDs alone or COX-1 versus COX-2 NSAIDs with low-dose aspirin.17 Owing to the cardiac benefit of low-dose aspirin for patients with moderate or high

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### Table 2

<table>
<thead>
<tr>
<th>Connective tissue diseases</th>
<th>Fibromyalgia</th>
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<tr>
<td>Other forms of arthritis (infectious, reactive, viral, osteoarthritis)</td>
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<tr>
<td>Seronegative spondyloarthropathies</td>
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<tr>
<td>Sarcoidosis</td>
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<td>Hemochromatosis</td>
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<td>Infectious carditis</td>
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<tr>
<td>Crystalline arthropathy (polyarticular gout, pseudogout, chronic calcium pyrophosphate arthropathy)</td>
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<tr>
<td>Acute rheumatic fever</td>
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<td>Thyroid disease</td>
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<td>Still disease</td>
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<td>Polymyalgia rheumatica</td>
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<tr>
<td>Malignancy-related arthritis</td>
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<td>Hypertrophic osteoarthropathy</td>
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</table>
Fig 2. Treatment algorithm for RA. aThe following laboratory tests should be performed before methotrexate therapy begins, every 2 weeks for 6 weeks, then, if normal, every 2 months: complete blood count with differential, platelets, aspartate transaminase levels, albumin levels, and creatinine levels. When starting methotrexate add 1 mg oral folic acid per day to decrease side effects, and caution the patient to avoid alcohol. bWhen adding another DMARD to methotrexate, decrease the dosage of methotrexate to 10 to 15 mg once per week. (Reprinted from Rindfleisch JA, D Muller. Diagnosis and management of rheumatoid arthritis. Am Fam Physician 2005;72(6):1042; with permission.)

cardiovascular risk (Framingham scores >10%), a reasonable and proven strategy is to use a nonselective NSAID in combination with misoprostol or a proton pump inhibitor, instead of celecoxib, for patients on low-dose aspirin therapy who are at high risk for gastropathy.18

Glucocorticoids at dosages of less than 10 mg of prednisone daily are also highly effective to treat RA pain and stiffness, and can slow joint damage. Because of the multiple adverse effects of steroid use, dosages should be kept to the lowest needed
to achieve therapeutic benefit. When discontinuing glucocorticoid therapy, a slow
taper is recommended over approximately 1 month. In addition, recent guidelines
by the American Association of Clinical Endocrinology recommend supplements of
1500 mg of calcium and 800 IU of Vitamin D3 daily for patients receiving glucocorticoid
therapy and bisphosphonate therapy for all adult women requiring more than 7.5 mg of
prednisone or its equivalent for over 3 weeks. When a single joint contributes to
disability, intra-articular glucocorticoids are a safe, yet temporary option. Intra-artic-
ular injections can also be used as bridge therapy until DMARDs become effective,
which has the potential to take several months. Infectious causes should be ruled
out before administering an injection.

The recently published 2008 ACR guidelines for management of RA recommend
using disease duration as a guide for treatment. There are 3 categories of disease
duration: less than 6 months (considered to be equivalent to early disease), 6 to 24
months (considered to be equivalent to intermediate disease duration), and more
than 24 months (considered to be long or longer disease duration). For biologic ther-
apies, early disease is further subdivided by disease duration of less than 3 months or
3 to 6 months, when disease activity is high. Most RA treatment plans include an
NSAID for pain control with careful use of oral or intra-articular glucocorticoids and
the initiation of a DMARD. Unlike past regimens, the ACR now recommends that
DMARDs be initiated early in the disease to reduce progression. Treatment proto-
cols have been modified as a result of research demonstrating that joint damage
begins early in RA, DMARDs have significant benefits when begun early, DMARD
benefits are enhanced when used in combination, and new DMARDs are available
with good therapeutic benefits.

The nonbiologic DMARDs addressed in the 2008 ACR recommendations are hydrox-
ychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine. The biologic
DMARDs included are abatacept, adalimumab, etanercept, infliximab, and rituximab.
The remaining DMARDs are not included because they were not subjected to a system-
atic review of the literature due to their infrequent use (<5% of RA patients, eg, anakinra)
and/or the high incidence of adverse events when they are used (cyclophosphamide,
D-penicillamine, staphylococcal immunoabsorption column, tacrolimus). Abatacept
and rituximab are the only 2 DMARDs that received an evidence-based recommenda-
tion (Level of Evidence for use: A). Disease activity (low, moderate, or high) and
prognostic features are included with disease duration in evidence-based recommend-
dations. Prognosis was defined as poor if patients had active disease with multiple
tender, swollen joints, elevated RF, elevated anti-CCP antibodies, elevated ESR or
CRP, and evidence of radiographic erosions. Important predictors for a worse
outcome include the presence of any of the aforementioned risk factors and poor
physical functioning.

DMARDs should be considered for all RA patients, regardless of stage. The DMARD
agent of choice depends on age, compliance, disease severity, physician comfort,
and comorbidities. Increasing evidence shows that DMARD combinations can be
more effective than single regimens. Regarding the nonbiologic DMARDs, the ACR
recommends the initiation of methotrexate or leflunomide therapy for patients with
all disease durations and all degrees of disease activity. Hydroxychloroquine or min-
ocycline monotherapy is recommended for patients without poor prognostic features,
with low disease activity and with disease duration of less than 24 months. Sulfasala-
zine monotherapy is recommended for patients with all disease durations without poor
prognostic features and with all degrees of disease activity.

Those with radiographic joint findings and more severe disease should begin dual
nonbiologic DMARD combination therapy. Methotrexate plus hydroxychloroquine is
recommended for patients with moderate to high disease activity, regardless of duration or presence of poor prognostic features. Methotrexate plus sulfasalazine is recommended in patients with all durations if they have high disease activity and poor prognostic features. Hydroxychloroquine plus sulfasalazine is recommended only in patients with 6 to 24 months of disease duration and with high disease activity yet without poor prognostic features.16

Triple DMARD combination therapy of sulfasalazine plus hydroxychloroquine plus methotrexate is recommended for all patients with poor prognostic features and moderate to high levels of disease activity, regardless of duration of disease.

Regarding biologic DMARDs (anti-TNFα agents), the ACR recommendations are divided into those with RA for less than 6 months and those with RA for longer than 6 months. The anti-TNFα agents are efficacious in improving disease activity, function, and quality of life when used alone or in combination with methotrexate or other nonbiologic DMARDs. Recommendations for the use of anti-TNFα agents with methotrexate are limited only to patients with early RA who have never received DMARDs, have had high disease activity for less than 3 months, a poor prognosis, and without cost restrictions. In those with longer RA duration, the ACR recommends the use of anti-TNFα agents in patients for whom methotrexate monotherapy or combination therapy with nonbiologic DMARDs was inadequate.16

The risk of death from infection in patients with RA is approximately 6 to 9 times greater than in non-RA populations.20 Risk factors for infections include corticosteroid therapy, comorbidities, skin breakdown, joint surgery, and established RA. Nonbiologic and biologic DMARDs and TNF antagonists may place patients at greater risk of infection. Therefore, when a fever presents in an RA patient, sepsis should be strongly considered and a rheumatologist should be consulted early during the initiation of care. However, patients on a DMARD and steroids may not mount a typical febrile response; therefore a thorough clinical examination is necessary, including a thorough joint examination in which joint pain might be the most significant sign of infection.20

The ACR recommends routine tuberculosis (TB) screening for all patients who are being considered for treatment with biologic DMARDs. This recommendation is based on the evidence of higher incidence of TB cases following the initiation of anti-TNFα therapy. All patients should be asked about their risk factors for TB. A negative TB skin test should not be considered an exclusion of latent TB infection because many RA patients are immunosuppressed. In cases of active or latent TB, anti-TNFα therapy can be started about 1 month after initiating anti-TB therapy with isoniazid.16

Contraindications to DMARD use include active bacterial infection requiring antibiotic therapy, active TB (untreated), active herpes zoster infection, RA-associated pneumonitis, or active life-threatening fungal infections. In addition, the ACR recommends against the use of biologic agents during a severe bacterial or viral upper respiratory infection. Each DMARD has its own monitoring requirements and contraindications that are discussed elsewhere.

Safety ratings vary for use of RA therapies during pregnancy. Methotrexate and leflunomide have been issued a safety rating “X” by the Food and Drug Administration. Safety ratings for other treatments include B for sulfasalazine, C or D for other nonbiologic DMARDs, and B or C for biologic DMARDs.

Several novel therapies have also been studied for RA. Statins (atorvastatin and pravastatin) may have anti-inflammatory properties in the synovium, with an ability to inhibit both the production and actions of CRP.21 Other novel therapies that are being studied for the treatment of RA include hematopoietic stem cell transplantation and
immunoadsorption. Lastly, nonpharmacologic therapies must also be considered in RA treatment. These treatments include physical therapy, occupational therapy, patient education, and nutrition guidance. Moreover, access to a multidisciplinary team is the best approach to improve symptoms, functional outcomes, and reduce the progress of disease in patients with RA.

SUMMARY

RA is an autoimmune disease that is characterized by synovitis, which eventually causes destruction of cartilage and bone. The pathogenesis is still being elucidated by ongoing research, but is generally described by a complicated interaction of genetics and arthrogenic antigens in the environment that interact to precipitate an inflammatory cascade, leading to bone and joint destruction. The course of the disease is unpredictable and usually varies among those who are afflicted. No single laboratory test or physical finding can diagnose RA because it is largely a clinical diagnosis. However, laboratory tests and radiologic findings when combined with the physical examination can help to increase diagnostic accuracy. Primary care physicians should include screening questions during routine visits to increase the early detection of RA. Patients who are diagnosed with RA by primary care physicians should be referred to a rheumatologist expeditiously to limit disease progression as well as to minimize the extra-articular disease involvement. If untreated, the great majority of these patients become disabled. The recent development of DMARDs has had a positive impact on disease progression and patient outcomes. Conversely, their use can be complicated by the development of adverse reactions, which always have the potential to complicate the symptoms of disease. The onset of RA can occur at any point in the life span, so that attention to the history and physical examination is the best means of uncovering this potentially aggressive disease. Nonpharmacologic therapies are also an important component of treatment.

There remain several issues that primarily limit our ability to provide optimal treatment. Access to many therapies continues to be limited by formulary restrictions, the costs of the DMARDs, prior authorization requirements by private insurers (which often include the requirement for inadequate responses to multiple DMARD treatments), and further limitation of the more expensive DMARD therapies to individuals with the most severe and longest duration of disease. Overcoming the barriers to optimal treatment requires the growth of awareness that the disabling and life-threatening elements of RA are comparable with those of many other diseases. Despite the remarkable progress made in delineating the pathogenesis of RA, as well as the development of disease-modifying treatment modalities, many questions remain unanswered and the cure remains elusive.

REFERENCES