reactants [ESR or CRP], and a functional assessment of disability using a self-administered patient questionnaire) are a composite index with a dichotomous response variable. The ACR improvement criteria are commonly used in clinical trials as an endpoint for comparing the proportion of responders between treatment groups. In contrast, the Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) are continuous measures of disease activity. These scales are increasingly used in clinical practice for tracking disease status and, in particular, for documenting treatment response.

Several developments during the past two decades have changed the therapeutic landscape in RA. They include (1) the emergence of methotrexate as the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of early RA; (2) the development of novel highly efficacious biologicals that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone. The medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional DMARDs; and biologic DMARDs **(Table 380-2)**. Although disease for some patients with RA is managed adequately with a single DMARD, such as methotrexate, the situation in most cases demands the use of a combination DMARD regimen that may vary in its components over the treatment course depending on fluctuations in disease activity and emergence of drug-related toxicities and comorbidities.

NSAIDs

NSAIDs were formerly viewed as the core of all other RA therapy, but they are now considered to be adjunctive therapy for management of symptoms uncontrolled by other measures. NSAIDs exhibit both analgesic and anti-inflammatory properties. The anti-inflammatory effects of NSAIDs derive from their ability to nonselectively inhibit cyclooxygenase (COX)-1 and COX-2. Although the results of clinical trials suggest NSAIDs are roughly equivalent in their efficacy, experience suggests that some individuals may preferentially respond to a particular NSAID. Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

GLUCOCORTICOIDS

Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1- to 2-week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5–10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy. Low-dose prednisone therapy has been shown in prospective studies to retard radiographic progression of joint disease; however, the benefits of this approach must be carefully weighed against the risks. Best practices minimize chronic use of low-dose prednisone therapy owing to the risk of osteoporosis and other long-term complications; however, the use of chronic prednisone therapy is unavoidable in many cases. High-dose glucocorticoids may be necessary for treatment of severe extraarticular manifestations of RA, such as ILD. Finally, if a patient exhibits one or a few actively inflamed joints, the clinician may consider intraarticular injection of an intermediate-acting glucocorticoid such as triamcinolone acetonide. This approach may allow for rapid control of inflammation in the setting of a limited number of affected joints. Caution must be exercised to appropriately exclude joint infection, as it often mimics an RA flare.

Osteoporosis ranks as an important long-term complication of chronic prednisone use. The ACR recommends primary prevention of glucocorticoid-induced osteoporosis with a bisphosphonate in any patient receiving 5 mg/d or more of prednisone for greater than 3 months. Although prednisone use is known to increase the risk of peptic ulcer disease, especially with concomitant NSAID use, no evidence-based guidelines have been published regarding the use of gastrointestinal ulcer prophylaxis in this situation.

DMARDs

DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of approximately 6–12 weeks. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. It was approved for the treatment of RA in 1986 and remains the benchmark for the efficacy and safety of new disease-modifying therapies. At the dosages used for the treatment of RA, methotrexate has been shown to stimulate adenosine release from cells, producing an anti-inflammatory effect. The clinical efficacy of leflunomide, an inhibitor of pyrimidine synthesis, appears similar to that of methotrexate; it has been shown in well-designed trials to be effective for the treatment of RA as monotherapy or in combination with methotrexate and other DMARDs.

Although similar to the other DMARDs in its slow onset of action, hydroxychloroquine has not been shown to delay radiographic progression of disease and thus is not considered to be a true DMARD. In clinical practice, hydroxychloroquine is generally used for treatment of early, mild disease or as adjunctive therapy in combination with other DMARDs. Sulfasalazine is used in a similar manner and has been shown in randomized, controlled trials to reduce radiographic progression of disease. Minocycline, gold salts, penicillamine, azathioprine, and cyclosporine have all been used for the treatment of RA with varying degrees of success; however, they are used sparingly now due to their inconsistent clinical efficacy or unfavorable toxicity profile.

BIOLOGICALS

Biologic DMARDs have revolutionized the treatment of RA over the past decade (Table 380-2). They are protein therapeutics designed mostly to target cytokines and cell-surface molecules. The TNF inhibitors were the first biologicals approved for the treatment of RA. Anakinra, an IL-1 receptor antagonist, was approved shortly thereafter; however, its benefits have proved to be relatively modest compared with the other biologicals and is rarely used for the treatment of RA with the availability of other more effective agents. Abatacept, rituximab, and tocilizumab are the newest members of this class.

Anti-TNF Agents The development of TNF inhibitors was originally spurred by the experimental finding that TNF is a critical upstream mediator of joint inflammation. Currently, five agents that inhibit TNF-α are approved for the treatment of RA. There are three different anti-TNF monoclonal antibodies. Infliximab is a chimeric (part mouse and human) monoclonal antibody, whereas adalimumab and golimumab are humanized monoclonal antibodies. Certolizumab pegol is a pegylated Fc-free fragment of a humanized monoclonal antibody with binding specificity for TNF-α. Lastly, etanercept is a soluble fusion protein comprising the TNF receptor 2 in covalent linkage with the Fc portion of IgG1. All of the TNF inhibitors have been shown in randomized controlled clinical trials to reduce the signs and symptoms of RA, slow radiographic progression of joint damage, and improve physical function and quality of life. Anti-TNF drugs are typically used in combination with background methotrexate therapy. This combination regimen, which affords maximal benefit in many cases, is often the next step for treatment of patients with an inadequate response to methotrexate therapy. Etanercept, adalimumab, certolizumab pegol, and golimumab have also been approved for use as monotherapy.

Anti-TNF agents should be avoided in patients with active infection or a history of hypersensitivity to these agents and are contraindicated in patients with chronic hepatitis B infection or class III/IV congestive