establish a diagnosis of RA, but it can help to confirm the clinical impression.

Anti-CCP antibodies are a more specific marker for RA. Anti-CCP antibodies have a higher specificity (>95%) than RF, with similar sensitivity (68% to 80%). These antibodies can be detected several years before the development of clinical RA (and before RF), and they are associated with severe RA outcomes, including radiographic joint damage and a poor prognosis. Because of their higher specificity for RA, anti-CCP antibodies are useful in differentiating RA from other conditions positive for RF, including Sjögren syndrome, infection, and hepatitis.

Acute phase reactants, such as the erythrocyte sedimentation rate and C-reactive protein, are usually elevated in active inflammation but are not sensitive or specific for the diagnosis of RA. They are useful for differentiating RA from noninflammatory conditions such as osteoarthritis or fibromyalgia. Even when there is clinical evidence of joint inflammation, the values for acute phase reactants may be normal. Inflammation in RA often leads to anemia of chronic disease and thrombocytosis.

Synovial fluid analysis is usually not necessary when the diagnosis is already established, but arthrocentesis should be performed to rule out infection or crystalline arthropathy if only one joint is involved. Synovial fluid analysis is nonspecific but indicates inflammation. Radiographs, although not part of the 2010 RA classification criteria, may show characteristic periarticular osteopenia, marginal erosions, and uniform joint space narrowing in a symmetrical distribution.

For a deeper discussion of these topics, please see Chapter 257, "Laboratory Testing in Rheumatoid Arthritis," Chapter 258, "Imaging Studies in the Rheumatic Diseases," Chapter 263, "Bursitis, Tendinitis, and Other Periarticular Disorders and Sports Medicine," and Chapter 264, "Rheumatoid Arthritis," in Goldman-Cecil Medicine, *25th Edition.*

TREATMENT

The ultimate goals of RA management are to reduce pain and discomfort, prevent deformities and loss of normal joint function, and maintain normal physical and social function. Although there is no cure for RA, remission can be maintained in a subset of patients. Treatment begins with effective communication between the physician and patient regarding the nature of the disease and the goals of treatment.

Nonpharmacologic therapeutic options include reduction of joint stress and physical and occupational therapy. Local rest of an inflamed joint can reduce joint stress, as can weight reduction, splinting, and the use of walking aids. Vigorous activity should be avoided during disease flares. Full range of motion of joints, however, should be maintained by a graded exercise program to prevent contractures and muscle atrophy. Physical therapy improves muscle strength and conditioning and maintains joint mobility. Occupational therapy can provide various appliances to protect joints and make daily activities easier.

Pharmacologic Approach

Studies have revealed that disease-modifying antirheumatic drug (DMARD) therapy early in the course of RA slows disease progression more effectively than delayed therapy. Effective treatment can improve signs, symptoms, and radiographic progression, even in long-standing disease. The inflammation of RA should be controlled as completely as possible, as soon as possible, and for as long as possible. Conventional DMARDs and biologic DMARDs prevent disease progression and disability.

Symptomatic Control and Bridging Therapy

DMARDs require 1 to 6 months to work. Consequently, nonsteroidal anti-inflammatory drugs (NSAIDs), which are not disease modifying, are frequently used early in the disease process for symptomatic control. NSAIDs have significant side effects, including renal failure and increased risk of gastrointestinal bleeding, and should be used with caution in patients with multiple medical comorbidities.

Glucocorticoids remain important in the treatment of RA, especially for acute exacerbations of disease. These agents are used sparingly in low to medium doses. Although glucocorticoids are useful for brief exacerbations and decrease bone erosions, the long-term side effects of glucocorticoids can be substantial. They should be used primarily as bridging therapy for further DMARD effects. Side effects include osteoporosis, avascular necrosis of bone, obesity, hypertension, and glucose intolerance. Screening, prevention, and treatment for osteoporosis should be considered for all patients who receive long-term glucocorticoid therapy for prevention of glucocorticoid-induced osteoporosis. Intra-articular glucocorticoids are extremely effective treatment for exacerbations involving only a few joints.

For a deeper discussion of these topics, please see Chapter 243, "Osteoporosis," in Goldman-Cecil Medicine, *25th Edition.*

Conventional and Biologic Disease-Modifying Antirheumatic Drugs

Many DMARDs are available for treating RA. All conventional DMARDs have a slow onset, taking 1 to 6 months to become fully effective, and they need close monitoring for toxicity.

Methotrexate is universally used as the initial DMARD in patients with moderate to severe RA because of its established efficacy and known toxicity profile (level A evidence, multiple randomized controlled trials). It can be administered once weekly by the oral or parenteral route. Known side effects include oral ulcers, nausea, hepatotoxicity, and pneumonitis.

After methotrexate failure, the subsequent choice of conventional and biologic DMARDs is not standardized and is instead based on the preferences of patients and physicians. For patients with mild RA, hydroxychloroquine or sulfasalazine, or both, may be used as first-line drugs (level B evidence). Triple therapy, the combination of methotrexate, hydroxychloroquine, and sulfasalazine, was shown in two randomized, controlled trials to be noninferior to biologic TNF-α inhibitors (level A). Tofacitinib is an oral Janus kinase inhibitor and the first kinase inhibitor of its class that reduces cytokine levels.

Biologic DMARDs are targeted, immune-based therapies that were introduced in the 1990s with the initiation of cytokine-directed TNF-α inhibitors. TNF-α inhibitors were the first of nine biologic DMARDs approved by the U.S. Food and Drug