Treatment of rheumatoid arthritis

ANGELO GAFFO, KENNETH G. SAAG, AND JEFFREY R. CURTIS

Purpose. Current and investigational treatments of rheumatoid arthritis (RA) are described.

Summary. The current therapies used to treat RA include nonsteroidal antiinflammatory drugs (NSAIDs), used for the management of pain and inflammation; disease-modifying antirheumatic drugs (DMARDs), used as first-line therapy for all newly diagnosed cases of RA; and biological-response modifiers, targeted agents that selectively inhibit specific molecules of the immune system. Glucocorticoids and other antirheumatic drugs are also used to treat RA. DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. NSAIDs and glucocorticoids are effective in controlling the pain, inflammation, and stiffness related to RA. Unlike NSAIDs, they slow clinical and radiographic progression of RA. The biological-response modifiers include infliximab, etanercept, and adalimumab (inhibitors of tumor necrosis factor [TNF]-α); anakinra, a recombinant inhibitor of interleukin-1; abatacept, the first costimulation blocker; and rituximab, a chimeric anti-CD20 monoclonal antibody. Investigational therapies for RA include anti-interleukin-6-receptor monoclonal antibodies, new TNF-α inhibitors (including one for oral administration), and antibodies against proteins critical for B-cell function and survival. Data accumulated in the past decade favor early aggressive therapy for patients suspected of having RA, including early referral to a rheumatologist, new diagnostic techniques, and aggressive therapy with DMARDs, glucocorticoids, and biological agents. The benefits of this approach have been demonstrated in clinical trials.

Conclusion. Pharmacologic treatments of RA include NSAIDs, glucocorticoids, DMARDs, and biological agents. With an improved understanding of the pathophysiology of RA and the evidence from various clinical trials with the agents, early aggressive therapy with a combination of drugs or biological agents may be warranted for the effective treatment of RA.

Index terms: Abatacept; Adalimumab; Anakinra; Antibodies; Antiinflammatory agents; Arthritis; Chondroprotective agents; Diagnosis; Drugs, investigational; Etanercept; Hydroxychloroquine; Immunomodulating agents; Infliximab; Leflunomide; Methotrexate; Rituximab; Steroids, cortico-; Sulfasalazine

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Rheumatoid arthritis (RA) is a common, chronic, and systemic inflammatory autoimmune disease. Although RA preferentially targets the synovial lining of the joints, it can affect other organ systems including the lungs, heart, and blood vessels. An estimated 0.5–1% of the general U.S. population has RA.[1] The disease, if untreated, often leads to permanent joint damage, significant impairment in quality of life, and eventual disability. Because of the substantial risk of morbidity, a heightened risk of premature mortality,[2] and an improved understanding of the pathophysiology of RA, the therapeutic approach to RA has moved rapidly toward early diagnosis and aggressive management. This article describes the current and investigational treatments for RA.

Pathogenesis

While much is still unknown about the specific triggers and exact mechanisms of tissue damage in RA, both genetic and environmental factors play a role in the initiation of an immunologic response against the synovium. Genetic polymorphisms of the major histocompatibility complex (MHC) II have been implicated in a predisposition to RA in various ethnic groups. MHC II encodes human leukocyte antigens (HLAs), and among those associated with an increased RA risk are HLA-DR1, HLA-DR4, HLA-DR6, and HLA-DR10.[3]

The antigen that, combined with certain MHC haplotypes, could inappropriately activate the immune system in RA has remained elusive. Infections and environmental trig-

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gers (e.g., tobacco use) have been proposed as initiators in genetically susceptible individuals.[4,5]

After some unknown initial environmental trigger, several circulating cell types and endothelial cells, along with their cytokine products, appear to play a role in the induction and maintenance of the deleterious immune reaction responsible for RA. This has been the subject of intense investigation in the past decade, and most of the more recent therapeutic developments have targeted these inflammatory pathways. A simplified model depicting the highlights of this cascade and the sites of action of some of the drugs used to treat RA is shown in Figure 1.

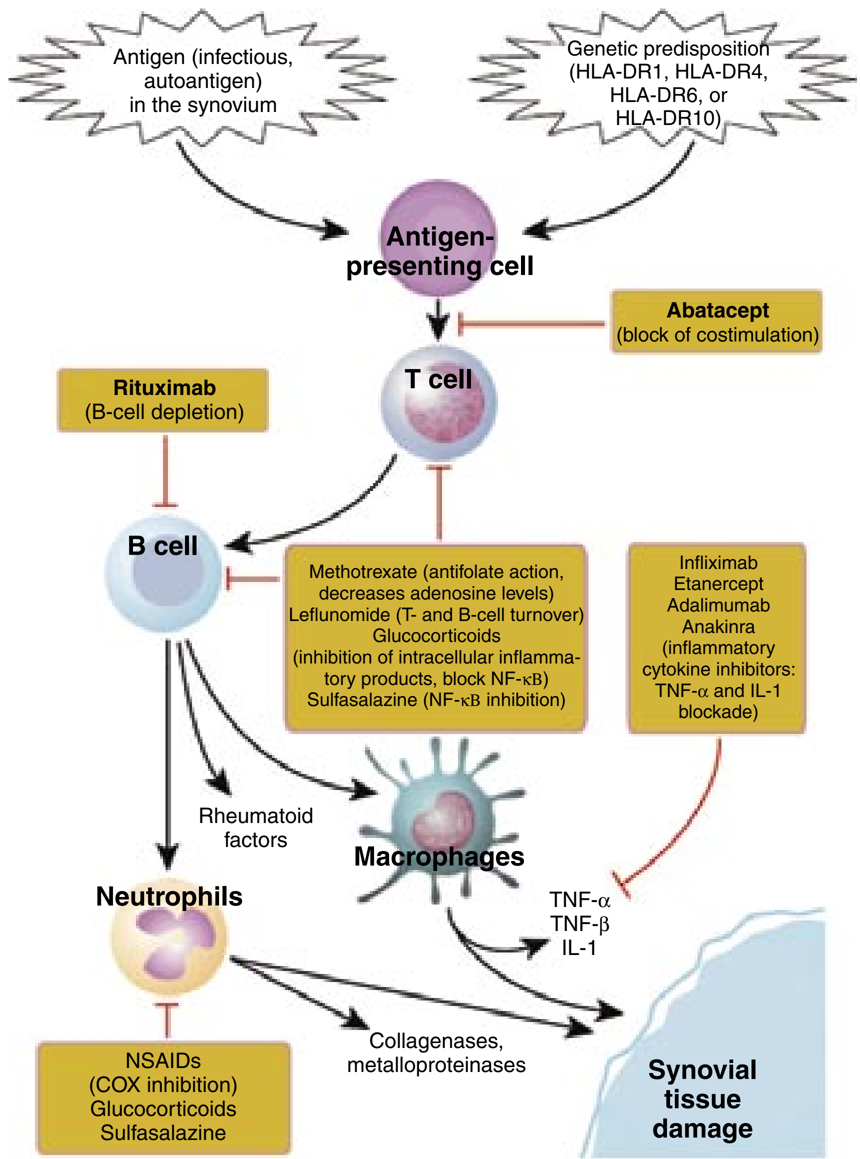
Epidemiology, clinical presentation, and diagnosis

RA affects twice as many women as men.[6] Its prevalence is fairly constant, with some variation depending on geographic location. The usual age of onset is between the third and fifth decades of life, though the frequency continues to rise after the sixth decade.

RA symptoms reflect the fact that it is a systemic, inflammatory condition. Fatigue, prolonged morning stiffness, and pain that improve with activity are prominent in early disease and may help differentiate RA from the more common, noninflammatory forms of arthritis, such as osteoarthritis. In contrast with RA, osteoarthritis is usually associated with minimal morning stiffness but pain that worsens with activity.

RA causes pain, swelling, and stiffness in the joints of the upper and lower extremities. It usually involves more than five joints, affects joints on both sides of the body, and preferentially targets the small joints of the wrists, hands, and feet. In the most common presentation of RA, the proximal interphalangeal joints, metacarpophalangeal joints, wrists, and metatarsophalangeal joints in the feet are persistently painful and swollen. The knees can also be involved in early disease; however, clinical manifestations in larger joints like the hips and shoulders develop later. After prolonged inflammation, RA can lead to destructive changes in the periarticular bone, referred to as bony erosions. These bone lesions are a hallmark of RA and serve as a measure of disease severity. Radiographic scoring systems have been developed to determine the number and severity of these erosions. These scoring systems are used to measure the

Figure 1. Overview of the inflammatory process in the synovium and mechanism of action of drugs used to treat rheumatoid arthritis. An infectious or environmental epitope in combination with a susceptible genetic background initiates the inflammatory cascade. The interaction between T and B cells often results in the production of rheumatoid factor and other auto-antibodies. B cells also stimulate the activation of neutrophils and macrophages. Neutrophils secrete enzymes that directly mediate tissue damage. Macrophages are responsible for the production of inflammatory mediators (e.g., TNF-α, TNF-β, IL-1). HLA = human leukocyte antigen, NF-κB = nuclear factor κB, TNF = tumor necrosis factor, IL = interleukin, NSAIDs = nonsteroidal antiinflammatory drugs, COX = cyclooxygenase.



ability of a drug or biological agent to modify the RA disease course.[7] Extraarticular manifestations can include painless subcutaneous rheumatoid nodules, typically over extensor surfaces prone to mechanical stress, like the elbows; anemia of chronic disease; various types of pulmonary manifestations, including fibrosis, effusions, and nodules; vasculitis; amyloidosis; leucopenia; and inflammatory eye disease.[8] Smokers have a greater risk for developing and display more frequent extraarticular involvement.[9,10]

Rheumatoid factors are immunoglobulins directed against the constant region (Fc) of the human immunoglobulins. Despite some limitations, rheumatoid factor seropositivity has been the traditional laboratory marker for RA and is present in about three fourths of RA patients.[11] As diagnostic markers, rheumatoid factors suffer from imperfect sensitivity and specificity. New laboratory markers, including antibodies against cyclic citrullinated peptides (anti-CCP) and antikeratin, show great promise in the early diagnosis of RA.[12] Anti-CCP antibodies have been found to have sensitivities comparable to traditional rheumatoid factors with superior specificity.[13,14] Magnetic resonance imaging and ultrasonography of the hand joints are also alternatives to conventional plain radiographs in the early diagnosis of RA; their cost-effectiveness and clinical usefulness continue to be investigated.[15]

Clinical criteria for the classification of RA were developed by the American Rheumatism Association (now the American College of Rheumatology [ACR]) in 1987[16]; these criteria include the clinical characteristics described above and have been used to enroll patients in RA clinical trials. They have also proved valuable in distinguishing patients with RA from other patients with different inflammatory and mechanical conditions. These criteria were not developed for the diagnosis of individual patients and may fail to diagnose cases of early RA. This traditional approach to diagnosing RA may change in the near future in light of the new tools available for early diagnosis.

Current treatments for RA

The current pharmacologic therapies for the treatment of RA are listed in Table 1. Because RA is an inflammatory condition, first-line therapy has traditionally included medications that suppress inflammation, such as nonsteroidal antiinflammatory drugs (NSAIDs) and glucocorticoids. These classes of medications also act rapidly to improve pain and swelling due to RA.

Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, hydroxychloroquine, sulfasalazine, and, more recently, leflunomide. Unlike NSAIDs, these slower-acting compounds not only improve symptoms but slow clinical and radiographic progression. Because their time to onset ranges from several weeks to months, more rapid-acting agents, like NSAIDs and glucocorticoids, are often used as “bridge” therapy when initiating therapy with DMARDs.

The newest class of medications used to treat RA—biological-response modifiers—has been available for almost 10 years. These agents, designed to target the inflammatory mediators of tissue damage in RA, include infliximab, etanercept, adalimumab, anakinra, abatacept, and rituximab. Many more are in different phases of clinical research and may be available in the next few years.

With the advent of new therapies for RA, ACR developed uniform measures for assessing response to therapy that evaluate the degree of clinical improvement, defined by specific variables (e.g., number of tender or swollen joints, patient and physician assessments of disease activity).[17] A 20% improvement in a combination of these variables is called the ACR20; similarly, 50% and 70% are known as the ACR50 and ACR70, respectively.

NSAIDs. This commonly used class of medications is effective for controlling the pain, inflammation, and stiffness related to RA. NSAIDs can be very useful in the first weeks after the onset of RA symptoms while a diagnostic workup is undertaken, before a diagnosis is certain, and as bridge therapy while waiting for a slow-acting DMARD to become ef-

Table 1.
Current Pharmacologic Therapies for the Treatment of Rheumatoid Arthritis

Category	Example(s)
NSAIDs[a]	Aspirin, ibuprofen
Glucocorticoids	Prednisone, methylprednisolone
DMARDs	Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide
Other antirheumatic drugs	Gold sodium thiomalate, cyclosporine, tetracyclines
Biological agents	
Anti-TNF-α	Infliximab, etanercept, adalimumab
IL-1 inhibitors	Anakinra
Costimulation blockers	Abatacept
B-cell targeted therapies	Rituximab

[a]NSAIDs = nonsteroidal antiinflammatory drugs, DMARDs = disease-modifying antirheumatic drugs, TNF = tumor necrosis factor, IL = interleukin.

fective. However, NSAIDs should not be used alone in confirmed RA because they have not been found to slow the clinical or radiographic progression of the disease.[18,19]

The efficacy of NSAIDs partially depends on the inhibition of cyclooxygenase (COX). COX is critical in the metabolism of cell membrane-derived arachidonic acid to the proinflammatory prostaglandins, which can induce local vasodilation and hyperalgesia.[20] Two isoforms of COX have been extensively studied in humans: COX-1 and COX-2. COX-1 is expressed constitutively in the stomach, intestines, kidneys, and platelets and is involved in functions such as gastric protection from hydrochloric acid. COX-2, a predominantly inducible isoenzyme, expressed constitutively in only some tissues (e.g., kidneys, brain), is involved in the production of prostaglandins E2 and I2, which are upregulated in the inflammatory response.[20,21] NSAIDs have been subclassified by their selectivity related to the inhibition of these isoenzymes (Table 2).[22]

NSAIDs are usually well tolerated for short periods of time; however, with chronic use they sometimes lead to gastrointestinal (GI) complications, such us ulcer formation, perforations, and bleeding,[23] estimated to account for more than 100,000 hospitalizations and 16,500 GI-related deaths annually in the United States.[24] These problems are more common among the elderly, users of concomitant glucocorticoids and anticoagulants, and in persons with preexisting peptic ulcer disease.[25] When administered with NSAIDs, GI-protective agents (e.g., misoprostol, proton pump inhibitors) reduce the likelihood of serious GI complications.[26,27] Histamine 2-receptor antagonists, such as ranitidine, are less effective and need to be used in high doses to prevent NSAID-related GI complications. Various specialty groups recommend measuring hematocrit or hemoglobin levels annually for high-risk patients on chronic NSAID therapy to monitor for occult GI bleeding,[28] though the effectiveness of this screening has yet to be demonstrated.

Another potential adverse effect of NSAIDs is their renal toxicity. The glomerular vasculature in the kidneys is tightly regulated by prostaglandins and thromboxanes in both the afferent and efferent arteries that regulate intraglomerular pressure.[29] NSAIDs can decrease the perfusion pressure, especially when combined with angiotensin-converting-enzyme inhibitors.[30] As with NSAID-related GI bleeding, age is a risk factor for renal failure in patients taking NSAIDs. Other mechanisms of NSAID-induced renal damage include interstitial nephritis and renal tubular acidosis. Liver toxicity, cytopenias, aseptic meningitis, fluid retention, exacerbation of heart failure, and angioedema have been associated with NSAID use.[31] According to ACR guidelines, patients with a high risk of developing renal complications should have their CL_{cr} checked on initiation of therapy and every week for the first several weeks of NSAID therapy.[28]

Much attention has recently been directed to the COX-2-selective NSAIDs. Their analgesic and antiinflammatory efficacy is identical to the traditional NSAIDs.[32-34] Moreover, their adverse-effect profile is similar to that of traditional NSAIDs, with the exception of a possible lower risk of adverse GI effects with certain agents. Several randomized clinical trials (RCTs) have found that rofecoxib, valdecoxib, and, to a lesser extent, celecoxib were associated with a reduced rate of adverse GI effects, including bleeding and dyspepsia.[32,35,36] Recently, this potential advantage has been challenged by extensions to the initial RCTs[37] and some postmarketing surveillance data.[38] Data from the Celecoxib Long-term Arthritis Safety Study (CLASS) with celecoxib and a clinical trial with a new COX-2 inhibitor, lumiracoxib, showed that any potential benefit on GI-related adverse effects seemed to be lost with the concomitant use of aspirin[35,39]; the same appears to be true in patients anticoagulated with warfarin.[40]

Initial evidence of the possible adverse cardiovascular effects of the COX-2-selective NSAIDs came from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which found that patients with RA taking 50 mg of rofecoxib daily had a higher rate of nonfatal myocardial infarction than patients taking naproxen 500 mg twice daily.[33] Subsequently, a meta-analysis of 18 randomized controlled trials (including VIGOR) and 11 observational studies also found a 2.3-fold increased risk of myocardial infarction in patients receiving rofecoxib compared with patients receiving placebo or other NSAIDs.[41] In a subsequent colorectal carcinoma prevention study with rofecoxib, cardiovascular events were prospectively defined and collected. Patients taking 25 mg of rofecoxib had a 1.92-fold increase in the rate of cardiovascular events (acute myocardial infarc-

Table 2.
Selectivity of NSAIDs Related to Their COX Inhibition[a]

COX Inhibition	Representative NSAID(s)
COX-1 specific	Low-dose aspirin
COX nonspecific	Ibuprofen, naproxen, indomethacin
COX-2 preferential	Etodolac, diclofenac, nabumetone, meloxicam
COX-2 specific	Celecoxib, rofecoxib,[b] valdecoxib[c]

[a]COX = cyclooxygenase, NSAIDs = nonsteroidal antiinflammatory drugs. Adapted from reference 22, with permission.
[b]Withdrawn from U.S. market in 2004.
[c]Withdrawn from U.S. market in 2005.

tion, stroke, or sudden death) with a clear divergence after 18 months of therapy.[42] Other COX-2-selective NSAIDs, such as valdecoxib and its parent drug, parecoxib, were found to increase the risk of cardiovascular events (myocardial infarction, cardiac arrest, stroke, and pulmonary embolism) when given as therapy for postoperative pain relief after coronary artery bypass grafting.[43] In light of this evidence, both rofecoxib and valdecoxib were withdrawn from the market in September 2004 and April 2005, respectively.[44,45]

In contrast, the initial data for celecoxib did not show an increased frequency in cardiovascular events compared with patients taking placebo or other NSAIDs either in a GI protection study[35] or subsequent meta-analysis with 31,000 patients.[46] However, these early data lacked prospective and validated identification of cardiovascular events and had a short duration of follow-up. In the Adenoma Prevention with Celecoxib Study, the risk of cardiovascular events (myocardial infarction, stroke, heart failure, and death from cardiovascular causes) was significantly increased in patients taking either 200 or 400 mg of celecoxib daily compared with placebo.[47]

The controversy regarding the cardiovascular safety of COX-2-selective NSAIDs continues, fueled by additional data provided by large epidemiologic studies. These data have generally failed to show an association between the use of COX-2-selective NSAIDs (except rofecoxib at daily doses of at least 25 mg) and increased cardiovascular mortality when compared with placebo or other NSAIDs.[48-50] While these studies are more representative of real-world settings than the selected patients that participate in RCTs, the findings of RCTs are typically considered to have a higher level of scientific significance.

Glucocorticoids. Glucocorticoids have been widely used in the treatment of RA. Although high doses of glucocorticoids clearly cause unacceptable toxicity, daily doses of prednisone (or its equivalent) of ≤15 mg may diminish pain and swelling in many patients.[51] This dosage of glucocorticoids may also have a limited disease-modifying effect in patients with RA.[52,53] These potent drugs oppose inflammation in at least three ways. First, they promote the expression of lipocortin-1, which inhibits the enzyme phospholipase A_2 and the generation of arachidonic acid. Second, their transcription products inhibit the action of the nuclear factor κB(NF-κB) and AP-1 protein, which act to upregulate proinflammatory molecules, like tumor necrosis factor (TNF) and interleukin-1 (IL-1). Third, they exert an effect through membrane-associated receptors and second messengers—a nongenomic effect, which may explain the rapid effects of glucocorticoids and may be important at high doses.[54-57]

The most common adverse effects of glucocorticoids are listed in Table 3. A recent review of the literature about adverse effects associated with low-dose glucocorticoids (equivalent to ≤10 mg of prednisone) has shown a relative lack of evidence relating these doses to important toxicity.[58] However, there is no safe glucocorticoid dosage from the perspective of bone metabolism, as shown in a recent RCT where healthy postmenopausal women were randomized to take 5 mg of prednisone per day or placebo. The prednisone-treated women had decreased bone formation, even after using prednisone for only a few weeks.[59] In light of the early bone loss often seen with glucocorticoid therapy, all patients

Table 3.
Common Adverse Effects of Glucocorticoid Therapy

Onset early in therapy, essentially unavoidable
Emotional lability
Enhanced appetite, weight gain, or both
Insomnia
Enhanced in patients with underlying risk factors or concomitant use of other drugs
Acne vulgaris
Diabetes mellitus
Hypertension
Peptic ulcer disease
When supraphysiologic glucocorticoid treatment is sustained
Cushingoid appearance
Hypothalamic–pituitary–adrenal suppression
Impaired wound healing
Myopathy
Osteonecrosis
Susceptibility to infections
Delayed and insidious, probably dependent on cumulative doses
Atherosclerosis
Cataracts
Fatty liver
Growth retardation
Osteoporosis
Skin atrophy
Rare and unpredictable
Glaucoma
Pancreatitis
Pseudotumor cerebri
Psychosis

who take at least 5 mg of prednisone or its equivalent daily for more than three months should also take vitamin D (800 IU/day) and calcium supplement (1–1.5 g/day); use of a biphosphonate is recommended for patients with a high risk of developing osteoporosis, including individuals older than 65 years, receiving a prednisone-equivalent dosage of >20 mg/day, or with a history of nontraumatic fracture.[60] For intermediate-risk patients, risk stratification with a bone mineral density test (i.e., dual-energy x-ray absorptiometry scan) is recommended.[61-63]

Given the slow onset of action of traditional DMARDs, low doses of glucocorticoids are often used as a bridge therapy to control symptoms until the DMARDs or biological agents become effective. Monotherapy with glucocorticoids is not recommended. Since adverse effects from glucocorticoids have been shown to increase in a dose-dependent manner,[64] tapering to the lowest dosage that maintains remission is recommended once RA is stabilized.

DMARDs. *Methotrexate.* For almost 20 years, methotrexate has been the cornerstone of therapy for RA in the United States.[65] It has demonstrated effectiveness, reliability, sustained long-term action, high tolerability, and low cost. Current data support the notion that methotrexate may reduce mortality (mainly cardiovascular) when compared with other DMARDs.[66] Up to four mechanisms of action have been proposed for the drug. First, it works as an antifolate agent, as it can inhibit the proliferation of rapidly dividing cells, including lymphocytes and other inflammatory-cell mediators.[67] Second, methotrexate may diminish the accumulation of toxic compounds, especially polyamines, which are dependent on tetrahydrofolate and contribute to tissue injury in RA.[65,68] Third, methotrexate may reduce intracellular levels of glutathione, leading to a reduction in damage by toxic oxygen metabolites.[69] Finally, it increases extracellular adenosine levels, an antiinflammatory action.[70,71] All of these mechanisms seem to be important in the action of the drug in treating RA.[65]

Methotrexate is usually administered orally in 15–25-mg doses once weekly, often starting at weekly doses of 10–15 mg. Its bioavailability is approximately 70% and varies with the dose but is not affected by food or protein binding.[72] Intramuscular and subcutaneous methotrexate may improve efficacy because oral bioavailability is reduced because of saturation of its GI transporter.[73] After absorption, the drug undergoes polyglutamation and deposition in the tissues, with a half-life of days to weeks.[74]

Potential adverse effects of methotrexate include hepatitis and cirrhosis, oral ulcers, cytopenias, and interstitial pneumonitis. Paradoxical worsening and an increase in rheumatoid nodules have also been reported.[75] All of these are more common in the setting of underlying renal dysfunction, since 80% of the methotrexate dose is excreted through the kidneys.[76] ACR has published guidelines for monitoring patients receiving methotrexate therapy, including laboratory testing for complete blood count, serum creatinine, and liver transaminases every four to eight weeks and reducing the dose or discontinuing therapy if persistent transaminitis is detected.[77] If the abnormality persists, a liver biopsy should be considered. Concomitant administration of folic acid (1–3 mg per day) or folinic acid (2.5–5 mg 12–24 hours after methotrexate administration) increases the tolerance of methotrexate by reducing adverse GI effects and is currently the standard of care in the United States.[78] It is unclear whether routine folate administration reduces the efficacy of methotrexate[79]; in Europe, folate supplementation is not routinely prescribed until methotrexate-related symptoms (e.g., oral ulcers) develop.

Methotrexate is the gold standard against which newer RA therapies are compared. Its efficacy is at least comparable to the other traditional DMARDs but appears inferior to newer biological agents for many patients.[80-86] However, given the combination of its high efficacy, low cost, and acceptable toxicity profile, it will likely continue to be the initial treatment of choice for the near future.

Hydroxychloroquine, sulfasalazine, and combination DMARDs. Hydroxychloroquine is an antimalarial that was introduced as therapy for RA and systemic lupus erythematosus in the 1950s. Its mechanism of action is not completely understood, but it appears to interfere with antigen presentation, promote lysosomal membrane stabilization, and inhibit the metabolism of deoxyribonucleotides.[87,88] Hydroxychloroquine is well absorbed orally, becomes extensively tissue bound, and has an elimination half-life of approximately 40 days. Its most common toxicities are GI-related (nausea, abdominal discomfort, diarrhea); periodic retinal examinations are advised due to the very rare but potentially preventable occurrence of retinopathy, almost exclusively seen at daily doses exceeding 6.5 mg/kg.[89]

The standard dosage of hydroxychloroquine sulfate is 400 mg daily by mouth. Its effectiveness appears to be modest at best, and the onset of action is usually slow.[90] The drug is rarely used as monotherapy for RA; its main clinical utility is in combination with other DMARDs.

Sulfasalazine was developed and synthesized in the 1930s under the unproven assumption that an infectious agent was responsible for RA. After absorption, the molecule is cleaved in the intestine by bacterial organisms into 5-aminosalicylic acid and sulfapyridine.[91] Sulfapyridine seems to exert most of the therapeutic action of sulfasalazine.[92] Sulfasalazine inhibits neutrophil function, reduces immunoglobulin levels, and interferes with T-cell function via suppression of NF-κB activation.[93-94]

The typical starting dosage of sulfasalazine is 500 mg by mouth once or twice daily; if tolerated, the dosage can be progressively increased to 1500 mg twice daily. The most common toxicities are GI-related (nausea, vomiting, diarrhea, abdominal pain) and hematologic in nature (neutropenia, thrombocytopenia), but the drug is generally considered safe and well tolerated.[95] Sulfasalazine has been the DMARD of choice in Europe because of its effectiveness and low cost. RCTs have shown that it is at least comparable to other DMARDs, such as gold sodium thiomalate, penicillamine, and leflunomide.[96-100]

Increased interest has focused on combination therapy with traditional DMARDs. In different clinical trials the superiority of the combination of three DMARDs (methotrexate, hydroxychloroquine, and sulfasalazine) versus single DMARD therapy has been clearly demonstrated.[101,102] There is also evidence that the combination of these three DMARDs is superior to the combinations of methotrexate–sulfasalazine and methotrexate–hydroxychloroquine.[103] Combination DMARD therapy is generally well tolerated and a reasonable alternative to more expensive biological therapies, though data from head-to-head trials are pending.

Leflunomide. Leflunomide is an immunomodulatory drug that inhibits the rate-limiting intracellular enzyme in the de novo synthesis of pyrimidines that is crucial for activating lymphocytes.[104,105] Leflunomide is administered by mouth at dosages of 10–20 mg daily, rapidly and almost completely absorbed, and processed by the liver to an active metabolite. This metabolite is almost 100% bound to albumin and other serum proteins and has a half-life of 15 days. Renal excretion of leflunomide appears to be minimal, and its dosage does not need to be adjusted in the presence of renal dysfunction.[106] It also undergoes extensive enterohepatic recirculation.

Leflunomide usually requires a loading dose of 100 mg for three days to achieve therapeutic concentrations rapidly, but this approach may cause GI intolerance.[104] The drug is generally well tolerated, and hepatotoxicity is its most important serious adverse reaction. Elevated liver enzymes have been reported in 2–4% of patients.[107] Cases of hepatocellular necrosis, hepatic dysfunction, and death attributed to the drug have been reported but are rare; in general, the risk: benefit ratio is acceptable for most patients.[108] However, patients with history of alcohol abuse and hepatitis should not be treated with leflunomide. Aspartate transaminase and alanine transaminase should be obtained at baseline and then monthly for six months.[107] If stable, liver enzyme monitoring can be performed every two to three months. Other adverse reactions include abdominal pain, diarrhea, nausea, weight loss, and unexplained hypertension.[109-111] Because leflunomide is a pregnancy category X drug, reliable contraception is recommended for women of childbearing age who take the drug. If a woman taking leflunomide does become pregnant, the drug should be discontinued, followed by an 11-day washout period with cholestyramine; serum drug levels should also be monitored due to the extensive hepatic and enteric circulation of leflunomide.[112,113]

Three placebo-controlled trials have demonstrated that leflunomide is similar in efficacy to methotrexate and sulfasalazine.[109-111] It is most commonly used as an alternative for methotrexate-intolerant patients. Leflunomide's mechanism of action appears to be complementary to methotrexate's, making combination therapy a potentially attractive option. While joint symptoms improved in patients taking combination leflunomide–methotrexate compared with methotrexate alone, the rate of liver enzyme elevations (of approximately 10–30%) was unacceptable for a majority of patients.[114,115]

Other antirheumatic drugs. Gold salts have been used for the management of articular symptoms since the 1920s.[116] Their mechanism of action has not been well established but may include the reduction of circulating B cells, immune complexes, rheumatoid factor, and immunoglobulin levels.[117-119] Their efficacy in the improvement of symptoms of RA has been demonstrated,[120,121] but few patients take gold salt therapy for longer than five years because of toxic reactions, including mucocutaneous reactions, proteinuria, and cytopenias.[122]

Various members of the tetracycline family, including minocycline, have been studied for the treatment of RA. In addition to their antimicrobial action, tetracyclines have antiinflammatory and immunomodulatory properties.[123] Four studies have found minocycline to be efficacious at a dosage of 200 mg once a day by mouth.[124-127] The reported toxicities include autoimmune syndromes (serum sickness, polyarthritis, drug-induced lupus, vasculitis), headaches, GI intolerance, and a graying skin pigmentation.[126,127]

Cyclosporine, a calcineurin inhibitor that is widely used for the prevention of rejection in organ transplant recipients, demonstrated efficacy in the treatment of RA in comparative clinical trials[128]; however, given the availability of safer DMARDs and biological agents, its role is now limited to a third-line agent after failure of first- and second-line drugs.

Biological agents. *TNF-α inhibitors.* Infliximab was the first anti-TNF-α agent studied for the treatment of RA but was first approved for treatment of Crohn's disease. Infliximab is a chimeric molecule that joins the Fc region of human immunoglobulin G1 (IgG1) with the variable region of a mouse antibody against TNF-α.[129] It binds to soluble and membrane-bound TNF-α, interfering with the binding of the cytokine to its receptor and inducing a complement and antibody-dependent response against cells that express TNF-α.

Infliximab is given by intravenous infusion at a dose of 3 mg/kg over two hours, though dose adjustment of up to 10 mg/kg may be necessary, depending on the patient's response. The standard administration schedule for RA is at weeks 0, 2, and 6, followed by a maintenance infusion every eight weeks.[130]

Etanercept is a soluble molecule composed of two recombinant p75 TNF-receptor proteins fused together to form a dimer.[131] Each of these molecules is linked to the Fc portion of human IgG1 to provide them a longer half-life. The fusion protein has the ability to bind both TNF-α and TNF-β (lymphotoxin), preventing them from interacting with their receptors. Unlike infliximab, etanercept cannot interact with membrane-bound TNF-α.

Etanercept is self-administered by subcutaneous injection at dosages of 25 mg twice weekly or 50 mg once weekly. These regimens have been found to be equivalent in efficacy.[132] The half-life of the drug after absorption is approximately four days.[133] Etanercept does not provide better efficacy at higher doses.

Adalimumab, a human-recombinant-IgG1 monoclonal antibody to TNF-α, received approved labeling from the Food and Drug Administration (FDA) for the treatment of RA in 2003.[134] It has a long circulating half-life (approximately 10–20 hours) and can be self-administered subcutaneously every two weeks at a dose of 40 mg, with a dosage increase up to 40 mg weekly if necessary.

The average monthly cost of TNF-α inhibitor therapy (drug only) ranges from $1200 to $1400.[135]

The three currently approved TNF-α inhibitors have been shown to be efficacious in the treatment of RA in several large RCTs. Clinical improvements in ACR outcome scales and radiographic progression have been observed with the use of each TNF-α antagonist combined with methotrexate versus methotrexate alone (Table 4).[85,86,136-142] Although the efficacy of monotherapy with TNF-α inhibitors is comparable to that of methotrexate alone,[143,144] the efficacy of combination therapy is greater than monotherapy with either agent.[140]

The efficacy of the TNF-α inhibitors appears to be comparable, though they have not been compared in head-to-head studies. The choice of TNF-α antagonist is often influenced by drug cost, patient preference for self-injection versus physician-administered medication, and health plan drug formularies. If a patient does not respond to a given TNF-α inhibitor, evidence supports a trial of a different TNF-α inhibitor.[145]

Numerous adverse events have been associated with TNF-α inhibitors, with infections being the most common.[129,130,137] Some data suggest that infliximab may cause more granulomatous infections (mainly tuberculosis) than does etanercept.[146] Before receiving TNF-α therapy, all patients should have a purified protein derivative tuberculin test. Histoplasmosis, aspergillosis, listeriosis, cytomegalovirus, and serious bacterial infections have been described in several series and case reports of patients receiving TNF-α inhibitor therapy.[147-152]

Infusion reactions (e.g., headache, nausea, urticaria, anaphylaxis) can be seen during the administration of infliximab. Minor reactions usually respond to antihistamines and slowing of the infusion rate.[85] Pretreatment with intravenous betamethasone sodium phosphate has shown no benefit in reducing the frequency of infusion reactions.[153] Etanercept can cause minor redness and itching around the injection site that can last a few days.[143] Pain at the injection site has also been described with adalimumab.[154]

The association between TNF-α inhibition and the rate of malignancies remains controversial, with recent data supporting an increased risk for lymphomas and malignancies in general.[155] Other adverse events linked to TNF-α inhibitor therapy include demyelination of the central nervous system[156,157] and heart failure.[158] A clear causal association for these serious reactions has not been well established. Clinically insignificant decreases in leukocyte and neutrophil counts and increased hemoglobin values have been reported with adalimumab.[142]

The formation of autoantibodies to DNA (e.g., antinuclear antibodies) has been reported during therapy with all three TNF-α antagonists,[85,141,143] though true lupus-like syndromes in treated patients are rare. Patients may also develop antibodies against the drugs themselves. Anti-infliximab antibodies developed in 61% percent of patients with Crohn's disease receiving infliximab as monotherapy, but the percentage of antidrug antibodies is lower in patients receiving concomitant immunosuppressive therapy.[159] In patients with RA, the frequency of antidrug antibodies found in some assays ranges between 5% and 20%,[132] but the clinical significance of these antidrug antibodies remains unclear. Some data suggest that these antidrug antibodies are associated with loss of efficacy and an increased frequency of infusion reactions.[160] Data are forthcoming regarding whether these antidrug antibodies are associated with the waning response to TNF-α antagonism observed in some patients who initially have a good response.

Anakinra. Anakinra is a recombinant inhibitor of the proinflammatory cytokine IL-1. It shares almost all of its amino acid sequence with a natural inhibitor that has been found

Table 4.
Clinical Trials Evaluating Efficacy of Current and Investigational Biological Agents for Treatment of RA[a]

Drug	Ref.	Patient Population	Treatment Group[b]	*n*	Response (% Patients)[c] ACR20	ACR50	ACR70
Infliximab	85	Active RA despite methotrexate therapy	Methotrexate + placebo	88	19	9	2
			Methotrexate + infliximab 3 mg/kg	86	48	24	11
	137	Active early RA, no prior treatment with methotrexate or TNF inhibitor	Methotrexate + placebo	274	53	32	21
			Methotrexate + infliximab 3 mg/kg	351	62	46	36
Etanercept	140[d]	Active RA, inadequate response to DMARDs	Methotrexate + placebo	228	75	43	19
			Etanercept 25 mg s.c. twice weekly + placebo	223	76	48	24
			Methotrexate + etanercept 25 mg s.c. twice weekly	231	85	69	43
	143	Active RA, inadequate response to DMARDs	Etanercept 25 mg s.c. twice weekly	78	59	40	15
			Placebo	80	11	5	1
Adalimumab	141	Active RA, no response to DMARDs, stable on methotrexate	Methotrexate + placebo	62	15	8	5
			Adalimumab 40 mg s.c. every 2 wk + methotrexate	67	67	55	27
	142	Active RA and inadequate response to methotrexate	Methotrexate + placebo	200	24	10	5
			Adalimumab 40 mg s.c. every 2 wk + methotrexate	207	59	41	23
Anakinra	163	RA on stable methotrexate	Methotrexate + placebo	48	23	4	0
			Anakinra 1 mg/kg/day s.c. + methotrexate	59	42	24	10
Abatacept	167	Active RA despite methotrexate	Methotrexate + placebo	119	36	20	8
			Abatacept 10 mg/kg i.v. + methotrexate	115	62	41	21
Rituximab	170	Active RA despite methotrexate	Methotrexate + placebo	40	20	5	0
			Rituximab 1 g i.v. + methotrexate on days 1 and 15	40	65	35	15
IL-6-receptor antibody	176	Active RA despite treatment with DMARD	IL-6-receptor antibody 8 mg/kg	55	78	40	16
			Placebo	53	11	2	0

[a]All differences between active treatment and placebo groups are statistically significant at $p < 0.05$. RA = rheumatoid arthritis, TNF = tumor necrosis factor, DMARD = disease-modifying antirheumatic drug, IL-6 = interleukin-6.
[b]Only the treatment groups taking doses commonly used in clinical practice and followed for at least 24 weeks were included.
[c]ACR20, 50, and 70 = clinical response parameter established by the American College of Rheumatology indicating a 20%, 50%, and 70% improvement in a combination of symptoms (assessed by physicians and patients) and radiological outcomes, respectively.
[d]There were significant differences between combination therapy and either methotrexate or etanercept.

to be decreased in the synovial tissue of patients with RA.[161] It has a short half-life and is administered in 100-mg daily subcutaneous injections.[117] The monthly cost of therapy (drug only) is approximately $1300.[135]

In two large clinical trials, anakinra appeared to be safe and effective as monotherapy and in combination with methotrexate for the treatment of RA.[162,163] Patients' ACR responses to anakinra are shown in Table 4. These responses appeared to be sustained for up to 48 weeks in an extension study.[164] Adverse effects of anakinra include local reactions and an increased susceptibility to infections. Given its inferior clinical efficacy compared with TNF-α antagonists and the need for daily injections, anakinra is appropriate for patients who cannot tolerate TNF-α inhibitors. Despite the theoretical attractiveness of combining anakinra with a TNF-α antagonist, this approach has not been shown to be superior to TNF-α inhibitor therapy alone and showed a marked increase in the rate of infections, local reactions, and neutropenia.[165]

Abatacept. Abatacept is the first member of a new class of drugs known as costimulation blockers. These agents act upstream compared with other biological agents in the inflammatory cascade, thereby preventing the costimulatory signal required for T-cell activation.[166] Abatacept has been shown to be effective in combination with methotrexate.[167,168] In short-term RCTs, the rate of adverse events with abatacept was found to be similar to that with placebo.[168] Abatacept is administered as a 30-minute intravenous infusion at a dose of 500 mg–1 g, depending on body weight.[169] The monthly cost of abatacept therapy is approximately $1350.[135]

Rituximab. Rituximab is a chimeric anti-CD20 monoclonal antibody. CD20 is a cell marker present on the surface of almost all normal and malignant B cells but is not expressed in long-lived plasma cells. Rituximab leads to a selective depletion of B cells and has been used in the treatment of low-grade or follicular $CD20^+$ non-Hodgkin's lymphoma for many years. One clinical trial found rituximab to be safe and effective in the treatment of RA in combination with methotrexate or cyclophosphamide[170]; this response was sustained at 48 weeks.[171] The most common adverse event found in the rituximab-treated groups was infusion reactions. Rituximab did not appear to increase susceptibility to infections when compared with placebo and did not adversely affect immunoglobulin levels.[170,171] The drug should be administered in two separate 1000-mg infusions two weeks apart. Administration of intravenous methylprednisolone or its equivalent is recommended at a dose of 100 mg 30 minutes before the infusion to prevent serious reactions.[172] Repeated administration of the drug six months to one year after the initial dose has been reported, but this approach is currently not supported by data from controlled trials. Rituximab received FDA-approved labeling in February 2006 for use in combination with methotrexate for the treatment of RA.[173]

Investigational treatments for RA

IL-6 is a pleiotropic cytokine with roles in inflammation and hematopoiesis. Anti-IL-6-receptor monoclonal antibodies have been tested in two open-label Phase I/II studies[174,175] and one randomized controlled trial[176] with promising results. Liver function abnormalities and elevations in total cholesterol, high-density-lipoprotein cholesterol, and triglycerides were reported in up to 44% of patients.[176]

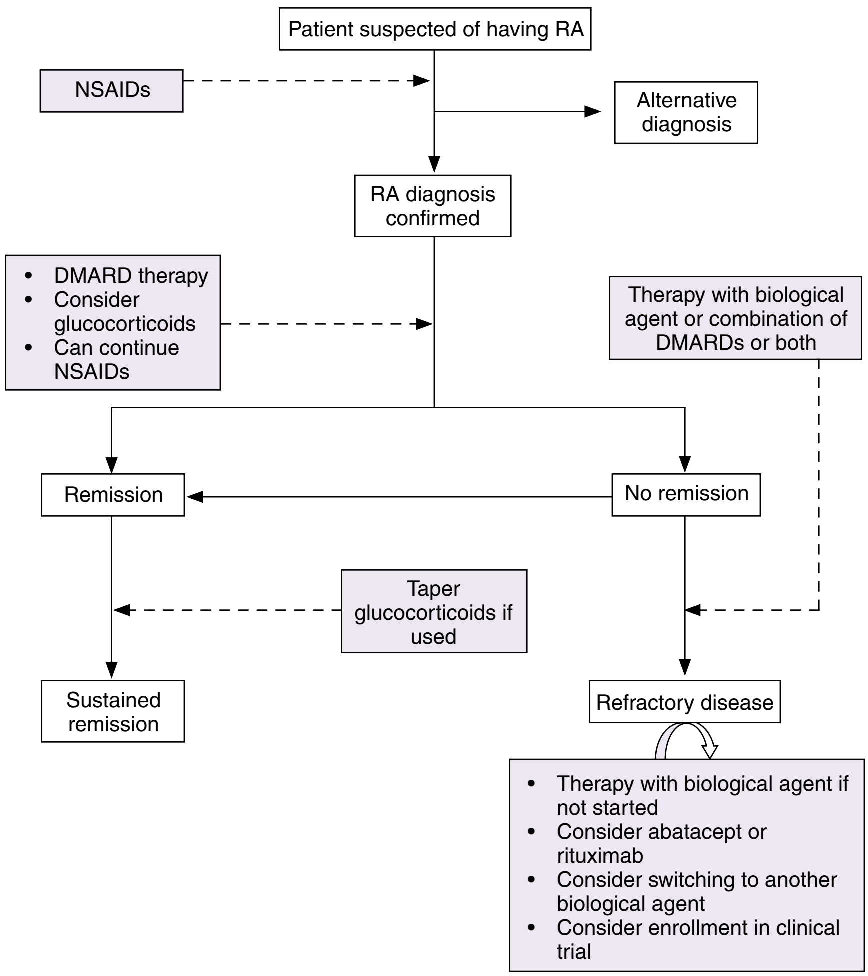
Novel therapies for RA are in different stages of development in the United States, Europe, and Japan.[177] Among these are new TNF-α inhibitors (including one for oral administration), inhibitors of other interleukins involved in the inflammatory cascade (e.g., IL-12, IL-15), and antibodies against proteins critical for B-cell function and survival. Further studies are needed to determine the safety and role of these new drugs in the long-term management of RA.

Management of RA

A proposed overview for the current management of RA is shown in Figure 2. NSAIDs or other analgesics are useful while the initial workup of the patient is being conducted and can continue to be used thereafter for the management of pain and inflammation. Once the diagnosis of RA is confirmed, methotrexate should be started alone or in combination with other DMARDs. Glucocorticoids may be necessary in some patients while waiting for slow-acting DMARDs to become effective. Methotrexate should be adjusted rapidly to an effective dosage (usually 12.5–25 mg/week) and glucocorticoids reduced to the lowest effective dose or discontinued. If remission is not achieved or glucocorticoid withdrawal is not possible, combination DMARD therapy or the addition of a biological agent (usually a TNF-α antagonist) should be initiated. If the patient does not tolerate or respond to the TNF-α antagonists, anakinra, rituximab, or abatacept may be appropriate.

For many years, a "pyramid" approach was advocated for the treatment of RA: after diagnosis, patients were started on NSAIDs and, after some period of time, DMARDs, glucocorticoids, or both were added. Data accumulated in the past decade have inverted the pyramid to favor early aggressive therapy for patients suspected of having RA, including early referral to a rheumatologist by primary care practitioners, new diagnostic techniques (e.g., anti-CCP antibody test, ultrasonography, and magnetic resonance imaging), and aggressive therapy with DMARDs, glucocorticoids, and biological

Figure 2. Proposed algorithm for the management of patients with suspected rheumatoid arthritis (RA). Shaded boxes and dashed lines represent recommendations for management. NSAIDS = nonsteroidal antiinflammatory drugs, DMARDs = disease-modifying antirheumatic drugs.



agents. The benefits of this approach have been demonstrated.[102,178-180] The effect of therapy with biological agents on early aggressive therapy is currently under investigation. Even with early aggressive combination therapy, only about one third of patients meet the criteria for clinical remission from RA.[180] However, because what is now considered a successful degree of disease control has been permanently changed since the introduction of the newer biological agents, the standard of care in the future may include early introduction of biological agents for the rapid achievement of a remission, with the long-term goal of preventing functional impairment and mortality. Clearly, there are still "unmet needs" for the many patients who fail to respond to traditional DMARD therapy and biological agents or for patients who lose that response over time.[181] Increased understanding of the pathogenic process in RA and new therapies in development may provide options to improve the quality of life for patients with RA and reduce the substantial morbidity and mortality associated with the disease.

Conclusion

Pharmacologic treatments of RA include NSAIDs, glucocorticoids, DMARDs, and biological agents. With an improved understanding of the pathophysiology of RA and the evidence from various clinical trials with the agents, early aggressive therapy with a combination of drugs or biological agents may be warranted for the effective treatment of RA.

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