

## Review article

# Disease-Modifying Anti-Rheumatic Drugs (DMARDs) used for Rheumatoid Arthritis- A review

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### Abstract:

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic feature of established RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Worldwide prevalence of RA is of approximately 0.5-1%. The treatment of RA has evolved dramatically over the past 30years, perhaps more so than any of the rheumatic diseases. Once a diagnosis is made, the main treatment goals are to control disease activity and slow the rate of joint damage, in addition to minimizing pain, stiffness, inflammation, and complications. Pharmacologic therapies that are used include nonbiologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) and adjunctive agents such as corticosteroids, NSAIDs, and analgesics. The majority of patients newly diagnosed with RA can expect to have their disease in remission if treated early by rheumatologist. This remarkable fact has come about because of tremendous expansion of the number of disease-modifying anti-rheumatic drugs (DMARDs) available, the realization that these drugs can and should be used in combination and the acceptance that all patients should be treated to a target or goal of remission or low disease activity. DMARDs represent the most important measure in the successful treatment of RA. These agents can retard or prevent disease progression and, thus, joint destruction and subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications; however, until the full action of DMARDs takes effect, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling.

**Keywords:** Biologic agents, DMARDs, Methotrexate, Monoclonal antibody

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### Introduction:

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic feature of established RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity is

the hallmark of the disease. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, but most will have a relentless progressive polyarthritis with marked functional impairment.<sup>1</sup> Worldwide prevalence of RA is of approximately 0.5-1%.<sup>2</sup> Women are affected approximately three times more often than men. The

prevalence increases with age, and sex differences diminish in the older age group. RA is seen throughout the world and affects all races.<sup>1</sup>

The cause of this autoimmune disease remains obscure, but greater understanding of the underlying mechanisms has facilitated the development of new drugs and revolutionized treatment.<sup>3</sup> Specific CD4+ T cells are involved in the induction of immune response in rheumatoid arthritis, most likely as a response to an unknown exogenous or endogenous antigen. Consequently, recruited monocytes, macrophages and fibroblasts produce cytokines such as TNF- $\alpha$  and interleukin-1 within the synovial cavity. These cytokines are central to a damaging cascade, ultimately triggering the production of matrix metalloproteinase and osteoclast, which results in irreversible damage to soft tissues and bones. The occurrence of B-lymphocyte dysregulation is suggested by association of erosive disease with the presence of rheumatoid factor, which mediates further damage through complement fixation.<sup>4</sup> To attempt preventing irreversible damage to joints, the diagnosis of RA should be confirmed or ruled out within 2 months after the onset of synovitis.<sup>5</sup> Classification criteria were revised in 2010 by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).<sup>5</sup> The 2010 ACR/European League Against Rheumatism (EULAR) criteria were therefore developed with the purpose of facilitating the early recognition of RA.<sup>6</sup>

The treatment of RA has evolved dramatically over the past 30 years, perhaps more so than any of the rheumatic diseases.<sup>7</sup> Once a diagnosis is made, the main treatment goals are to control disease activity and slow the rate of joint damage, in addition to minimizing pain, stiffness, inflammation, and

complications. Pharmacologic therapies that are used include nonbiologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) and adjunctive agents such as corticosteroids, NSAIDs, and analgesics. The majority of patients newly diagnosed with RA can expect to have their disease in remission if treated early by rheumatologist. This remarkable fact has come about because of tremendous expansion of the number of disease-modifying anti-rheumatic drugs (DMARDs) available, the realization that these drugs can and should be used in combination and the acceptance that all patients should be treated to a target or goal of remission or low disease activity.<sup>7</sup> The present article, reviews the available DMARDs.

DMARDs represent the most important measure in the successful treatment of RA. These agents can retard or prevent disease progression and, thus, joint destruction and subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications; however, until the full action of DMARDs takes effect, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling.

Many studies have revealed that early treatment of RA (i.e. within months of onset) with DMARDs not only can retard disease progression more efficiently than later treatment but also may induce more remissions.<sup>8,9,10</sup> Thus early DMARD therapies (< 6 months after the onset of symptoms) has become the standard of care.<sup>11</sup> Patients with early forms of arthritis should be evaluated by and, if necessary, referred to physicians who are experienced in the diagnosis and treatment of RA.

### **Classification DMARDs:**

DMARDs can be classified into nonbiologic (conventional) and biologic agents.

The nonbiologic or conventional DMARDs includes hydroxychloroquine (HCQ), azathioprine (AZA), sulfasalazine (SSZ), methotrexate (MTX), leflunomide, cyclosporine, gold salts, D-penicillamine, and minocycline, corticosteroids.

Biologic DMARDs- the recognition of TNF- $\alpha$  and interleukin (IL)-1 as central proinflammatory cytokines has led to the development of biologic agents that block these cytokines or their effects. In addition to improving signs and symptoms and quality of life, all biologic agents significantly retard radiographic progression of joint erosions. These include agents such as adalimumab, certolizumab, etanercept, golimumab and infliximab, anakinra, abatacept, rituximab, tocilizumab.

By this definition, all 10 conventional DMARDs and the 9 biologic DMARDs qualify with the possible exception of minocycline and hydroxychloroquine, where only weak evidence exists for radiographic benefits.<sup>7</sup>

In terms of frequency of remissions and time to onset of action, MTX and SSZ are the most active compounds and provide the best risk-benefit ratios. MTX, either alone or in combination with other agents, has become the standard of care for moderate to severe RA. Injectable gold salts and penicillamine rarely induce sustained remission and thus have largely been supplanted by more effective agents.

In October 2013, the US Food and Drug Administration (FDA) approved the first single-dose, self-administered, disposable MTX subcutaneous autoinjector (Otrexup).<sup>12</sup> Otrexup is indicated for adults with severe, active RA who have either responded inadequately to or cannot tolerate first-line

therapy, as well as for children with active polyarticular juvenile idiopathic arthritis (JIA) (also known as juvenile rheumatoid arthritis).<sup>12</sup>

### **Nonbiologic or conventional DMARDs:-<sup>13</sup>**

#### **Methotrexate:**

Methotrexate is now considered the DMARD of first choice to treat rheumatoid arthritis and is used in 50–70% of patients. It is active in this condition at much lower doses than those needed in cancer chemotherapy.

#### **Mechanism of action**

Methotrexate's principal mechanism of action at the low doses used in the rheumatic diseases probably relates to inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase, with secondary effects on polymorphonuclear chemotaxis. There is some effect on dihydrofolate reductase and this affects lymphocyte and macrophage function, but this is not its principal mechanism of action. Methotrexate has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells. Additionally, inhibition of proinflammatory cytokines linked to rheumatoid synovitis has been shown, leading to decreased inflammation seen with rheumatoid arthritis.

#### **Pharmacokinetics**

The drug is approximately 70% absorbed after oral administration. It is metabolized to a less active hydroxylated metabolite, and both the parent compound and the metabolite are polyglutamated within cells, where they stay for prolonged periods. Methotrexate's serum half-life is usually only 6–9 hours, although it may be as long as 24 hours in some individuals. Methotrexate's concentration is increased in the presence of hydroxychloroquine, which can reduce the clearance or increase the tubular

reabsorption of methotrexate. This drug is excreted principally in the urine, but up to 30% may be excreted in bile.

#### **Indications**

Although the most common methotrexate dosing regimen for the treatment of rheumatoid arthritis is 15–25 mg weekly, there is an increased effect up to 30–35 mg weekly. The drug decreases the rate of appearance of new erosions. Evidence supports its use in juvenile chronic arthritis.

#### **Adverse effects**

Nausea and mucosal ulcers are the most common toxicities. Progressive dose-related hepatotoxicity in the form of enzyme elevation occurs frequently, but cirrhosis is rare (< 1%). Liver toxicity is not related to serum methotrexate concentrations, and liver biopsy follow-up is only recommended every 5 years. A rare hypersensitivity-like lung reaction with acute shortness of breath is documented, as are pseudolymphomatous reactions. The incidence of gastrointestinal and liver function test abnormalities can be reduced by the use of leucovorin 24 hours after each weekly dose or by the use of daily folic acid, although this may decrease the efficacy of the methotrexate. This drug is contraindicated in pregnancy.

#### **Chloroquine & Hydroxychloroquine:-**

##### **Mechanism of action**

Chloroquine and hydroxychloroquine are used mainly in malaria and in the rheumatic diseases. The mechanism of the anti-inflammatory action of these drugs in rheumatic diseases is unclear. The proposed mechanism is suppression of T-lymphocyte responses to mitogens, decreased leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA and RNA synthesis, and the trapping of free radicals.

#### **Pharmacokinetics**

Antimalarials are rapidly absorbed and 50% protein-bound in the plasma. They are very extensively tissue-bound, particularly in melanin-containing tissues such as the eyes. The drugs are deaminated in the liver and have blood elimination half-lives of up to 45 days.

#### **Indications**

Antimalarials are approved for rheumatoid arthritis, but they are not considered very effective DMARDs. Dose-response and serum concentration-response relationships have been documented for hydroxychloroquine and dose-loading may increase rate of response. Although antimalarials improve symptoms, there is no evidence that these compounds alter bony damage in rheumatoid arthritis at their usual dosages (up to 6.4 mg/kg/d for hydroxychloroquine or 200 mg/d for chloroquine). It usually takes 3–6 months to obtain a response.

#### **Adverse effects**

Although ocular toxicity may occur at dosages greater than 250 mg/d for chloroquine and greater than 6.4 mg/kg/d for hydroxychloroquine, it rarely occurs at lower doses. Nevertheless, ophthalmologic monitoring every 6–12 months is advised. Other toxicities include dyspepsia, nausea, vomiting, abdominal pain, rashes, and nightmares. These drugs appear to be relatively safe in pregnancy.

#### **Sulfasalazine:**

##### **Mechanism of action**

Sulfasalazine is metabolized to sulfapyridine and 5-aminosalicylic acid, and it is thought that the sulfapyridine is probably the active moiety when treating rheumatoid arthritis. Some authorities believe that the parent compound, sulfasalazine, also has an effect. In treated arthritis patients, IgA and IgM rheumatoid factor production are decreased.

Suppression of T-cell responses to concanavalin and inhibition of in vitro B-cell proliferation have also been documented. In vitro studies have shown that sulfasalazine or its metabolites inhibit the release of inflammatory cytokines, including those produced by monocytes or macrophages, eg, interleukins-1, -6, and -12, and TNF-These findings suggest a possible mechanism for the clinical efficacy of sulfasalazine in rheumatoid arthritis.

#### **Pharmacokinetics**

Only 10–20% of orally administered sulfasalazine is absorbed, although a fraction undergoes enterohepatic recirculation into the bowel where it is reduced by intestinal bacteria to liberate sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is well absorbed while 5-aminosalicylic acid remains unabsorbed. Some sulfasalazine is excreted unchanged in the urine whereas sulfapyridine is excreted after hepatic acetylation and hydroxylation. Sulfasalazine's half-life is 6–17 hours.

#### **Indications**

Sulfasalazine is effective in rheumatoid arthritis and reduces radiologic disease progression. It has been used in juvenile chronic arthritis and in ankylosing spondylitis and its associated uveitis. The usual regimen is 2–3 g/d.

#### **Adverse effects**

Approximately 30% of patients using sulfasalazine discontinue the drug because of toxicity. Common adverse effects include nausea, vomiting, headache, and rash. Hemolytic anemia and methemoglobinemia also occur, but rarely. Neutropenia occurs in 1–5% of patients, while thrombocytopenia is very rare. Pulmonary toxicity and positive double-stranded DNA are occasionally seen, but drug-induced lupus is rare. Reversible infertility occurs in men, but

sulfasalazine does not affect fertility in women. The drug does not appear to be teratogenic.

#### **Leflunomide:**

##### **Mechanism of action**

Leflunomide undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, A77-1726. This metabolite inhibits dihydroorotate dehydrogenase, leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G<sub>1</sub> phase of cell growth. Consequently, leflunomide inhibits T-cell proliferation and production of autoantibodies by B cells. Secondary effects include increases of interleukin-10 receptor mRNA, decreased interleukin-8 receptor type A mRNA, and decreased TNF-dependent nuclear factor kappa B (NF- $\kappa$ B) activation.

##### **Pharmacokinetics**

Leflunomide is completely absorbed and has a mean plasma half-life of 19 days. A77-1726, the active metabolite of leflunomide, is thought to have approximately the same half-life and is subject to enterohepatic recirculation. Cholestyramine can enhance leflunomide excretion and increases total clearance by approximately 50%.

##### **Indications**

Leflunomide is as effective as methotrexate in rheumatoid arthritis, including inhibition of bony damage. In one study, combined treatment with methotrexate and leflunomide resulted in a 46.2% ACR20 response compared with 19.5% in patients receiving methotrexate alone.

##### **Adverse effects**

Diarrhea occurs in approximately 25% of patients given leflunomide, although only about 3–5% discontinue the drug because of this effect. Elevation in liver enzymes also occurs. Both effects can be reduced by decreasing the dose of

leflunomide. Other adverse effects associated with leflunomide are mild alopecia, weight gain, and increased blood pressure. Leukopenia and thrombocytopenia occur rarely. This drug is contraindicated in pregnancy.

#### **Azathioprine:**

##### **Mechanism of action**

Azathioprine acts through its major metabolite, 6-thioguanine. 6-Thioguanine suppresses inosinic acid synthesis, B-cell and T-cell function, immunoglobulin production, and interleukin-2 secretion.

##### **Pharmacokinetics**

The metabolism of azathioprine is bimodal in humans, with rapid metabolizers clearing the drug four times faster than slow metabolizers. Production of 6-thioguanine is dependent on thiopurine methyltransferase (TPMT), and patients with low or absent TPMT activity (0.3% of the population) are at particularly high risk of myelosuppression by excess concentrations of the parent drug if dosage is not adjusted.

##### **Indications**

Azathioprine is approved for use in rheumatoid arthritis and is used at a dosage of 2 mg/kg/d.

##### **Adverse effects**

Azathioprine's toxicity includes bone marrow suppression, gastrointestinal disturbances, and some increase in infection risk. As noted in Chapter 55, lymphomas may be increased with azathioprine use. Rarely, fever, rash, and hepatotoxicity signal acute allergic reactions.

#### **Cyclosporine:**

##### **Mechanism of action**

Through regulation of gene transcription, cyclosporine inhibits interleukin-1 and interleukin-2 receptor production and secondarily inhibits

macrophage-T-cell interaction and T-cell responsiveness. T-cell-dependent B-cell function is also affected.

##### **Pharmacokinetics**

Cyclosporine absorption is incomplete and somewhat erratic, although a microemulsion formulation improves its consistency and provides 20–30% bioavailability. Grapefruit juice increases cyclosporine bioavailability by as much as 62%. Cyclosporine is metabolized by CYP3A and consequently is subject to a large number of drug interactions (including many antimicrobials and nonantimicrobials).

##### **Indications**

Cyclosporine is approved for use in rheumatoid arthritis and retards the appearance of new bony erosions. Its usual dosage is 3–5 mg/kg/d divided into two doses. Anecdotal reports suggest that it may be useful in systemic lupus erythematosus, polymyositis and dermatomyositis, Wegener's granulomatosis, and juvenile chronic arthritis.

##### **Adverse effects**

Cyclosporine has significant nephrotoxicity, and its toxicity can be increased by drug interactions with diltiazem, potassium-sparing diuretics, and other drugs inhibiting CYP3A. Serum creatinine should be closely monitored. Other toxicities include hypertension, hyperkalemia, hepatotoxicity, gingival hyperplasia, and hirsutism.

##### **Minocycline:**

Tetracycline and derivatives have a long and somewhat checkered history with regard to the treatment of RA. Mechanism of action is poorly understood. Tetracyclines are of course, antibiotics, but additionally they inhibit metalloproteinases, modulate immune responses, and have anti-inflammatory effects.

**Adverse effects:-** Hepatotoxic, nephrotoxicity, vestibular damage, gastrotoxicity

**Gold salts, Penicillamine:-**

These older agents have unclear mechanisms of action and tend to have slight efficacy and significant side effects. Gold injections have been used in the treatment of RA for close to century-initially intramuscularly and, more recently, orally. With advent of newer agents, gold is rarely used in most part of world.

**Biologic DMARDs<sup>13</sup>**

**Etanercept:-**

**Mechanism of action**

Etanercept is a recombinant fusion protein consisting of two soluble TNF p75 receptor moieties linked to the F<sub>c</sub> portion of human IgG<sub>1</sub>; it binds TNF- $\alpha$  molecules and also inhibits lymphotoxin- $\alpha$ .

**Pharmacokinetics**

Etanercept is given subcutaneously in a dosage of 25 mg twice weekly or 50 mg weekly. In psoriasis, 50 mg is given twice weekly for 12 weeks followed by 50 mg weekly. The drug is slowly absorbed, with peak concentration 72 hours after drug administration. Etanercept has a mean serum elimination half-life of 4.5 days. Fifty milligrams given once weekly, gives the same area under the curve and minimum serum concentrations as 25 mg twice weekly.

**Indications**

It can be used as monotherapy although over 70% of patients taking etanercept are also using methotrexate. Etanercept decreases the rate of formation of new erosions relative to methotrexate alone.

**Infliximab:-**

**Mechanism of action**

Infliximab (Figure 36-4) is a chimeric (25% mouse, 75% human) IgG<sub>1</sub> monoclonal antibody that binds with high affinity to soluble and possibly membrane-bound TNF- $\alpha$ . Its mechanism of action probably is the same as that of adalimumab.

**Pharmacokinetics**

Infliximab is given as an intravenous infusion at doses of 3-10 mg/kg, although the usual dose is 3-5 mg/kg every 8 weeks. There is a relationship between serum concentration and effect, although individual clearances vary markedly. The terminal half-life is 9-12 days without accumulation after repeated dosing at the recommended interval of 8 weeks. After intermittent therapy, infliximab elicits human antichimeric antibodies in up to 62% of patients. Concurrent therapy with methotrexate markedly decreases the prevalence of human antichimeric antibodies.

**Indications**

Infliximab is approved for use in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. It is being used in other diseases, including psoriasis, ulcerative colitis, juvenile chronic arthritis, Wegener's granulomatosis, giant cell arteritis, and sarcoidosis. In rheumatoid arthritis, a regimen of infliximab plus methotrexate decreases the rate of formation of new erosions more than methotrexate alone over 12-24 months. Although it is recommended that methotrexate be used in conjunction with infliximab, a number of other DMARDs, including antimalarials, azathioprine, leflunomide, and cyclosporine, can be used as background therapy for this drug.

**Anakinra:-**

Anakinra is a recombinant nonglycosylated form of the human IL-1 receptor antagonist (IL-1ra). IL-1ra

occupies the IL-1 receptor without triggering it and prevents receptor binding of IL-1. In clinical trials, a significant response was observed in approximately 40% of patients with RA.

#### **Adverse effects<sup>14</sup>**

Dose dependent skin irritation at injection site, occurring in 50 to 80 percent of patients in trials. Most reactions appeared to be mild, and resolved within few weeks. A small number of patients reported more severe allergic-type reactions involving itching, swelling and pain.

The risk of infection, primarily bacterial, appears to be increased. Serious infections occurred in 2.1percent patients receiving anakinra, as compared with 0.4percent of those receiving placebo, in one study involving 1000 patients (P=0.07); no opportunistic infections were observed.

#### **Adalimumab:-**

##### **Mechanism of action**

Adalimumab is a fully human IgG<sub>1</sub> anti-TNF monoclonal antibody. This compound complexes with soluble TNF- and prevents its interaction with p55 and p75 cell surface receptors. This results in down-regulation of macrophage and T cell function.

##### **Pharmacokinetics**

Adalimumab is given subcutaneously and has a half-life of 10–20 days. Its clearance is decreased by more than 40% in the presence of methotrexate, and the formation of human antimonoelonal antibody is decreased when methotrexate is given at the same time. The usual dose in rheumatoid arthritis is 40 mg every other week, although increased responses may be evident at higher dosages. In psoriasis, 80 mg is given at week 0, 40 mg at week 1, and then 40 mg every other week thereafter.

#### **Indications**

The compound is approved for the treatment of rheumatoid arthritis. It decreases the rate of formation of new erosions. It is effective both as monotherapy and in combination with methotrexate and other DMARDs.

A 5-year analysis of an open-label extension (OLE) study concluded that a delay of 52 weeks for adding adalimumab to concomitant MTX therapy contributed to inferior radiographic, functional, and clinical outcomes in patients with active RA.<sup>15</sup>

According to data from a study of 221 consecutive RA patients, adalimumab blood levels of 5 to 8 µg/mL have the greatest effect on disease activity. In the study, adalimumab trough levels greater than 8 µg/mL had no additional beneficial effect on disease activity.<sup>16,17</sup> Study participants were treated with 40 mg adalimumab subcutaneously every other week for 28 weeks and stratified according to whether or not they were taking concomitant methotrexate (MTX). Patients treated with concomitant methotrexate reached recommended blood levels at lower adalimumab doses. At 28-week follow-up, mean adalimumab levels were 4.1 µg/mL in patients receiving monotherapy and 7.4 µg/mL in patients receiving concomitant methotrexate.

#### **Adverse effects**

In common with the other TNF-blocking agents, the risk of bacterial infections and macrophage-dependent infection (including tuberculosis and other opportunistic infections) is increased, although it remains very low. Patients should be screened for latent or active tuberculosis before starting adalimumab or other TNF- α blocking agents. There is no evidence of an increased incidence of solid malignancies. It is not clear if the incidence of lymphomas is increased by adalimumab. A low



incidence of newly formed double-stranded DNA (dsDNA) antibodies and antinuclear antibodies (ANAs) has been documented when using adalimumab, but clinical lupus is extremely rare. Rare leukopenias and vasculitis, apparently associated with adalimumab, have been documented.

**Abatacept:-**

**Mechanism of action**

Abatacept is a costimulation modulator that inhibits the activation of T cells. After a T cell has engaged an antigen-presenting cell (APC), a signal is produced by CD28 on the T cell that interacts with CD80 or CD86 on the APC, leading to T-cell activation. Abatacept (which contains the endogenous ligand CTLA-4) binds to CD80 and 86, thereby inhibiting the binding to CD28 and preventing the activation of T cells.

**Pharmacokinetics**

Abatacept is given as an intravenous infusion in three initial doses (day 0, week 2, and week 4), followed by monthly infusions. The dose is based on body weight, with patients weighing less than 60 kg receiving 500 mg, that 60–100 kg receiving 750 mg and those more than 100 kg receiving 1000 mg. Dosing regimens in any adult group can be increased if needed. The terminal serum half-life is 13–16 days. Coadministration with methotrexate, NSAIDs, and corticosteroids does not influence abatacept clearance.

**Indications**

Abatacept can be used as monotherapy or in combination with other DMARDs in patients with moderate to severe rheumatoid arthritis who have had an inadequate response to other DMARDs. It reduces the clinical signs and symptoms of rheumatoid arthritis, including slowing of radiographic

progression. It is also being tested in early rheumatoid arthritis.

Maintenance doses of abatacept may be administered as a monthly intravenous (IV) infusion or by the patient as a weekly SC injection.<sup>18</sup> In patients with RA who have previously had treatment failure with anti-TNF therapy, abatacept has been shown to demonstrate consistent safety and efficacy that are maintained from 6 months to 5 years of therapy.<sup>19</sup>

A head-to-head phase IIIb randomized noninferiority trial found that subcutaneous (SC) abatacept and SC adalimumab were equally effective in RA patients, with comparable safety (though adalimumab was associated with more injection-site reactions).<sup>20,21</sup> Adding either treatment to background methotrexate produced similar American College of Rheumatology 20% improvement response (ACR20) rates and similar rates of radiographic nonprogression. In view of these findings, clinicians may reasonably conclude that the 2 agents are substantially equivalent for treating RA.

**Rituximab:-**

**Mechanism of action**

Rituximab is a chimeric monoclonal antibody that targets CD20 B lymphocytes. This depletion takes place through cell-mediated and complement-dependent cytotoxicity and stimulation of cell apoptosis. Depletion of B lymphocytes reduces inflammation by decreasing the presentation of antigens to T lymphocytes and inhibiting the secretion of proinflammatory cytokines. Rituximab rapidly depletes peripheral B cells although this depletion neither correlates with efficacy nor with toxicity. Rituximab has shown benefit in the treatment of rheumatoid arthritis refractory to anti-TNF agents. It has been approved for the treatment of

active rheumatoid arthritis when combined with methotrexate.

#### **Pharmacokinetics**

Rituximab is given as two intravenous infusions of 1000 mg, separated by 2 weeks. It may be repeated every 6–9 months, as needed. Repeated courses remain effective. Pretreatment with glucocorticoids given intravenously 30 minutes prior to infusion (usually 100 mg of methylprednisolone) decreases the incidence and severity of infusion reactions.

#### **Indications**

Rituximab is indicated for the treatment of moderately to severely active rheumatoid arthritis in combination with methotrexate in patients with an inadequate response to one or more TNF-antagonists. Rituximab is most often used in combination with MTX. It has been shown to be effective for reducing signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response to therapy with 1 or more TNF inhibitors.<sup>22,23,24</sup>

#### **Adverse effects**

About 30% of patients develop rashes with the first 1000 mg treatment; this incidence decreases to about 10% with the second infusion and progressively decreases with each course of therapy thereafter. These rashes do not usually require discontinuation of therapy although urticarial or anaphylactoid reactions, of course, preclude further therapy. Immunoglobulins (particularly IgG and IgM) may decrease with repeated courses of therapy and infections can occur, although they do not seem directly associated with the decreases in immunoglobulins. Rituximab has not been associated with activation of tuberculosis, nor with the occurrence of lymphomas or other tumors. Other adverse effects, eg, cardiovascular events, are rare.

#### **Certolizumab:**

Fleischmann et al found that monotherapy with certolizumab effectively reduced the signs and symptoms of active RA in patients in whom DMARD therapy had failed.<sup>26</sup> In this study, 200 patients were randomized on a 1:1 basis to receive certolizumab 400 mg or placebo every 4 weeks for 24 weeks. At 24 weeks, 45.5% of the certolizumab group achieved a 20% improvement, according to ACR criteria, compared with 9.3% of the placebo group. Statistically significant differences were observed as early as week 1 through week 24.<sup>26</sup>

#### **Golimumab:**

##### **Mechanism of action**

Golimumab is a human anti-TNF- $\alpha$  monoclonal antibody that inhibits TNF- $\alpha$  bioactivity, thereby modulating immune activity in patients with RA. Using a modified intention-to-treat analysis, researchers demonstrated that golimumab plus MTX is more efficacious than MTX alone (and that golimumab alone is about as efficacious as MTX alone) in reducing disease signs and symptoms in MTX-naive patients.<sup>28</sup>

In this 52-week, randomized, double-blind, placebo-controlled study, which was followed by an open-label extension through 5 years, 637 patients were randomized to receive placebo plus MTX (group 1), golimumab 100 mg SC plus placebo (group 2), golimumab 50 mg SC plus MTX (group 3), or golimumab 100 mg SC plus MTX (group 4).<sup>28</sup>

Intent-to-treat analysis showed no significant differences in the primary endpoint between group 1 and groups 3 and 4 combined, indicating efficacy of subcutaneous golimumab. The incidence of serious adverse events was similar across all groups.

In July 2013, the FDA approved golimumab IV.<sup>29,30,31</sup> Approval was supported by a phase 3 study of 592

patients with moderately to severely active RA who had been receiving background MTX for at least 3 months.

In this study, 58.5% (n = 231/395) of patients receiving treatment with golimumab IV plus MTX experienced significant improvements in signs and symptoms at week 14 compared with 24.9% of patients receiving placebo plus MTX (n = 49/197).<sup>31</sup> Improvement was demonstrated by at least a 20% increase in ACR 20 score, the study's primary endpoint. A higher proportion of patients receiving golimumab plus methotrexate achieved at least a 50% improvement in ACR criteria (ACR 50) at week 14 (30%) compared with patients receiving placebo plus MTX (9%).

The rate of adverse events and serious adverse events, respectively, at week 24 were 53% and 4% in the golimumab group and 49% and 2% in the placebo group.<sup>29, 30</sup> The most common adverse events were "infections and infestations," including upper respiratory tract infection (>5% of patients), urinary tract infection, and nasopharyngitis. Exacerbation of RA occurred in 5.6% of patients receiving placebo plus MTX.<sup>29</sup>

At week 52, the rate of adverse events and serious adverse events in the golimumab group were 65% and 9%, respectively.<sup>29</sup> No serious opportunistic infections occurred through week 52. However, in the golimumab group, a single case of tuberculosis was reported, and a patient died from a myocardial infarction secondary to community-acquired pneumonia.<sup>29</sup>

#### **Adverse effects**

Increase risk of serious infections including tuberculosis, fungal and other opportunistic pathogens. Prior to treatment, testing for latent

tuberculosis should be performed. Association with solid tumors possibly non-melanotic skin cancer.

#### **Tocilizumab:**

Tocilizumab, an IL-6 receptor inhibitor, is available as either an IV infusion or SC injection. It is indicated for moderate-to-severe active RA in adults who have had an inadequate response to 1 or more TNF-antagonist therapies. It may be used either alone or in combination with MTX or other DMARDs. However, Dougados et al found that in patients with active RA, combination therapy with IV tocilizumab and MTX did not yield better clinical results than tocilizumab monotherapy and that was more often associated with transaminase increases.<sup>32</sup>

In patients with inadequate response to TNF inhibitors, tocilizumab treatment results in significant, clinically meaningful, rapid, and sustained improvements in a number of patient-reported outcomes.<sup>33,34</sup>

In October 2013, the FDA approved a SC injection of tocilizumab that can be self-administered after proper training. The SC formulation has been shown to be equally efficacious compared to the IV infusion and has the same safety profile except for increased injection site reactions with SC administration.<sup>34</sup>

A 2012 consensus statement confirmed the efficacy and safety of IL-6 pathway blockade in adult rheumatoid arthritis.<sup>35</sup>

#### **Adverse effects**

Serious infections, elevated liver enzymes neutropenia, decreased platelet counts, lipids should be monitored. GI perforation has been reported when using tocilizumab in patients with diverticulitis or who are using corticosteroids.

#### **Tofacitinib:**

Janus kinases (JAKs) consist of a group of intracellular tyrosine kinases that transmit signals

from cytokine or growth factor–receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which modulate intracellular activity, including gene expression.

JAK inhibitors modulate the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. These signals maintain the inflammatory condition in RA. Inhibition of JAKs reduces production of and modulates proinflammatory cytokines central to RA.

Tofacitinib is an oral JAK inhibitor<sup>36</sup> that was approved by the US Food and Drug Administration (FDA) in November 2012 as second-line treatment for moderate to severe active RA.<sup>37</sup> The indication is specific for patients who have had an inadequate response to or are intolerant of MTX. Tofacitinib may be given as monotherapy or in combination with MTX or other nonbiologic DMARDs. It should not be used in combination with biologic DMARDs or potent immunosuppressive agents (eg, azathioprine or cyclosporine).

Tofacitinib has been associated with reductions in signs and symptoms of RA and improvement in physical function. Fleischmann et al demonstrated that ACR criteria for a 20% response were met in 59.8% of patients receiving monotherapy with tofacitinib 5 mg twice daily, compared with 26.7% of patients receiving placebo.<sup>38</sup> Health Assessment Questionnaire Disability Index (HAQ-DI) reduction was also greater in the tofacitinib group (–0.50 points) than in the placebo group (–0.19 points).

In another study, in which 717 patients who received stable MTX doses over 12 months were randomized to also receive 5 mg or 10 mg of tofacitinib orally

twice daily, adalimumab 40 mg every 2 weeks, or placebo, ACR 20% response rates at 6 months were higher among patients receiving 5 mg or 10 mg of tofacitinib (51.5% and 52.6%, respectively) and among those receiving adalimumab (47.2%) than among those receiving placebo (28.3%).<sup>39</sup>

#### **Corticosteroids:**

Corticosteroids are potent anti-inflammatory drugs that are commonly used in patients with RA to bridge the time until treatment with DMARDs is effective.<sup>40</sup> <sup>41</sup> These agents are effective adjuncts to DMARD or NSAID therapy. Timely dose reductions and cessation are important because of the adverse effects associated with long-term steroid use. Corticosteroids can be administered by oral, IV, or intra-articular routes.

When Buttgerit et al studied circadian rhythms in 288 patients with active RA, half of whom were randomly assigned to a modified-release (MR) prednisone tablet and the other half to an immediate-release (IR) prednisone tablet, there was a clinically relevant reduction of morning stiffness of the joints with the MR product as compared with the IR product.<sup>42</sup>

A 9- months extension of the same study showed that the MR prednisone taken at bedtime was well tolerated and provided a sustained improvement.<sup>43</sup> A third study that added low-dose MR prednisone to existing DMARD treatment also showed improvements in RA signs and symptoms, including a reduction in morning stiffness as compared with baseline (35% vs 55%).<sup>44</sup>

A comparison of high-dose IV steroids with infliximab in the 18-month randomized, double-blind IDEA study found similar rates of remission induction and sustained remission, as well as the time to sustained remission, with the two agents. The

study, which included 112 patients with new-onset DMARD-naïve RA, compared the efficacy of infliximab and IV steroid therapy, both in combination with methotrexate, as remission induction in early RA, followed by a treat-to-target approach.

#### **Adverse effects**

Hyperglycemia, osteoporosis, hypertension. One study found that the use of corticosteroids was associated with heart failure in patients with RA, independent of cardiovascular risk factors and coronary heart disease (CHD). Those patients who currently used MTX showed a lower risk of heart failure.<sup>45</sup>

#### **Combination Therapy of DMARDs**

In a 1998 study, approximately half of North American rheumatologists treated moderately aggressive rheumatoid arthritis with combination therapy, and the use of drug combinations is probably much higher now. Combinations of DMARDs can be designed rationally on the basis of complementary mechanisms of action, nonoverlapping pharmacokinetics, and nonoverlapping toxicities.

When added to methotrexate background therapy, cyclosporine, chloroquine, hydroxychloroquine, leflunomide, infliximab, adalimumab, rituximab, and etanercept have all shown improved efficacy. In contrast, azathioprine, auranofin, or sulfasalazine plus methotrexate results in no additional therapeutic benefit. Other combinations have occasionally been used, including the combination of intramuscular gold with hydroxychloroquine.

While it might be anticipated that combination therapy might result in more toxicity, this is often not the case. Combination therapy for patients not responding adequately to monotherapy is becoming the rule in the treatment of rheumatoid arthritis.

The ACR recommends that before patients undergo pharmacologic treatment with either nonbiologic or biologic DMARDs, they receive not only the pneumococcal, hepatitis, and influenza vaccinations (as indicated in the 2008 ACR recommendations)<sup>11</sup> but also vaccinations for HPV and HZV (added in the 2012 updated ACR recommendations).<sup>46</sup>

#### **Complications of DMARDs treatment**

Patients with an established diagnosis of RA who are being treated with DMARDs, particularly those treated with combination therapy, including biologic agents such as TNF antagonists, may present with serious infections, malignancies, or both.<sup>47,48,49</sup> Additionally, adverse events from RA medications may include liver toxicity, renal toxicity, bone marrow depression, lung inflammation, and skin manifestations.

#### **TNF precautions and mortality**

Patients taking anti-TNF agents must avoid live-virus vaccines (eg, measles-mumps-rubella [MMR], HZV, varicella-zoster virus [VZV], and bacillus Calmette-Guérin [BCG] vaccines) to avoid the potential for serious infection.

A large national prospective cohort study over a mean of 4 years demonstrated that anti-TNF therapy for RA was not associated with a significant increase or decrease in mortality when compared with standard nonbiologic DMARD therapy.<sup>50</sup> The results from another study confirmed that the risk of serious infection and malignancy is not increased in patients receiving anti-TNF therapy when the patients have early RA and have not been previously treated with MTX or other DMARDs.<sup>51</sup>

In a systematic review and meta-analysis reporting on the risk of malignancy in patients with RA treated with TNF inhibitors, the data reviewed showed that these agents did not increase the risk of malignancy,

particularly lymphoma; however, they did appear to increase the risk of skin cancer, including melanoma.<sup>52</sup>

**Conclusion:**

DMARDs represent the most important measure in the successful treatment of rheumatoid arthritis. These agents can retard or prevent disease progression and, thus, joint destruction and

subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications; however, until the full action of DMARDs takes effect, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling.

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