Emerging Treatments for Rheumatoid Arthritis:

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**ABSTRACT:** Early treatment with disease-modifying anti-rheumatic drugs (DMARDs)--alone or in combination--can prevent joint damage and minimize disability. Until recently, the DMARDs used predominantly in patients with rheumatoid arthritis had been methotrexate, sulfasalazine, and hydroxychloroquine. Older DMARDs such as gold, d-penicillamine, and azathioprine have fallen out of favor because of their long-term toxicities or modest benefit. Six newer DMARDs--leflunomide, etanercept, infliximab, adalimumab, rituximab, and anakinra--have greatly expanded the current treatment options.

Disease progression in patients with rheumatoid arthritis (RA) frequently leads to joint destruction, physical dysfunction, and reduced quality of life--sometimes culminating in work disability and even premature death. Patients with RA are usually treated with disease-modifying anti-rheumatic drugs (DMARDs) to control arthritis activity. These diverse agents exhibit a broad range of anti-rheumatic properties that reduce joint inflammation and slow the progression of radiologically assessed joint damage.

However, the clinical efficacy of individual DMARDs varies--as does patient response. DMARD therapy, although effective, usually results in partial improvement but not complete remission. Residual disease activity is the rule rather than the exception, which explains the progressive course suffered by most patients with RA. Because joint damage often occurs more rapidly early in the course of the disease, it is best prevented by early intensive DMARD therapy. The extent to which DMARD therapy will improve long-term outcomes of RA is not known. However, the short-term effectiveness observed with newer RA therapies provides hope that long-term improvement is an attainable goal. In this article, we discuss the rationale for early, intensive treatment. In addition, we provide an overview of the major comorbidities associated with RA, and we review current DMARD therapies and their side effects.

**DISEASE BURDEN OF RA**

Uncontrolled RA leads to poor outcomes, which include joint damage, increased costs of medical care, disability, need for joint replacement surgery, and increased mortality. Table 1. The clinical and laboratory parameters of disease that correlate with these outcomes include persistent joint inflammation, presence of serum rheumatoid factor (RF), elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and reduced functional status. Intervention with DMARDs has been shown to improve these clinical and laboratory disease measures, reduce structural damage and physical disability, lower direct medical and nonmedical costs, and enhance quality of life. Whether DMARD therapy improves other important outcomes of RA, such as hospitalization rates and mortality, is not known.

**Structural damage.** Erosive changes occur in 50% to 70% of patients within 2 years of disease onset. Although patterns vary, damage generally accrues more rapidly during the first 5 to 10 years of disease onset. Therefore, patients with early disease or patients with active RA are at high risk for further joint destruction.

It is becoming easier to predict the future development of joint damage in patients with RA. Risk factors for subsequent joint damage and more rapid disease progression include elevated serum RF levels, multiple erosions on x-ray films, metatarsophalangeal (MTP) involvement, more than 3 affected joints, and active disease for more than 3 months. Elevated ESR and the presence of disease-related HLA-DRB1 alleles are variable risk factors for subsequent joint damage.

Thus, we can generally identify patients who have a greater likelihood of a poor prognosis. What is difficult, however, is predicting individual responses to DMARD therapy.

**Disability.** Functional disability often occurs early in RA and usually increases if disease control is inadequate. In early disease, high functional disability scores derived from self-administered health assessment questionnaires are the strongest predictors of future disability.
Functional disability often leads to work disability. In a review of cross-sectional and longitudinal surveys for work disability in patients with RA, an average of 13% of patients became work-disabled after 6 months and 67% became disabled after 15 years. Factors that are predictive of work disability include lower socioeconomic status, physically demanding occupations, elevated ESR, increased joint pain and involved joint counts, more damage evident on radiographs, and reduced functional status. Because RA usually begins in the third or fourth decade of life, such a progressive course translates into substantial income loss during a worker's most productive years.

**Total joint replacement and hospitalization.** RA is responsible for more than 250,000 hospitalizations per year. The most common reason for hospitalization is total joint arthroplasty. In one study, 25% of patients underwent total joint replacement within 22 years of the development of RA. Among patients who underwent a first total joint replacement, about 50% required a second joint replacement procedure 7 years later. The need for joint replacement is predicted by a persistently elevated ESR, poor functional status, and high disease severity.

**Mortality.** Patients with RA may die prematurely. The 5-year survival rate of patients with moderate to severe RA is 40% to 60%. This rate is similar to that of patients who have 3-vessel coronary artery disease or stage IV Hodgkin lymphoma. Among 609 RA patients aged 40 and older, the most common cause of premature death was cardiovascular disease and infection. RA disease severity is independently associated with mortality despite the presence of comorbid disease. Some evidence suggests that effective DMARD therapy prolongs survival. In one study, premature death occurred less frequently in patients with RA who responded to therapy with methotrexate (MTX) than in nonresponders to MTX.

**Economic burden.** RA imposes a significant economic burden on patients and society. The 10-year medical costs for patients with RA average nearly $60,000 (1996 dollars). Costs are highly skewed; annual medical costs for patients in the quartile of worst functional status are 2.5 times those in the best quartile. Furthermore, hospital costs for those with the worst functional status were nearly 7 times those with the best functional status.

The greatest economic burden for patients with RA comes from lost wages, work disability, and difficulty in functioning in the family environment. Families with a work-disabled RA patient, for example, have a 35% lower income than families unaffected by RA. The earnings gap between persons with RA and the healthy population is estimated to be $17.6 billion (1986 dollars).

**EARLY TREATMENT WITH DMARDs**

New knowledge about the radiographic progression of joint damage in RA has had a major impact on therapy for this disease. The onset of radiographic joint damage varies among patients with RA, but it is now known that erosive disease develops in more than 50% within the first 2 years. Once erosive disease develops, it is irreversible with currently available treatment. Thus, DMARD therapy is now being initiated earlier in the disease course to prevent joint damage.

A growing body of evidence indicates that 2- and 3-drug combinations of DMARDs are superior to DMARD monotherapy for improving outcomes in RA. With better understanding of the progression of RA and the availability of more effective drugs, the goals of therapy have been broadened from simply reducing the signs and symptoms of RA to include preventing joint damage. It is hoped that timely and intensive DMARD therapy will improve quality of life, reduce disability, and prolong survival—as well as reduce the economic burden associated with the disease.

**CURRENT RA THERAPY**

**Initial therapy.** Patients with inflammatory arthritis of new onset are usually treated with NSAIDs, and their course is carefully observed over the next several weeks to a few months. Some inflammatory arthritides (eg, viral arthritis) are self-limited and will resolve on their own within 6 weeks. Other patients with inflammatory arthritis may exhibit features of axial disease, and a spondyloarthropathy (eg, ankylosing spondylitis) may ultimately be diagnosed. Extra-articular features point toward a diagnosis other than RA, such as systemic lupus erythematosus. In certain patients, moderate to severe joint pain and swelling may prompt the addition of low-dose corticosteroids (prednisone, 5 to 10 mg/d) to relieve symptoms adequately. Intra-articular corticosteroid injection may help control isolated joint inflammation.

If inflammatory arthritis symptoms do not resolve within 1 to 2 months of onset, the patient probably has persistent disease and will require long-term treatment. At this point, NSAID therapy alone may not be appropriate. Consultation with a rheumatologist is recommended to confirm the diagnosis of RA and weigh therapeutic options.

Most rheumatologists initiate DMARD therapy within 3 to 6 months of RA onset to prevent the development of joint damage. The choice of an initial DMARD depends on the severity of joint disease. For example, mildly active disease can be managed with hydroxychloroquine (HCQ) or...
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sulfasalazine (SSZ). Moderate to severe arthritis activity often calls for MTX therapy, which has proven long-term clinical benefits and tolerability. The primary treatment objectives are to reduce rapidly the signs and symptoms of joint inflammation and to improve functional status. In addition to drug therapy, initial management of RA should include appropriate patient education, a rest and exercise prescription, and physical and occupational therapy.

**DMARD combination versus monotherapy.** Complete resolution of RA symptoms occurs in fewer than 20% of patients treated with a single DMARD. Therefore, rheumatologists increasingly rely on 2- or 3-drug DMARD combinations to obtain superior clinical responses. Several trials have shown that certain DMARD combinations have greater clinical efficacy than DMARD monotherapy. Moreover, in short-term studies, most combination regimens have acceptable levels of drug toxicity. MTX is used as a first-line agent in the treatment of RA and is the anchor drug of most DMARD combinations because of its proven efficacy and tolerability. In one study, patients who had RA for less than 1 year and who were treated with a combination of MTX, SSZ, HCQ, and prednisolone experienced 2-year remission rates of 40%, compared with 18% for patients receiving SSZ or MTX alone. Remission rates remained higher in the combination group at 5-year follow-up, but the differences between the combination therapy and monotherapy groups no longer reached statistical significance. Rates of radiographic disease progression were also significantly lower in the group receiving combination therapy. Improved results have also been reported for MTX combined with cyclosporine, leflunomide, and etanercept or infliximab compared with MTX alone. Although the advantages of combination DMARD therapy are evident, the long-term benefits of this approach are not fully known. Despite the increasing use of combination DMARD therapy, the manner in which these agents are introduced remains controversial. Most rheumatologists use a "step-up" approach in which DMARDs are added sequentially if patients do not respond adequately to the first agent. MTX is usually the first DMARD used, and the dose may be adjusted upward rapidly to a maximally therapeutic dosage (eg, 15 to 20 mg/wk) within 2 to 4 months. Patients with persistent disease activity may then receive a second DMARD to further control the disease. An alternative is to treat initially with a 2- or 3-DMARD combination to maximize initial clinical improvement, but this approach has not yet gained wide acceptance. More clinical studies are needed to determine the advantages and disadvantages of each approach.

**THE NEWER THERAPIES**

Until recently, the DMARDs used predominantly in patients with RA had been MTX, SSZ, and HCQ. Older DMARDs such as gold, d-penicillamine, and azathioprine have fallen out of favor because of their long-term toxicities or modest benefit. Six newer DMARDs--leflunomide, etanercept, infliximab, adalimumab, rituximab, and anakinra--have greatly expanded the current treatment options (Table 2).

Leflunomide is an oral medication that interferes with pyrimidine synthesis and modifies the function of T lymphocytes, macrophages, and neutrophils. Results from clinical trials have shown that joint tenderness and swelling and radiologically assessed progression of joint damage were reduced in patients treated with leflunomide. Etanercept, infliximab, and adalimumab are genetically engineered biologic response modifiers that inhibit the action of tumor necrosis factor a (TNF-a), a pro-inflammatory cytokine that plays a central role in the pathogenesis of joint inflammation. Etanercept, a soluble TNF receptor fusion protein, has been shown to neutralize TNF-a activity and reduce the signs and symptoms of RA. Infliximab, a chimeric monoclonal antibody, and adalimumab, a fully human monoclonal antibody, both bind to TNF-a and have been shown to produce beneficial clinical effects in RA.

All these approved TNF-a inhibitors slow the progression of joint damage in RA when used alone or in combination with MTX. These agents have rapidly emerged as important new therapies for favorably altering the disease course. Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist that resembles the naturally occurring antagonist. By inhibiting IL-1 from engaging the IL-1 receptor, anakinra reduces the inflammatory response. Anakinra produces a significant, albeit modest, improvement in RA symptoms after 52 weeks, compared with placebo. Anakinra is generally well tolerated and has a safety profile similar to that of placebo, except for the frequent occurrence of injection site reactions.

However, the drug's modest clinical effects and dosing requirement of daily injections have limited its use. A DMARD that may emerge shortly as an approved drug for the treatment of RA is rituximab. Commonly used to treat lymphoma, rituximab is currently under investigation for the treatment of RA. Rituximab is a genetically engineered, chimeric anti-CD20 monoclonal antibody that profoundly...
depletes mature B-cell populations but not plasma cells. B cells are believed to play a role in the pathogenesis of RA because they produce autoantibodies and can efficiently activate T cells. Initial studies have shown that when rituximab is used with MTX, it significantly reduces RA symptoms compared with MTX alone. The primary care role

Early evaluation of polyarthritis. Primary care physicians are usually the first to evaluate a patient with early arthritis. RA is typically characterized as a symmetric polyarthritis of the small joints of the hands and feet as well as of the wrists, ankles, knees, elbows, and shoulders. The clinical features of RA at onset are quite variable, and a definitive diagnosis may be difficult to make during the first few months after symptom onset. Common symptoms of RA at presentation are joint pain and swelling, fatigue, and varying degrees of impaired physical function. The course of joint disease at onset can be additive, migratory, or explosive. Often, the patient reports joint stiffness in the morning or after prolonged rest. Joint inflammation and fatigue may impair a patient's ability to work or enjoy leisure activities. Many patients report difficulties in performing routine household chores. Impaired functional status is a poor prognostic sign in patients with newly diagnosed RA.

When you examine a patient with possible joint inflammation, confirm the presence of synovitis. Musculoskeletal pain is common and is not necessarily caused by an inflammatory arthritis. A systematic joint assessment may be performed in 10 minutes or less. To do this, apply pressure firm enough to blanch your fingernail to each joint. This maneuver usually elicits tenderness in an actively inflamed rheumatoid joint. Swelling of the joint capsule may be visible and feel spongy on palpation. The primary objective is to identify overtly swollen and tender joints rather than to detect subtle degrees of synovitis or impaired range of motion.

The laboratory evaluation of a patient with inflammatory polyarthritis should include testing for serum RF and acute phase reactants (ESR, CRP). Fewer than 50% of patients with newly diagnosed RA have a positive test for serum RF, which limits its diagnostic utility. However, patients with an inflammatory arthritis, a positive test for serum RF, and an elevated ESR have at least a 95% probability of meeting diagnostic criteria for RA within 5 years and are at increased risk for erosive, debilitating disease. The anti-cyclic citrullinated peptide (anti-CCP) antibody test is now available. In patients with early inflammatory synovitis, the presence of anti-CCP antibodies may increase specificity for RA. However, the exact role of anti-CCP antibody testing in RA remains to be fully elucidated. Initially, the patient may be treated with an NSAID. Follow up the patient closely over the next 1 to 2 months to monitor disease activity. Consider consulting a rheumatologist if inflammatory arthritis persists. Prompt rheumatologic evaluation may be particularly valuable for patients who have a poor prognosis (decreased function, increased ESR, and positive serum RF). These patients stand to benefit the most from early initiation of DMARD therapy.

Monitoring of patients receiving DMARD therapy. You and the rheumatologist can work together to monitor RA-associated comorbidities and potential treatment toxicity. Rates of cardiovascular disease, GI toxicity, lymphoma, and osteoporosis are higher among patients with RA than among the general population. To help decrease cardiovascular complications in patients with RA, emphasize smoking cessation and treat patients for hypertension and dyslipidemia. Patients at higher risk for GI bleeding while taking NSAIDs or glucocorticoids can be given proton pump inhibitors or misoprostol (200 µg bid) to help reduce this risk. Be alert to the development of unexplained constitutional symptoms, such as fevers, chills, weight loss, anorexia, or lymphadenopathy, and evaluate for infection or lymphoproliferative disease.

A baseline bone mineral density test using dual x-ray absorptiometry (DXA) scanning may identify RA patients at high risk for fracture. Consider a DXA scan for all patients receiving continuous glucocorticoid therapy within the first 3 months of treatment. Conservative interventions that may reduce bone loss include:

• Daily calcium (1500 mg) and vitamin D (800 IU) supplementation.
• Weight-bearing exercise.
• Smoking cessation.
• Minimizing glucocorticoid use.

Monitor RA patients who have evidence of osteopenia or osteoporosis with DXA every 1 to 2 years; institute bisphosphonate therapy if possible. The American College of Rheumatology has established guidelines for appropriate monitoring of toxicity related to anti-rheumatic drugs. Side effects associated with the most commonly used DMARDs and recommendations for appropriate monitoring are shown in Table 3.
Periodic laboratory monitoring is important for early detection of toxicity caused by certain DMARDs. For example, liver function studies and a complete blood cell count every 4 to 8 weeks are recommended to monitor hepatic and hematologic toxicity in patients taking MTX and leflunomide. These studies may be performed at the primary care physician’s office for the convenience of the patient.

Patients who have RA are at increased risk for infection, mostly resulting from therapies that suppress immune function. Temporarily suspend DMARDs with immunosuppressive properties in patients who have serious bacterial infections, such as pneumonia, abdominal infection, or deep tissue infection. Although caution should be exercised in the face of any infection, DMARD therapy is usually continued during the course of uncomplicated urinary tract infections, upper respiratory tract viral infections, and superficial skin infections.

Several cases of reactivated tuberculosis (TB) have been discovered in patients receiving adalimumab, etanercept, and infliximab. Patients with positive results on a purified protein derivative test and no prior anti-TB therapy should not be given a TNF-α inhibitor before appropriate treatment of latent TB, to prevent reactivation of this infection. Because there are no guidelines for managing the risk of TB reactivation in this situation, physicians must rely on their clinical judgment and seek appropriate consultation.

References: REFERENCES:


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