Strategies for the Management of Rheumatoid Arthritis

W.S. Wilkie, PharmD; Philip Schwieterman, PharmD

Abstract: Rheumatoid arthritis is a chronic, systemic inflammatory autoimmune disease that, untreated, can lead to permanent joint damage, decrease in quality of life, and disability. Health care professionals play a vital role in caring for patients with rheumatoid arthritis. The therapeutic possibilities in the management of rheumatoid arthritis have changed, with newer biologic therapies that target the inflammatory cascade seen in rheumatoid arthritis. As new treatments become increasingly available, it is important for health care professionals to stay informed. This article provides physicians with a review of biologic therapies currently used for the treatment of rheumatoid arthritis and describe how those therapies are used to manage rheumatoid arthritis.

Rheumatoid arthritis is a chronic, systemic inflammatory autoimmune disease affecting >1.3 million people in the United States. Rheumatoid arthritis is defined as persistent joint inflammation that is marked as joint pain, stiffness, and swelling, resulting in progressive destruction of cartilage in the joints. Although rheumatoid arthritis primarily targets the synovial lining of joints, it has extra-articular effects, including the lungs, heart, and blood vessels. If untreated, rheumatoid arthritis can lead to permanent joint damage, a decrease in quality of life, and disability. Approximately 20% of patients are retired completely or partially within 2 years of disease onset, and 50% of patients are unable to work after 10 years. Furthermore, rheumatoid arthritis may reduce life expectancy between 2 and 18 years. As a result, rheumatoid arthritis is a burden on patients’ quality of life and health care systems.

Traditional Approach

Pharmacologic approaches have traditionally relied on steroids (eg, prednisone, methylprednisolone), nonsteroidal anti-inflammatory drugs (eg, aspirin, ibuprofen), and disease-modifying antirheumatic drugs (DMARDs) (eg, methotrexate [MXT], hydroxychloroquine). Disease-modifying antirheumatic drugs are commonly used in patients newly diagnosed with rheumatoid arthritis. Because of its safety profile, long-term effectiveness, and low cost, MXT is the most commonly used DMARD. Other DMARDs used less frequently include leflunomide, gold salts, azathioprine, cyclosporine, and minocycline.

Unfortunately, some patients with rheumatoid arthritis fail to respond to DMARD therapy, with up to one-third of patients discontinuing DMARD therapy due to a lack of efficacy. Thus, newer treatments involving the use of biologicals may provide alternatives to traditional DMARD therapy.

Biological Therapies

Although the precise etiology of rheumatoid arthritis is unknown, evidence exists that proinflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6), play a role in the pathogenesis of rheumatoid arthritis. Thus, biologic agents have been developed to target specific inflammatory mediators of tissue damage. The use of biologics has led to improved outcomes. Although expensive, biologics appear to be cost-effective due to the clinical benefits patients experience.
Etanercept, the first targeted biologic for rheumatoid arthritis, is a TNFα antagonist that was approved by the US Food and Drug Administration in 1998. Since then, other agents have become available: the TNFα antagonists infliximab, adalimumab, certolizumab pegol, and golimumab; the IL-1 receptor antagonist anakinra; the IL-6 receptor antagonist tocilizumab. Moreover, 3 new drugs are currently undergoing clinical trials: Janus kinase inhibitor Tofacitinib (Pfizer, New York, New York); Syk kinase inhibitor Postamatinib (Rigel, San Francisco, California); and receptor activator of nuclear factor kappa beta ligand (RANKL) inhibitor Denosumab (Amgen, Thousand Oaks, California). Table 1 provides a guide of the drugs currently used for the treatment of rheumatoid arthritis.

**TNF Antagonists**

Physiological responses to TNFα include induction of proinflammatory cytokines (IL-1 and IL-6) and increasing the synthesis of prostaglandins. However, concern exists regarding the association between TNFα inhibition and the occurrence of serious infections and the development of lymphoma. Histoplasmosis, aspergillosis, listeriosis, and cytomegalovirus have been described in several case reports of patients receiving TNFα inhibitor therapy. Black box warnings include fungal infection, mycobacterial infection, viral infection, neoplastic disease, and tuberculosis. Heart failure and sepsis are absolute contraindications.

Infliximab is a chimeric IgG1 molecule with a mouse antibody against TNFα. Infliximab binds to the soluble and membrane-bound TNFα and is commonly administered with MTX to suppress production of the mouse portion of the molecule. Infliximab is approved for rheumatoid arthritis at a dose of 3 mg/kg infused intravenously over 2 hours, followed by additional doses at 2 and 6 weeks and then every 8 weeks indefinitely. The infliximab dose may be increased in the absence of clinical response. In MTX-naive patients with disease duration <3 years, concurrent use of infliximab and MTX reduced the signs and symptoms of rheumatoid arthritis and improved physical function to a greater extent than MTX monotherapy. Infusion reactions (eg, headache, nausea, urticaria, and anaphylaxis) regularly occur with the administration of infliximab.

Approximately 10% of patients treated with infliximab develop antibodies, and these patients are more likely to have infusion reactions. However, development of infliximab antibodies was lower among patients receiving concurrent immunosuppressive therapy (eg, azathioprine or methotrexate). Minor reactions usually respond to antihistamines and decreasing the infusion rate.

Etanercept is a dimer composed of 2 recombinant TNFα-receptor proteins, which are linked to human IgG1. This extends the half-life of the drug for up to 4 days. Unlike infliximab, etanercept cannot interact with membrane-bound TNFα. A benefit of etanercept is that it is self-administered by subcutaneous injection at doses of 25 mg twice weekly or 50 mg once weekly. Although etanercept does not provide better efficacy at higher doses, clinical responses are seen within 1 to 2 weeks. When etanercept was prescribed to patients who had persistent disease despite receiving MTX, rapid and sustained improvement was observed. Patients receiving etanercept combined with MTX had significantly better outcomes than those receiving MTX alone.

Adalimumab is a recombinant human IgG1 monoclonal antibody that neutralizes membrane-associated and soluble human TNFα. Unlike etanercept, infliximab, and adalimumab, certolizumab pegol does not cause antibody-dependent cell-mediated cytoxicity. A 400-mg subcutaneous dose is given in two 200 mg injections at weeks 0, 2, and 4, and then a 200-mg subcutaneous dose is given every other week. For patients who did not have a positive response to MTX, the addition of certolizumab led to a positive response in 53% of patients compared with a 13% response for recipients of MTX only. No further benefit is seen with doses higher than 400 mg administered every 2 weeks.

In patients who failed at least 1 DMARD, monotherapy with certolizumab led to a positive response in 45.5% of patients. Optimal response is reported after 16 weeks of therapy. Patients must be evaluated for latent tuberculosis infection before treatment. The most common adverse reactions leading to discontinu-
Golimumab is a monoclonal antibody with a human-derived antibody against TNFα. It binds the soluble and membrane forms of TNFα. Among patients with symptoms of rheumatoid arthritis despite MTX treatment, a 50-mg subcutaneous dose of golimumab every 4 weeks led to a 20% improvement in 55% patients; 33% of patients who received a placebo plus MTX met the endpoint.19 Due to a longer half-life, golimumab is administered less frequently than adalimumab and etanercept.20

### IL-1 Inhibitors

Anakinra is a recombinant human IL-1 receptor antagonist that competitively inhibits the binding of IL-1 to its receptor. IL-1 is a major proinflammatory cytokine and causes cartilage degradation. A 100-mg subcutaneous dose is administered every 24 hours. Higher doses do not result in an increased response. Anakinra is renally eliminated, with a half-life up to 6 hours. Anakinra should not be administered with anti-TNFα therapies because an increased infection risk exists with minimal clinical benefit. Injection site reactions such as erythema, edema, and inflammation are the most common side effects, which usually occur during the first 4 weeks of treatment. During clinical trials, the infection incidence was 40% in patients treated with anakinra and 35% in patients treated with a placebo. Reported infections included upper respiratory tract infections (13%), sinusitis (6%), and influenza-like symptoms (5%).

### T-cell Costimulation Blocker

Abatacept (CTLA4-Ig) is a fusion protein that blocks the binding of CD80/CD86 and prevents the second costimulatory signal that is required for optimal T-cell activation. Although the mechanism is unclear, Abatacept decreases IL-6, rheumatoid factor,
C-reactive protein, and TNFα in patients with rheumatoid arthritis. A therapeutic response after administration of a 10-mg/kg dose of abatacept in combination with MTX was seen in 14% of patients, whereas 2% of patients who received a placebo and MTX had a therapeutic response. Although abatacept may be used with MTX, concurrent use of abatacept and TNF-inhibitors is not recommended.

A 125-mg subcutaneous dose of abatacept is administered within a day after a single intravenous loading dose, then weekly thereafter. Infusion doses are based on weight but are administered intravenously over 30 minutes twice every 2 weeks (ie, a dose at weeks 0, 2, and 4) and then every 4 weeks beginning at week 8. Infusion reactions occur within 1 hour of the start of the infusion, and most reactions are mild to moderate. Medications that decrease mucociliary function or cough reflex can facilitate the ability of bacteria to enter the lungs and proliferate. Of the patients with chronic obstructive pulmonary disease who received abatacept, 43% had an exacerbation, cough, rhonchi, or dyspnea compared with 24% of patients who received a placebo. Headache and dizziness may be associated with the infusion and are reported at a rate of <2%.

B-cell Depleting Agent

Rituximab is a chimeric murine/human IgG1 monoclonal antibody that binds specifically to CD20, which results in the rapid and sustained depletion of B-cells. The US Food and Drug Administration approved the use of rituximab in combination with MTX to reduce the signs and symptoms of rheumatoid arthritis in adults with an inadequate response to TNFα antagonist therapies. A 1000-mg intravenous dose is administered on days 1 and 15. Black box warnings include infusion-related reactions because approximately 80% of fatal infusion reactions occur with the first infusion of rituximab. All patients should receive diphenhydramine, acetaminophen, and possibly corticosteroids (100 mg of methylprednisolone intravenously or its equivalent) as premedication. In clinical trials, adverse events reported include fever (53%), chills (33%), peripheral edema (16%), night sweats (15%), fatigue (13%), pain (12%), and flushing (5%).

IL-6 Inhibitor

Tocilizumab is a humanized IL-6 receptor-inhibiting monoclonal antibody, which competes with IL-6 for binding to the IL-6 receptor. IL-6 correlates with disease severity, and patients with rheumatoid arthritis have elevated IL-6 concentrations in serum and synovial fluid. Tocilizumab binds to soluble and membrane-bound IL-6 receptors and inhibits IL-6-mediated signaling through these receptors, and thus attenuates rheumatoid arthritis associated symptoms and joint damage.

IL-6 is produced by synovial and endothelial cells, leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis. The use of tocilizumab for patients with no prior inadequate response to TNFα antagonists is not recommended. A 4-mg/kg intravenous dose of tocilizumab is administered over 1 hour every 4 weeks. If needed, the dose can be increased to 8 mg/kg intravenously every 4 weeks (800 mg per dose maximum). Adverse reactions include upper respiratory tract infections, nasopharyngitis, opportunistic infections, pneumonia, urinary tract infections, and tuberculosis.

**Table 2**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Disease Activity</th>
<th>Poor Prognosis</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
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<tr>
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<td>&lt;3 months</td>
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<td>Anti-TNFα + MTX</td>
</tr>
<tr>
<td>≥6 months</td>
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<td></td>
<td>Low</td>
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<td>Non-biologic DMARDs</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>Without</td>
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<td>Non-biologic DMARDs</td>
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<td>Without</td>
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<td></td>
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<td>With</td>
<td>Abatacept, anti-TNFα, or Rituximab</td>
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**Abbreviations:** DMARDs, disease-modifying anti-rheumatic drugs; MTX, methotrexate.

*Failed prior MTX monotherapy.
*Failed prior MTX combination therapy or after sequential non-biologic DMARDs.
hhibited structural damage in patients with rheumatoid arthritis for up to 12 months, with no increase in the rates of adverse events compared with the placebo.\textsuperscript{25}

Janus kinase plays an important role in cytokine-induced signal transduction. Tofacitinib is a selective janus kinase inhibitor that has shown promise in clinical trials. In phase II clinical trials, tofacitinib monotherapy improved symptoms in 67% of patients versus 25% who received a placebo. Another study showed that when combined with MTX, symptoms improved in 59% of patients versus 35% who received MTX alone. The most important side effects in Phase II studies were increased cholesterol levels, neutropenia, and elevations of transaminase enzymes. Phase III trials testing the use of the drug in patients with rheumatoid arthritis began in 2007 and are scheduled to run until 2015. In April 2011, Genetic Engineering & Biotechnology News reported that 2 phase III studies confirmed the benefits of Tofacitinib for use with active rheumatoid arthritis. If approved, this medication will be available on the market.

Syk kinase is a cytoplasmic tyrosine kinase involved in up-regulation of TNF{\textalpha} and IL-6 synthesis. Thus, Syk kinase inhibitors may play a role in the treatment of rheumatoid arthritis. Fostamatinib is an oral inhibitor that is converted to an active drug, which is a potent Syk kinase inhibitor.\textsuperscript{26} One phase II trial demonstrated that patients in the Fostamatinib group had significantly better outcomes than patients in the placebo group (67% vs 35%, respectively).\textsuperscript{26}

Adverse events arising during the study included diarrhea, upper respiratory tract infections, and neutropenia. It was concluded that, in this phase II study involving patients who had active rheumatoid arthritis despite treatment with MTX, the addition of a Syk kinase inhibitor led to reduced disease activity (Table 2).

**THE BOTTOM LINE**

Patients who take biologic DMARDS typically see improvements after the first or second dose. Abatacept and rituximab may be useful alternatives in patients with long-standing rheumatoid arthritis who have an inadequate response to combination therapy with TNF{\textalpha} antagonists plus MTX. Several new rheumatoid arthritis treatments have novel mechanisms of action and are at different stages of development. Overall, the use of biologics in the treatment of rheumatoid arthritis has led to improved outcomes, and although biologics are costly, they remain cost-effective due to the clinical benefits patients may experience.

**REFERENCES**


