A Review of Pathophysiology and Medicinal Treatment Options of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is considered the most common chronic inflammatory autoimmune disease, occurring in 1 to 2% of the worldwide population.\textsuperscript{1-4} However, certain ethnic groups such as Native American Indians (Pima and Chippewa) report a higher incidence, reaching approximately 5%.\textsuperscript{1,2,5} The hallmark of rheumatoid arthritis consists of synovial joint inflammation, leading to bone and cartilage destruction. Extra-articular manifestations, including rheumatoid nodules, vasculitis, lymphadenopathy, cardiopulmonary disease and eye inflammation, may also occur.\textsuperscript{1,3} While the exact etiology is unknown, genetic predisposition in combination with environmental triggers are theorized to increase the risk for rheumatoid arthritis. Incidence increases throughout life, affecting women two to three times more often than men. Early aggressive treatment to manage symptoms and slow disease progression include disease-modifying antirheumatic drugs (DMARDs), adjunctive non-steroidal anti-inflammatory agents and corticosteroids, physical therapy, exercise and rest.\textsuperscript{1-4} This article focuses on the pathophysiology of rheumatoid arthritis, current medicinal treatment options, and side effects.

Pathophysiology of Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease of the joints, consisting of hyperplasia of synovial tissue due to chronic inflammation. This proliferation of tissue, otherwise known as pannus, invades and erodes cartilage and bone, leading to destruction of the joint. While the exact pathophysiology is not known, autoreactivity of the immune system is thought to be due to genetic predisposition along with environmental triggers.\textsuperscript{1,3,5}

Genetic susceptibility is thought to account for 40 to 60% of people that develop RA.\textsuperscript{1,2} Specific genes located in the major histocompatibility complex (MHC) on chromosome 6 have been implicated in the
predisposition and severity of rheumatoid arthritis. Human leukocyte antigens (HLAs), known to define tissue types, are cell-surface proteins that are encoded by the MHC. Approximately 70% of Caucasians with rheumatoid arthritis have the HLA-DR4 (DRB1*0401 and *0404) class II antigen. Caucasians with the HLA-DR4 and Native Americans with the HLA-DR9 polymorphic genes are 3.5 times more likely to develop rheumatoid arthritis.\textsuperscript{1,5} In addition to genetic predisposition, environmental triggers, such as smoking, alcohol, periodontitis, infectious agents and non-inherited maternal HLA antigens, are thought to initiate the development of rheumatoid arthritis.\textsuperscript{1,5,6}

Infectious agents linked to the development of RA include mycoplasma, mycobacterium, parvovirus, Epstein-Barr virus, and retroviruses. Theories suggest that infectious agents may initiate the disease in genetically prone individuals through direct synovial infection, molecular mimicry or activation of innate immunity.\textsuperscript{1,5,6} Recently, studies have found a link between antibodies produced in response to Porphyromonas gingivalis (P. gingivalis) and development of RA. Associated with periodontitis, P. gingivalis antibodies in RA patients have been linked to the production of anti-citrullinated protein antibodies (ACPAs) known to enhance the autoimmune response seen in RA.\textsuperscript{6} Additionally, new reports suggest that smoking simultaneously increases the production of ACPAs and pro-inflammatory cytokines responsible for the development of RA.\textsuperscript{1,6} Likewise, recent reports suggest an association between increased alcohol intake and increased levels of inflammatory markers. However, once RA has been established, other studies suggest alcohol may decrease severity of disease and joint destruction.\textsuperscript{6}

Lastly, non-inherited maternal HLA antigens (NIMAs) have been implicated as a trigger for the development of RA in offspring. An increased susceptibility to RA may be due to maternal cells entering the child either during or shortly after childbirth, remaining in the offspring for several years thereafter.\textsuperscript{7}

The inflammatory process of RA is complicated by many factors. The synovial joint is infiltrated with T cells, B cells, macrophages, plasma cells along with cytokines, fibroblasts, growth factors, chemokines,
adhesion molecules and matrix metalloproteinases.\textsuperscript{1,2,5,8} Arthrogenic T cells are activated when presented with antigenic peptides, initially resulting in joint swelling and pain.\textsuperscript{1,5,8} Two sets of CD4+ T cells are known to exist based on the cytokines they produce. Activation of CD4+ T-helper 1 cells (Th1) produce pro-inflammatory molecules (interleukin-2, interferon γ, tumor necrosis factor α, granulocyte-macrophage colony-stimulating factor) responsible for delayed-type hypersensitivity reactions that are commonly seen during early-onset RA. T-helper 2 cells (Th2) produce interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin 6 (IL-6) and interleukin 10 (IL-10) known to affect B cell differentiation and activation. Bone and cartilage destruction seen later in the course of the disease are caused by IL-1, TNF-α, IL-6 and IL-8.\textsuperscript{1,2,5,8}

Cytokines (responsible for intercellular communication during immune system activation) implicated in pro-inflammatory responses in rheumatoid arthritis include IL-1, IL-6, IL-8, IL-17 and TNF-α.\textsuperscript{2,5,8} Interleukin-1 is released by macrophages, monocytes, activated T and B cells, stimulating the release of matrix metalloproteinases; thereby, causing cartilage destruction. Interleukin-6, produced by T cells, fibroblasts, monocytes and macrophages, promotes B cell differentiation and maturation, causing increases in the production of rheumatoid factor.\textsuperscript{5,8} While the role of rheumatoid factor in RA is unknown, theories suggest that it may cause the formation of immune complexes, leading to the activation of the complement immune response.\textsuperscript{8} Additionally, IL-6 enhances bone resorption, induces the acute-phase response (erythrocyte sedimentation rate, C-reactive protein), and stimulates the proliferation of synovial fibroblasts that cause tissue and cartilage destruction by releasing matrix metalloproteinases.\textsuperscript{5,8,10} Interleukin-8, produced by macrophages, is thought to promote bone and cartilage destruction by causing recruitment of inflammatory cells such as neutrophils.\textsuperscript{5,8} While B cells, T cells and fibroblasts produce TNF-α, the primary producers include monocytes and macrophages. The actions of TNF-α in RA include proliferation of synovial tissue, release of metalloproteinases, increased fibroblast expression of adhesion-molecules to allow the transport of leukocytes into the synovium,
secretion of other cytokines (IL-1, IL-6, IL-8, granulocyte-monocyte colony-stimulating factor) as well as prostaglandin production, all resulting in cartilage and bone destruction.\textsuperscript{2,5,8} IL-17, now emerging as an important cytokine related to joint inflammation and destruction, is a product of Th17 T cells increased in the synovial joints of RA patients.\textsuperscript{1,6} However, the low production of IL-17 from CD4+ cells in the synovium prompts theorists to suggest an alternative source for the production of IL-17, primarily mast cells. Additionally, the Th17 phenotype may be able to convert to Th1 cells in response to inflammation, promoting the production of well known pro-inflammatory cytokines.\textsuperscript{6}

Fibroblasts play an important role in the amplification of inflammation in rheumatoid arthritis by promoting chemotaxis, increasing inflammatory cytokines, matrix metalloproteinases and adhesion molecules.\textsuperscript{1,6} Recent studies report an increase in fibroblast-like synoviocytes (FLS) may cause hypoxia, leading to the development and necessity of angiogenesis for the continuation of rheumatoid arthritis. Moreover, fibroblasts may perpetuate RA by invading unaffected joints through vascular migration.\textsuperscript{6}

Angiogenesis is another highly occurring phenomenon of RA, especially during the early-onset of disease. While allowing for the recruitment of inflammatory cells to the synovium, angiogenesis supplies oxygen and nutrients to the proliferating synovial tissues. Generally, angiogenesis is highly regulated with rapid vascular endothelial cell division occurring during wound repair and menstruation. However, theories suggest that stimulation of angiogenesis in RA may be due to an abundance of cytokines, growth factor and adhesion molecules promoted by fibroblasts, or a lack of inhibiting cytokines, chemokines, and cryptic cleavage products.\textsuperscript{2,6,8}

**Classification Criteria for Rheumatoid Arthritis**

Common signs and symptoms of RA include pain and swelling of joints, warmth or redness over the affected joints, morning stiffness lasting longer than 30 minutes along with fatigue, weakness, weight loss, and low-grade fever.\textsuperscript{3,11} In September 2010 new classification criteria for RA were approved by the
American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) to include features of persistent/erosive disease associated with earlier stages of RA (Table 1). The criteria recommend people be tested who have at least 1 joint with swelling (clinical synovitis) when likely disease states such as systemic lupus erythematosus have been ruled out. Joint involvement, serology, acute phase reactants, and duration of symptoms are determined for each patient. A classification of “definite RA” is concluded with at least one clinically diagnosed joint erosion or a score of at least 6 points. People not reaching a status of “definite RA” may do so at a later time. Patients may be considered to have RA off of disease duration and joint involvement without serological evidence. Likewise, symmetrical joint involvement is no longer needed, recognizing that the likelihood of symmetry increases as the number of joints involved increase.

Early Intensive Treatment Strategies and ACR/EULAR Guidelines in Rheumatoid Arthritis

Medicinal treatment for RA has evolved significantly over the last two decades, incorporating biologics with traditional DMARDs. Treatment guidelines, based on ACR and EULAR recommendations, call for early referral to rheumatologists, immediate use of DMARDs, and tight control of disease activity with frequent monitoring (every 1 to 3 months) to adjust treatment if needed. Moreover, the guidelines state that people suspected of having RA using the 2010 RA classification criteria may benefit from treatment with a DMARD as a result of erosive changes that occur as early as the first year of active disease, leading to irreversible joint damage and loss of function. Furthermore, EULAR recommendations state that disease activity experienced at 3 to 6 months after starting treatment can predict future outcomes.

Depending on poor prognostic factors (Table 2) and severity of disease, monotherapy or combination therapy may be used. Several clinical trials, including the CAMERA, BeSt, and TICORA studies, have shown lower disease activity, improved physical function and quality of life with early, tightly controlled
more aggressive treatments. The ACR criteria for clinical improvement and remission requires either a 20% (ACR 20), 50% (ACR 50), or 70% (ACR 70) improvement in swollen and tender joint counts and improvement in 3 of 5 core areas, including patient global assessment, physician global assessment, patient’s assessment of pain, degree of physical function, and level of acute-phase reactant. The standard treatment group in the TICORA trial received DMARD monotherapy (switching to an alternative monotherapy with treatment failure), or an addition of a second or third drug based on the rheumatologist’s discretion. The standard group obtained 64%, 40% and 18% improvements in ACR 20, 50 and 70, respectively. The intensive treatment group in the TICORA trial reported 91%, 84%, and 71% improvements in ACR 20, 50 and 70, respectively. Tight control was achieved in the intensive treatment group using standard DMARDs without the use of anti-tumor necrosis factor biological drugs. The primary outcome studied in the CAMERA trial looked at the percentage of patients achieving remission from disease. A reported 50% of patients in the intensive treatment group achieved remission during a two year period while only 37% of patients on conventional therapy experienced remission. The criteria for remission in the CAMERA trial included no swollen joints and documentation of at least 2 of 3 other criteria, including ≤ 3 tender joints, ESR ≤ 20 mm/hr and ≤ 20 mm (0 – 100 mm scale) on the visual analog scale for general well-being. Like the CAMERA trial, the BeSt trial studied treatment strategies in very early RA patients (within 2 weeks of diagnosis). Using sequential monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab, the primary objective was rapid reduction in disease activity. While there were no significant differences between groups for toxic side effects, low disease activity was achieved after one year by 53%, 64%, 71% and 74%, respectively. The combination groups experienced clinical improvement at an earlier time with less progression of radiographic joint destruction.
Currently, inconsistencies exist in treating patients with either step-up therapy versus initial combination therapy, primarily due to the plethora of clinical and observational studies of drugs and varying treatment strategies. Because of these inconsistencies, the ACR and EULAR have created guidelines for using biological and traditional DMARDs in RA.\textsuperscript{10, 16, 18, 19} As stated previously, traditional DMARDs should be initiated as soon as possible post diagnosis to obtain remission or very low disease activity. Methotrexate is recommended as monotherapy or in combination with other DMARDs in all patients, regardless of duration, poor prognostic indicators, or disease activity (if tolerated). Combination therapy may be appropriate for individuals possessing poor prognostic factors or moderate to high disease activity. In general, biological DMARDs are to be started after traditional DMARDs have failed. However, the combination of a biological DMARD in conjunction with methotrexate or other DMARDs may be used initially in high disease activity.\textsuperscript{10, 14} The optimal method to taper biological and traditional DMARDs in people who have achieved remission is currently unknown, but tapering should only be done in persistent remission. While the exact time frame is unknown, expert opinion deems approximately 12 months as persistent remission. Glucocorticoids must have been tapered and discontinued with no effects on the status of remission. Traditional DMARDs may be tapered following the discontinuation of biological drugs. The incidence of disease flares while taking DMARDs occurs in one third of patients while two thirds experience flares off of medication. Furthermore, remission may be more difficult to achieve after stopping treatment.\textsuperscript{10}

**Treatment Goals and Medications Used in Rheumatoid Arthritis**

The current treatment goal in RA is to achieve remission. In people who are unable to achieve remission, the aim is to control disease activity, maintain daily function, maximize quality of life and alleviate pain.\textsuperscript{4, 10} Many definitions of remission exist, making it difficult to compare clinical trials using remission as an outcome measure. The ACR and EULAR formed a committee to determine a stringent
and achievable definition of remission in RA. In March of 2011, the published provisional definition of remission to be used in rheumatoid arthritis clinical trials state that the patient must display ≤1 tender joint count, ≤ 1 swollen joint count, ≤ 1 mg/dL C-reactive protein, and ≤ 1 (on a 0-10 scale) patient global assessment or the patient must have a Simplified Disease Activity Index score of ≤ 3.3. Early diagnosis and initiation of medicinal treatment is key to suppressing disease activity and reducing radiological joint damage. Ideally, people should be referred to a rheumatologist within six weeks of symptom onset with initiation of DMARD therapy no later than 12 weeks after symptom onset. Patients treated within 12 weeks have shown an altered disease course with less joint destruction along with a better chance of achieving remission. However, one study reported only 31% of patients with RA were seen by a rheumatologist within 12 weeks of symptom onset. People experiencing a gradual onset of symptoms, females, and older age at onset have all been documented reasons for delay in care. Therefore, initiating DMARD therapy directly after diagnosis is crucial in slowing the progression of joint destruction and improving quality of life as people tend to become less responsive to treatment over time. The following section will focus on the drugs used most often in the treatment of rheumatoid arthritis.

**Methotrexate.** Methotrexate is the gold standard drug used as monotherapy or in combination therapy with other DMARDs in RA. Known to slow the rate of joint destruction and improve quality of life in RA, methotrexate is an inexpensive and well tolerated drug with 45% to 67% of patients remaining on therapy even 5 to 7 years after initiating treatment. The ACR and EULAR recommendations state methotrexate should be initiated early regardless of poor prognostic features either as monotherapy or in combination therapy as it has been shown to increase the efficacy of biological DMARDs. The onset of action is rapid with some patients seeing improvements within 2 to 3 weeks after starting therapy. Clinical response should be seen within four months. While the exact action of methotrexate in RA is unknown, it is thought to inhibit the proliferation or induce apoptosis in activated lymphocytes.
The anti-inflammatory properties of methotrexate include inhibition of cytokine production and purine biosynthesis. Another possible anti-inflammatory property is the release of adenosine known to reduce TNF-α, inhibit macrophage and T cell inflammatory activities. Methotrexate may be given orally, subcutaneously, intramuscularly or intravenously. Oral bioavailability is decreased at doses larger than 15 mg per week. Common oral doses range between 7.5 mg to 20 mg taken once weekly. However, doses as high as 30 mg have been used in some clinical trials. Contraindications include pregnancy, breast feeding, alcoholism, hepatic disease, immunodeficiency syndromes, preexisting bone marrow suppression, leucopenia, thrombocytopenia, significant anemia or in people with a known hypersensitivity reaction. Methotrexate is hepatically and intracellularly metabolized with renal excretion being the primary route of elimination. Patients with renal impairment require careful monitoring with dosage reductions or discontinuation of therapy in those experiencing toxicities.

Common toxicities affect the gastrointestinal, cutaneous, immunologic, hematologic, pulmonary and hepatic systems (Table 3). Approximately 10% of patients will experience nausea, vomiting, and diarrhea while ulcerative stomatitis and thrombocytopenia have been reported in 3% to 10% of patients. Interstitial pneumonitis has a reported incidence of 1% to 7% in patients taking 7.5 mg to 15 mg orally per week. While rare, it may be life-threatening and can appear at any time during therapy. Discontinuation of therapy is warranted with further investigation in anyone experiencing a dry, nonproductive cough. Possible predictive factors associated with the development of pneumonitis include hypoalbuminemia, prior DMARD use, diabetes, and older age. Elevated liver enzymes occur in 15% of patients, rarely leading to fibrosis. Liver function tests (LFTs), including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), along with albumin levels should regularly be checked (every 4 to 8 weeks) to detect hepatic inflammation. Liver function tests greater than twice the upper limit of normal warrant immediate discontinuation of treatment. However, many patients
may only experience temporary elevations with spontaneous recovery while others may only need a temporary discontinuation of treatment.\textsuperscript{3,25-28}

Methotrexate acts as a folic acid antagonist, leading to folate deficiency in some users. Folic acid supplementation is thought to reduce certain toxicities induced by methotrexate, resulting in a decrease in the discontinuation of therapy. Reports suggest a significant reduction in the rates of stomatitis, diarrhea, anorexia, nausea, vomiting, dyspepsia, constipation and liver function abnormalities without impacting efficacy.\textsuperscript{3,4,25-29}

**Leflunomide (Arava\textsuperscript{®}).** Leflunomide is an antiproliferative isoxazol derivative, inhibiting dihydroorotate dehydrogenase. The exact mechanism of action in RA is unknown. Theories suggest leflunomide works by affecting lymphocyte functions. Leflunomide is a pro-drug that is enzymatically converted to its active metabolite A771726. The long half-life of approximately 2 weeks requires a loading dose of 100 mg for 3 consecutive days to obtain a steady-state level. Onset of action is rapid with a sustained response seen as early as 7 to 8 weeks after initiation.\textsuperscript{2,4,10} Maintenance doses range between 10 mg to 20 mg daily. Enterohepatic recirculation is the primary pathway of metabolism with biliary/fecal and renal involvement being the primary routes of elimination.\textsuperscript{2,4,30-32}

Leflunomide is an established alternative to methotrexate in RA. Like methotrexate, the ACR recommends leflunomide monotherapy in RA patients regardless of disease duration or poor prognostic factors.\textsuperscript{14,30} Reportedly, leflunomide efficacy is similar to methotrexate monotherapy and combination therapy, showing similar ACR 20 response rates, swollen joint counts, and pain intensity along with slowing the progression of joint destruction and improving overall quality of life. Moreover, leflunomide in combination with methotrexate has shown beneficial results after treatment failure on maximum doses of methotrexate. The combination is recommended by the ACR in patients with disease duration of \( \geq 6 \) months and experiencing a high level of disease activity.\textsuperscript{14} Recent reports state that concomitant
administration of leflunomide with methotrexate in RA obtains higher rates of ACR 20, ACR 50 and ACR 70, improvement in tender joint counts and swollen joints, and a reduction in pain than either drug alone.\textsuperscript{2,24,32}

The side effect profile for leflunomide is slightly more than methotrexate, leading to higher discontinuation rates. Common side effects are similar to methotrexate, including gastrointestinal upset, hepatotoxicity, alopecia, and infection. Additionally, leflunomide may induce hypertension, oral ulcers, neutropenia, pancytopenia, serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), headache, and peripheral neuropathy.\textsuperscript{2,24,30,32} Increased liver enzymes over two times the upper limit of normal has been reported in up to 35% of patients taking leflunomide. Although rare, hepatotoxicity can be a serious and life-threatening side effect, necessitating monthly monitoring of LFTs for the first six months of therapy followed by monitoring every 6 to 8 weeks for the remainder of treatment. Additionally, leflunomide is contraindicated in patients with pre-existing acute or chronic liver disease and pregnancy. Leflunomide is not recommended in severely immunosuppressed individuals. Patients experiencing serious infections while taking leflunomide require discontinuation of therapy along with administration of cholestyramine or charcoal for enhanced drug elimination.\textsuperscript{30,32}

**Sulfasalazine (Azulfidine\textsuperscript{®}).** Sulfasalazine is metabolized intestinally by bacteria to form sulfapyridine (SP) and 5-aminosalicylic acid (5-ASA). Known to be poorly absorbed, 5-ASA bioavailability ranges between 10 to 30%. The sulfapyridine metabolite, reaching approximately 60% bioavailability, is metabolized systemically through acetylation and is thought to possess the primary anti-rheumatic properties of sulfasalazine. A reported 60% of Caucasians are considered to be slow acetylators, causing an accumulation of sulfapyridine. While the implications of accumulation are unclear, slow acetylators are thought to be at a higher risk for toxic side effects.\textsuperscript{3,33}
EULAR recommends sulfasalazine as an alternative in patients unable to take methotrexate with benefits seen as early as one month after initiating therapy.\textsuperscript{10} Shown to decrease radiographic joint destruction, ACR recommendations suggest the use of sulfasalazine monotherapy in patients with mild to moderate disease activity without poor prognostic factors regardless of disease duration. Additionally, sulfasalazine combinations with methotrexate are recommended in patients displaying high disease activity while triple combination therapy, consisting of methotrexate, hydroxychloroquine and sulfasalazine, are recommended in moderate to high disease activity. Dual and triple combinations are recommended for people with poor prognostic factors, regardless of disease duration. Sulfasalazine with hydroxychloroquine is only recommended in patients displaying high disease activity without poor prognostic factors and a disease duration of 6 to 24 months.\textsuperscript{4,10,14}

Sulfasalazine is contraindicated in people allergic to sulfonamides or salicylates, suffering from urinary or intestinal obstruction, or in patients with porphyria. Common side effects include nausea, vomiting, dyspepsia, rash, headache, photosensitivity, and mood alterations. Additionally, the development of oligospermia (low sperm count) has been reported. Rare, serious side effects with sulfasalazine use include hepatic damage (hepatitis, hepatic failure), renal damage (nephritis, hemolytic-uremic syndrome) along with blood dyscrasias, including leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia and hemolytic anemia caused by a deficiency of glucose-6 phosphate (G6PD). Caution is recommended when using in patients with blood dyscrasias, hepatic or renal damage. Laboratory monitoring of LFTs and complete blood cell counts with differential is recommended, especially during the first six months of therapy.\textsuperscript{4,28,33}

**Hydroxychloroquine (Plaquenil\textsuperscript{®}).** New information on the effect of hydroxychloroquine (HCQ) has recently been published. Known to have lysomotropic action, HCQ raises lysosomal pH, causing dysfunction in protein processing. This disruption affects antigen presentation to CD4+ T cells and
possibly pro-inflammatory cytokines such as TNF, IL-1, IL-6 and IFN gamma. Additionally, inhibition of toll-like receptors (TLRs), implicated in the activation of innate immunity, are thought to play a role in the antirheumatic properties of HCQ.\textsuperscript{34}

Hydroxychloroquine is orally well absorbed, partially metabolized by the liver and excreted renally. Used primarily in combination therapy, HCQ alone has not been shown to significantly decrease radiologic joint destruction. However, data suggests early treatment plays a significant role in long-term outcomes. Onset of action may take up to 6 weeks. Patients taking HCQ for 6 months with no response are considered treatment failures, requiring drug discontinuation. The lack of hepatic, renal and immunosuppressive tendencies make monitoring of HCQ less complicated.\textsuperscript{3,4}

Initial gastrointestinal side effects with HCQ, including nausea, vomiting, diarrhea and abdominal cramps, may be reduced when taken with food. Additionally, rash, pigmentation changes, myopathy, blurred vision, accommodation difficulty, benign corneal deposits, night blindness, peripheral neuropathy and weight loss have been reported. Since dermatological reactions may occur, caution should be used with concomitant administration of medication known to induce dermatitis. The main rare, serious side effect, requiring a baseline and periodic ophthalmological exam, is ocular retinal damage. Occurring in as little as 2.7% of patients, risk increases with prolonged use (cumulative dose \(> 800\) mg), age \(> 70\), and a daily dose \(> 6\) to \(6.5\) mg/kg.\textsuperscript{3,28,35}

**Other DMARDs.** In the past, gold salts, minocycline, cyclosporine, cyclophosphamide, azathioprine, and D-penicillamine were all used in the treatment of RA. Current evidence suggests other medications with less toxicity and better efficacy should be used. These medications are reserved for specific situations; namely, refractoriness.\textsuperscript{3,4,10}

**Biological DMARDs.** Over the last decade, biological DMARDs have become standard practice in RA. Blocking proinflammatory pathways such as TNF-\(\alpha\), IL-1, and depleting B cells, biological DMARDs are
either used as monotherapy or in combination with traditional DMARDs, especially methotrexate. ACR and EULAR recommendations state that biological DMARDs should be used after treatment failure with methotrexate or initially in combination therapy for patients experiencing high disease activity. While no intensive laboratory monitoring is necessary, a small increase in serious and life-threatening infections, including sepsis, has been reported. Underlying conditions, such as diabetes, or congestive heart failure, along with concomitant administration with other immunosuppressive drugs, including anakinra and abatacept, increase serious infection risk. Furthermore, contraindications to TNF antagonists include moderate to severe heart failure, according to ACR recommendations. Rare cases of tuberculosis have also been reported with TNF antagonists. Prior to initiating therapy, patients should be tested for latent TB. If positive, TB should be treated before starting any biologic drugs. Patients developing infections during therapy should be closely monitored. Invasive fungal infections related to TNF antagonists include histoplasmosis, coccidiodomycosis, aspergillous, candidiasis and blastomycosis. The risk of malignancy is slightly increased in all patients taking TNF antagonists. Recently, a black boxed warning for lymphoma and other malignancies in children and adolescents taking TNF antagonists have been included in the prescribing information.  

Etanercept (Enbrel®). Etanercept, a dimeric fusion protein, is indicated for moderate to severe rheumatoid arthritis to inhibit the progression of radiological joint destruction. Tumor necrosis factor regulates or induces expression of adhesion molecules, serum cytokines and matrix metalloproteinases all involved in the immunologic inflammatory process of RA. Etanercept binds to the soluble p75 TNF receptor linked to the Fc portion of IgG1, inhibiting the binding of TNF-α and TNF-β; thereby, causing TNF to become biologically inactive. Given as a subcutaneous injection, etanercept is taken in combination with methotrexate or alone as a twice weekly 25 mg or once weekly 50 mg dose. Studies report etanercept has shown greater clinical efficacy and tolerability than methotrexate, achieving a response in 60% to 75% of patients.
Injection site reactions, reported in up to 37% of patients, are the most common side effect.\textsuperscript{3,31,37} Occurring primarily during the first month of treatment, injection reactions usually cause mild to moderate erythema, itching, pain or swelling. The frequency of reactions decrease with continued use. Rotating injection sites is recommended. Patients developing infections while taking etanercept should be closely monitored. Other rare side effects include neurological demyelinating syndromes and hematologic aplastic anemia. Etanercept should be avoided in patients with multiple sclerosis.\textsuperscript{3,36,37}

**Infliximab (Remicade)\textsuperscript{®}**. Infliximab, made up of both human and murine portions, is a chimeric IgG1 monoclonal antibody targeting TNF-α. Indicated for use in combination with methotrexate in RA, infliximab is given as a 3 mg/kg intravenous infusion at 0, 2 and 6 weeks followed by a 3 mg/kg dose every 8 weeks thereafter for moderate to severe RA. Patients with an inadequate response may receive up to 10 mg/kg or a dose every 4 weeks, keeping in mind that at higher doses chances for infections are increased.\textsuperscript{2,3,38} Antibody production in response to infliximab has been reported in 7 to 15% of patients, increasing the risk for infusion reactions. Approximately 20% of patients experience infusion reactions, consisting of fever, chills, urticaria, rash, nausea, headache or dyspnea within 24 hours of infusion. Treatment consists of reducing the infusion rate and giving diphenhydramine, acetaminophen, or short-acting corticosteroids. Delayed reactions, appearing 24 hours to 14 days later, have also been reported. Corticosteroids, diphenhydramine and epinephrine should be readily accessible for rare, severe reactions such as bronchospasm and anaphylaxis. Antibody production along with infusion related reactions are reduced when used with methotrexate. Additionally, worsening of heart failure, autoantibody production inducing a lupus-like syndrome, reactivation of hepatitis B, hepatotoxicity and cytopenias may occur. The most common infections include upper respiratory, sinusitis and pharyngitis.\textsuperscript{2,3,8,31,38} Infliximab is not recommended concomitantly with anakinra or abatacept. Clinical studies report that infliximab in combination with methotrexate significantly reduced radiographic
progression, achieving higher rates of ACR 20, ACR 50 and ACR70, than methotrexate monotherapy.²,⁸, ¹⁹

**Adalimumab (Humira®).** Adalimumab may be used alone or in combination therapy with methotrexate or other traditional DMARD. A subcutaneous dose of 40 mg every other week is recommended in RA.³⁹

In the PREMIER study, 62% of patients taking combination methotrexate with adalimumab achieved an ACR 50 response versus 46% and 41% on methotrexate or adalimumab monotherapy, respectively. Additionally, twice as many patients on combination therapy achieved remission (49%).⁴⁰ The side effect profile is similar to other biologics with injection site reactions being the most common.³⁹

**Certolizumab (Cimzia®).** Certolizumab is a humanized anti-TNF antibody, consisting of a PEGylated Fab’ fragment. Indicated for moderate to severe RA, certolizumab may be given alone or in combination with traditional DMARDs. A 400 mg dose given as two 200 mg subcutaneous injections is administered at weeks 0, 2 an 4 followed by 200 mg doses every other week, thereafter. Certolizumab has been shown to significantly reduce radiographic progression of RA, and rapidly improve physical function and quality of life.⁴¹,⁴² In combination with methotrexate, the RAPID 2 study reported 57.6% of patients achieved an ACR 20 response. Furthermore, improvements were seen as early as one week after initiation.⁴² The side effect profile is similar to other TNF antagonists. However, rare cases of neurological demyelinating syndromes, cytopenias and autoantibody production inducing a lupus-like syndrome may occur. The use in multiple sclerosis patients is not recommended. Antibody production against certolizumab has been documented in approximately 8% of patients, possibly reducing efficacy. Patients concomitantly taking methotrexate had lower rates of neutralizing antibody formation.⁴¹,⁴²

**Tocilizumab (Actemra®), Golimumab (Simponi®), Abatacept (Orencia®) and Rituximab (Rituxan®).**

EULAR recommendations state that abatacept, golimumab, rituximab and tocilizumab are all effective treatment options for patients who fail initial TNF inhibitor therapy. Recommended as second-line
agents, they inhibit proinflammatory cytokines TNF-α (golimumab), IL-1 (tocilizumab, anakinra), diminish peripheral B cells (rituximab), or prevent full activation of T cells by binding to CD80/86 on T cells (abatacept). Side effect profiles and dosage schedules are listed in Table 4.  

Corticosteroids. Glucocorticoids have anti-inflammatory and disease-modifying actions. Inhibiting the occurrence and progression of joint damage, glucocorticoids interact with several inflammatory processes, including antigen presentation to T cells, prostaglandin and leukotriene synthesis, migration of monocytes, lymphocytes and neutrophils, macrophage and fibroblast production of cytokines and matrix metalloproteinases; thereby, hampering the inflammatory and autoimmune response.  

Glucocorticoids in combination with DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to significantly decrease joint erosions. High doses of oral steroids (prednisone, methylprednisolone) are given to suppress disease flares. Doses are tapered over several days to the lowest effective doses. Daily doses < 7.5 mg are well tolerated to control pain. However, ACR recommendations prefer 5 mg daily doses due to glucocorticoid side effects. Additionally, intramuscular, intravenous and intra-articular injections may also be used. Joints should not be injected greater than 3 times per year.

The side effect profile for corticosteroids include osteoporosis, hypothalamic-pituitary-adrenal suppression, cataracts, glaucoma, weight gain, emotional lability, hypertension, myopathy, impaired wound healing, Cushing’s syndrome, gastritis, glucose intolerance, and skin atrophy. Side effects may be minimized with the lowest effective dose. Calcium and vitamin D supplementation is recommended in the prevention and treatment of osteoporosis. Prophylactic bisphosphonates may also be considered in chronic corticosteroid users.

NSAIDs. Used adjunctively with DMARDs and glucocorticoids, NSAIDs reduce joint pain and improve joint function through anti-inflammatory and analgesic properties. They do not prevent the progression
of disease. NSAIDs mainly inhibit prostaglandins that are present in many cell types. Significant side effects occur twice as often in RA than osteoarthritis. The side effect profile for NSAIDs include gastrointestinal (GI) ulceration and bleeding, renal insufficiency, and elevated liver enzymes. Risk factors for GI complications include history of ulcer, concomitant use of glucocorticoids or anticoagulants, cardiovascular disease, dosage, and age > 75. High-dose H2 blockers and proton-pump inhibitors are gastroprotective agents, helping decrease NSAID-associated gastrointestinal ulcerations. Renal complications are increased in people with preexisting renal disease, congestive heart failure, coronary artery disease, cirrhosis, those receiving diuretics, and the elderly. NSAIDs are not recommended in patients with edema, congestive heart failure, nephritic syndrome, cirrhosis or serum creatinine ≥ 2.5 mg/dL.\textsuperscript{3,4,28}

**Treatment of RA is Constantly Changing**

Rheumatoid arthritis, the most common inflammatory arthritis, is a complicated disease with progressive joint destruction, leading to profound decreases in quality of life. Early diagnosis is critical as response to disease-modifying drugs decrease over time. Tightly controlled and aggressive treatments with traditional and biological DMARDs have been shown to significantly alter the disease course with an increased chance of obtaining remission. Adjunctive corticosteroids and NSAIDs significantly impact pain and quality of life. The introduction of several new treatment options in RA has lead to an overwhelming amount of conflicting data, making it difficult for specialists to choose the best options for their patients. Newly released ACR and EULAR recommendations help determine proper treatment based on poor prognostic factors, disease duration and disease activity. However, side effects are common with any RA treatment, and careful monitoring is crucial in preventing serious, life-threatening events.
References


41. Cimzia [prescribing information]. UCB Web site.


<table>
<thead>
<tr>
<th>TABLE 1. 2010 ACR/EULAR RA CLASSIFICATION CRITERIA</th>
<th>SCORE&lt;sup&gt;h&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joint Involvement</strong></td>
<td></td>
</tr>
<tr>
<td>1 large joint&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints&lt;sup&gt;b&lt;/sup&gt; (with or without large joint involvement)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without large joint involvement)</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 10 joints</td>
<td>5</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
</tr>
<tr>
<td>(≥ 1 test result is needed for classification)</td>
<td></td>
</tr>
<tr>
<td>Negative RF&lt;sup&gt;c&lt;/sup&gt; and negative ACPA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td><strong>Acute-Phase Reactants</strong> (≥ 1 test result is needed for classification)</td>
<td></td>
</tr>
<tr>
<td>Normal CRP&lt;sup&gt;e&lt;/sup&gt; and normal ESR&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>Duration of Symptoms</strong>&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥ 6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>
*Source: References 11-12*

- **a** Large joints include shoulders, elbows, hips, knees and ankles.
- **b** Small joints include metacarpophalangeal and proximal interphalangeal joints, 2nd through 5th metatarsophalangeal joints, thumb and wrists.
- **c** RF = rheumatoid factor
- **d** ACPA = anti-citrullinated protein antibody
- **e** CRP = c-reactive protein
- **f** ESR = erythrocyte sedimentation rate
- **g** Patient’s own assessment of sign and symptom duration
- **h** Score must be ≥ 6 to be classified as having RA

### TABLE 2. POOR PROGNOSTIC FACTORS IN RA

<table>
<thead>
<tr>
<th>Factor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High tender/swollen joint count</td>
<td></td>
</tr>
<tr>
<td>Elevated RF&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>High levels of ACPA&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>High levels of CRP&lt;sup&gt;c&lt;/sup&gt;, ESR&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>High disease activity measured by DAS, DAS28&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Early occurrence of erosions</td>
<td></td>
</tr>
<tr>
<td>Older age</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>HLA-DRB genotype</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
</tr>
<tr>
<td>Extra-articular disease&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*Source: References 10,14*

- **a** RF= rheumatoid factor
- **b** ACPA = anti-citrullinated peptide antibodies
- **c** CRP = c-reactive proteins
- **d** ESR = erythrocyte sedimentation rate
**e DAS, DAS28 = The Disease Activity Score, The Disease Activity Score using 28 joints**

**f Extra-articular disease = vasculitis, Sjögren’s syndrome, RA lung disease**

<table>
<thead>
<tr>
<th>TABLE 3. METHOTREXATE TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Stomatitis</td>
</tr>
<tr>
<td><strong>IMMUNOLOGIC</strong></td>
</tr>
<tr>
<td>Upper respiratory infections&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td><strong>HEPATIC</strong></td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Cirrhosis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibrosis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
</tr>
<tr>
<td>Headache&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fatigue/malaise</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Source: References 3, 25-27*

<sup>a</sup> Uncommon
<table>
<thead>
<tr>
<th>DRUG</th>
<th>SIDE EFFECTS</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tocilizumab</strong> (IL-1 Antagonist)</td>
<td>Gastrointestinal perforations&lt;br&gt;Upper respiratory tract infections&lt;br&gt;Nasopharyngitis&lt;br&gt;Headache&lt;br&gt;Hypertension&lt;br&gt;Increased ALT&lt;br&gt;Serious/Opportunistic infections&lt;br&gt;Demyelinating disorders&lt;br&gt;Immunosuppression&lt;br&gt;Infusion reactions&lt;br&gt;Elevated lipids&lt;br&gt;Malignancies</td>
<td>Starting dose: 4 mg/kg every 4 weeks as a 60 minute IV infusion&lt;br&gt;Increases to 8 mg/kg dependent on clinical response</td>
</tr>
<tr>
<td><strong>Anakinra</strong> (IL-1Ra Antagonist)</td>
<td>Injection site reactions&lt;br&gt;Serious infections&lt;br&gt;Decreased blood counts, platelets, absolute neutrophil count&lt;br&gt;Upper respiratory tract infections&lt;br&gt;Headache&lt;br&gt;Nausea&lt;br&gt;Diarrhea&lt;br&gt;Arthralgia&lt;br&gt;Malignancies</td>
<td>100 mg/day by subcutaneous injection*</td>
</tr>
</tbody>
</table>

*Serious/Opportunistic infections<br>Malignancy<br>Upper respiratory tract infections<br>Nasopharyngitis

50 mg once monthly by
| **Golimumab**  
| (TNF Antagonist) | Heart failure  
| Demyelinating disorders  
| Hepatitis B reactivation  
| Cytopenias  
| Increased liver enzymes  
| Injection site reactions | subcutaneous injection |

| **Rituximab**  
| (peripheral B cell depletion) | Tumor lysis syndrome  
| PML\(^a\)  
| Hepatitis B reactivation  
| Serious infections  
| Cardiac arrhythmias/angina  
| Bowel obstruction/perforation  
| Cytopenias  
| Upper respiratory tract infections  
| Nasopharyngitis  
| Urinary tract infections  
| Bronchitis  
| Infusion reactions  
| Mucocutaneous reactions | 1000 mg IV infusion separated by 2 weeks every 24 weeks  
| 100 mg IV methylprednisolone is recommended 30 minutes prior to infusions |

| **Abatacept**  
| (Binds CD80/86 on T cells, preventing activation) | Hypersensitivity reactions  
| Serious infections  
| Headache  
| Upper respiratory tract infections  
| Nasopharyngitis  
| Nausea  
| Malignancies  
| Infusion reactions | < 60 kg  
| 500 mg  
| 60 to 100 kg  
| 750 mg  
| > 100 kg  
| 1000 mg  
| All infusions are IV over 30 minutes given at 0, 2, 4 weeks followed by every 4 week infusions |

*Source: References 3,10,43-46*

\(^a\)PML= Progressive Multifocal Leukoencephalopathy