Chapter 4: Rheumatoid Arthritis

INTRODUCTION

- *Rheumatoid arthritis* (RA) is a chronic, progressive autoimmune condition that primarily affects joints and the synovium but can also have systemic manifestations.

PATHOPHYSIOLOGY

- RA results from a combination of genetic susceptibility, nongenetic factors, and a triggering event. An unknown infectious process is thought to be the primary trigger.
- Antigen-presenting cells process and present antigens to T cells; activated T cells stimulate B cells to produce autoantibodies that form large complexes that deposit throughout the body. Antibodies to immunoglobulin G (IgG) are known as rheumatoid factor (RF) and have a strong correlation to the pathogenesis and poor prognosis of RA. B cells also produce proinflammatory cytokines, including tumor necrosis factor (TNF) and the interleukin (IL) system, which induce expression of adhesion molecules on the endothelium, further enhancing T-cell proliferation and differentiation, encouraging cell migration, and regulating matrix modeling.
- Overexpression of tumor suppressor gene p53 prevents normal DNA repair and interferes with appropriate cell apoptosis and increased anti-citrullinated protein antibodies (ACPA). ACPA positivity is associated with a worse prognosis in patients with RA.
- Migration of lymphocytes, macrophages, and mononuclear cells into the synovium and synovial cavity increases synovial mass, causing hypertrophy and angiogenesis. Angiogenesis is driven by IL-8, prostaglandins, vascular endothelial growth factor, and macrophage angiogenic factor. As the vessels develop, cytokines stimulate further migration of cells into the synovium, causing inflammation. The inflamed, fibrotic synovium (*pannus*) invades cartilage and bone around it, promoting further destruction and dysregulation.
- Cytokines within cartilage cause generation of reactive nitrogen and oxygen species and increase chondrocyte catabolism, inhibit chondrocyte anabolism, and increase extracellular matrix destruction. Proinflammatory cytokines travel to bone, provide the source for receptor activator of NFkB ligand (RANKL), and enhance osteoclast activity, leading to bone matrix destruction.
- Chronic inflammation in vascular endothelial and visceral, cutaneous, and pleural tissues leads to complications including vasculitis, fibrosis, anemia, and renal amyloidosis.

CLINICAL PRESENTATION

- Nonspecific prodromal symptoms developing over weeks to months include fatigue, weakness, low-grade fever, anorexia, and joint pain. Stiffness and myalgias may precede development of synovitis.
- Joint involvement tends to be symmetric and affects small joints of the hands, feet, wrists, and ankles; elbows, knees, shoulders, hips, cervical spine, and temporomandibular joints may also be affected.
- Joint stiffness is typically worse in the morning, usually exceeds 30 minutes, and may persist all day.
- On examination, joint swelling may be visible or apparent only by palpation. Tissue is soft, spongy, warm, and may be erythematous. If left untreated, long-term joint inflammation may lead to bony erosions and subluxations of wrists, metacarpophalangeal joints, and proximal interphalangeal joints (swan neck deformity, boutonnière deformity, and ulnar deviation).

- Extra-articular involvement may include rheumatoid nodules, interstitial lung disease, pleural effusions, vasculitis, ocular manifestations, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.
- RF is detected in 70%–80% of patients; higher titers generally reflect a more severe disease course. ACPA antibodies are more specific for RA and may be detectable very early in the disease; they generally predict a more aggressive disease course. Antinuclear antibodies (ANAs) are detected in 25% of patients with RA. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) indicate the presence of a nonspecific inflammatory process. Normocytic anemia, thrombocytosis or thrombocytopenia, and leukopenia may also be present. Analysis of aspirated synovial fluid typically demonstrates a high white blood cell count without crystals or infection.
- Early radiologic findings include soft tissue swelling and periarticular osteoporosis. With disease progression, joint space narrowing, bony erosions, and joint subluxations and deviations may occur.

DIAGNOSIS

- The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010. These criteria are intended for patients early in their disease to allow for earlier treatment targeted toward preventing structural joint damage. Patients with synovitis of at least one joint and no other explanation for the finding are candidates for assessment. The criteria use a scoring system with a combined score of 6 or more out of 10 indicating that the patient has definite RA.

TREATMENT

- Goals of Treatment: The ultimate goal is to induce complete remission or low disease activity (referred to as “treat to target”). Additional goals are to reduce inflammation and symptoms, maintain ability to function in daily activities, slow destructive joint changes, and delay disability.

Nonpharmacologic Therapy

- Patient education about the disease and medications (eg, potential adverse effects, self-administration of injectable agents) is important.
- Physical therapy can reduce pain and inflammation while preserving joint function. Exercise and physical activity (including aerobic activity and muscle-strengthening exercises) can improve disease outcomes.
- Assistive devices and orthoses such as braces and supports are useful to improve pain and function. Occupational therapy can provide benefits such as appropriate footwear and splinting.
- Weight loss can help decrease stress on joints.
- Surgical options (eg, joint replacements) are reserved for patients with more severe disease with significant cartilage loss.

Pharmacologic Therapy

General Approach

- Therapies to treat RA and slow disease progression include conventional and biologic disease-modifying antirheumatic drugs (DMARDs) and the small-molecule oral Janus-kinase (JAK) inhibitors.

  ✔ Conventional DMARDs include **methotrexate**, **leflunomide**, **sulfasalazine**, and **hydroxychloroquine**.

  ✔ Biologic DMARDs include TNF inhibitors (**adalimumab**, **certolizumab**, **etanercept**, **golimumab**, and **infliximab**) and non-TNF biologics (**abatacept**, **sarilumab**, **tocilizumab**, **rituximab**, and **anakinra**).

  ✔ JAK inhibitors include **baricitinib**, **tofacitinib**, and **upadacitinib**.

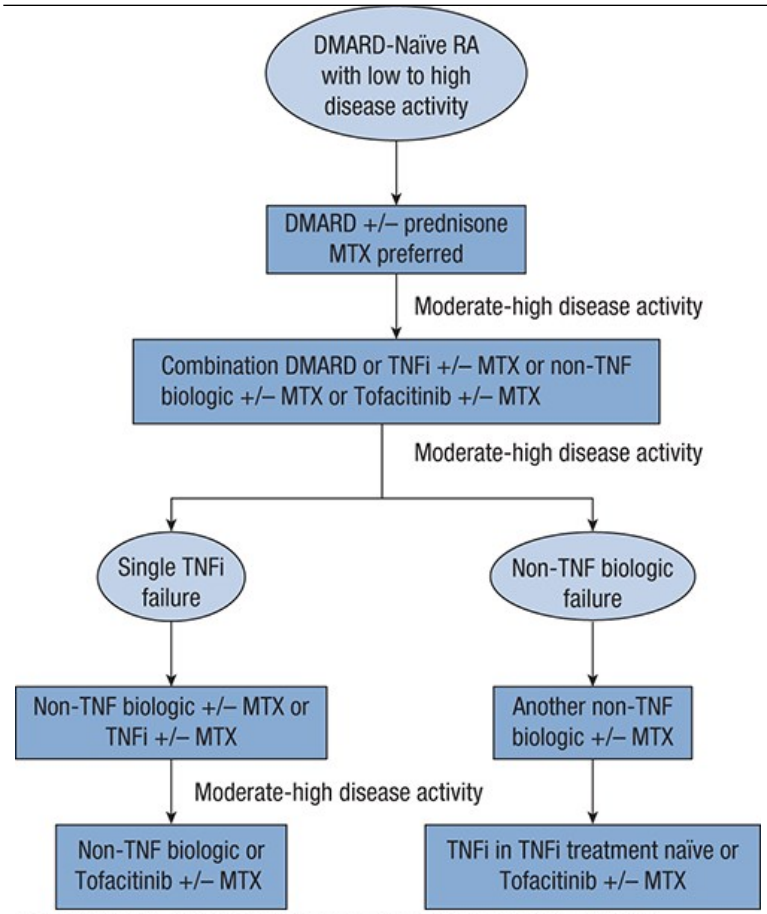
- Current RA treatment guidelines recommend initiating conventional DMARDs irrespective of disease activity in treatment-naive patients once a diagnosis is established (**Fig. 4-1**).

- The preferred conventional DMARD is methotrexate unless a contraindication exists. However, choice of therapy may depend on the level of disease activity, comorbid conditions, patient preference, and insurance coverage.
- For patients with early RA (<6 months duration) and low disease activity, DMARD monotherapy is recommended. Double or triple DMARD therapy is recommended for moderate or high disease activity. A biologic agent can be used as monotherapy or with conventional DMARD(s) in patients with moderate or high disease activity. A JAK inhibitor is an alternate option if disease activity remains moderate or high with combination conventional DMARDs.
- If disease activity remains moderate or high despite conventional DMARDs or biologics, a low-dose glucocorticoid (prednisone ≤10 mg/day or equivalent) can be added for the shortest duration necessary. If patients achieve remission, DMARDs and biologic agents can be tapered, but patients should remain on DMARD therapy at some dosage level.
- For patients with established RA (duration ≥6 months), DMARD monotherapy is recommended despite disease activity in DMARD-naive patients. Combination conventional DMARDs, a biologic DMARD, or a JAK inhibitor can be used if disease activity remains moderate or high after an adequate trial with DMARD monotherapy. In patients taking TNF inhibitor monotherapy with moderate or high disease activity, one or two conventional DMARDs can be added to the TNF inhibitor. A non-TNF biologic can be used in place of a TNF inhibitor if disease activity remains moderate or high on a TNF inhibitor and is recommended over a JAK inhibitor. Therapy can be switched to another non-TNF biologic if the first non-TNF agent cannot adequately control disease activity. A non-TNF biologic can also be started if separate courses of two different TNF inhibitors have not adequately controlled disease activity. A JAK inhibitor can be initiated if disease activity persists despite multiple TNF inhibitors in patients for whom non-TNF biologics are not an option. Dual biologic therapy should be avoided due to the risk of infection associated with immunosuppression. A glucocorticoid can be added if disease flares occur or disease activity is inadequately controlled despite DMARD, TNF inhibitor, or non-TNF biologic therapy.
- Because DMARDs can take weeks to months to take effect, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and other analgesics (eg, acetaminophen) can be used to provide more rapid symptomatic relief ("bridge therapy"). NSAIDs do not slow disease progression, and glucocorticoids can have serious side effects, making both drug classes less desirable for long-term use.
- See **Tables 4-1** and **4-2** for usual dosages and monitoring parameters for NSAIDs, glucocorticoids, and conventional and biologic DMARDs.

FIGURE 4-1

Algorithm for treatment of rheumatoid arthritis (RA) in early (<6 months) or established (≥6 months) RA with low to high disease activity.

(DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor.)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 4-1

Usual Doses for Disease-Modifying Antirheumatic Drugs

Drugs	Brand Names	Routes of Administration	Starting Dose	Usual Ranges or Maintenance Dose	Comments
Conventional DMARDs					
Methotrexate	Rasuvo Trexall Otrexup (SC)	Oral, SC, IM	Oral: 7.5 mg once weekly or 2.5 mg every 12 hours for 3 doses once weekly SC/IM: 7.5 mg once weekly	7.5–20 mg every week	May be given with folic acid 1–5 mg/day to reduce adverse effects
Leflunomide	Arava	Oral	Loading dose: 100 mg daily for 3 days, then 20 mg daily or 10–20 mg daily without loading dose	10–20 mg daily	Not recommended in liver disease (ALT >3 times ULN)
Hydroxychloroquine	Plaquenil	Oral	200 mg twice daily or 400 mg daily	200 mg twice daily or 400 mg daily	Take with food or milk; use with caution in renal or hepatic impairment

Sulfasalazine	Azulfidine	Oral	500 mg once or twice daily	1000 mg twice daily (maximum dose 3000 mg/day if inadequate response after 12 weeks of 2000 mg/day)	Not recommended in renal or hepatic impairment
Tumor Necrosis Factor (TNF) Inhibitors					
Adalimumab	Humira	SC	40 mg every 2 weeks	40 mg every 2 weeks (may increase to 40 mg once weekly if not taking methotrexate)	
Certolizumab	Cimzia	SC	400 mg at 0, 2, 4 weeks	200 mg every other week or 400 mg every 4 weeks	
Etanercept	Enbrel	SC	50 mg once weekly or 25 mg twice weekly	Same as starting dose	
Golimumab	Simponi	SC	50 mg once monthly	Same as starting dose	
Infliximab	Remicade	IV	3 mg/kg at 0, 2, 6 weeks, and then every 8 weeks	3–10 mg/kg every 4–8 weeks	Given in combination with methotrexate; pretreat with methylprednisolone, acetaminophen, and antihistamine
Costimulation Modulator					
Abatacept	Orencia	IV, SC	IV: <60 kg: 500 mg, 60–100 kg: 750 mg, >100 kg: 1000 mg at 0, 2, and 4 weeks or initial IV dose followed by 125 mg SC within 24 hours SC: 125 mg weekly	IV: dose based on weight every 4 weeks SC: 125 mg weekly	
IL-6 Receptor Antagonists					
Sarilumab	Kevzara	SC	200 mg every 2 weeks	Same as starting dose	
Tocilizumab	Actemra	IV, SC	IV: 4 mg/kg every 4 weeks, SC: <100 kg: 162 mg every other week, >100 kg: 162 mg weekly	IV: 4–8 mg/kg every 4 weeks (maximum 800 mg per infusion) SC: <100 kg: 162 mg every other week, followed by an increase to weekly injections if needed; >100 kg: 162 mg weekly	Can increase metabolism of CYP3A4 substrates
Janus Kinase (JAK) Inhibitors					

Baricitinib	Olumiant	Oral IR	2 mg once daily	Same as starting dose	1 mg once daily in patients taking strong organic anion transporter 3 (OAT3) inhibitors (eg, probenecid)
Tofacitinib	Xeljanz	Oral	IR: 5 mg twice daily ER: 11 mg daily	Same as starting dose	5 mg once daily in moderate-to-severe renal insufficiency, moderate hepatic impairment, or concomitant CYP3A4 or CYP2C19 inhibitors
Upadacitinib	Rinvoq	Oral ER	15 mg once daily	Same as starting dose	Use with caution with strong CYP3A4 inhibitors; coadministration with strong CYP3A4 inducers is not recommended.
Anti-CD20 Monoclonal Antibody					
Rituximab	Rituxan	IV	1000 mg in 2 doses given 2 weeks apart	Initial dose may be repeated every 16–24 weeks based on response	Pretreat with methylprednisolone, acetaminophen, and antihistamine
IL-1 Receptor Antagonist					
Anakinra	Kineret	SC	100 mg once daily	Same as starting dose	

ALT, alanine transaminase; CYP, cytochrome P; ER, extended release; IM, intramuscular; IR, immediate release; IV, intravenous; SC, subcutaneous; ULN, upper limit of normal.

TABLE 4-2

Clinical Monitoring of Drug Therapy in Rheumatoid Arthritis

Drugs	Adverse Drug Reactions	Initial Monitoring	Maintenance Monitoring
NSAIDs	GI ulceration, bleeding, perforation; renal damage	SCr, CBC every 2–4 weeks after starting therapy	Same as initial plus stool guaiac every 6–12 months
Corticosteroids	Fluid retention, hyperglycemia, hypertension, behavioral and mood changes, increased appetite, weight gain, electrolyte imbalances, impaired healing, hirsutism, Cushing syndrome, HPA axis suppression, osteonecrosis of femoral and humeral heads, osteoporosis and fractures, myopathy, glaucoma, cataracts	Glucose, CBC periodically, BP every 3–6 months	Same as initial
Methotrexate	Infection, hepatic fibrosis, cirrhosis, interstitial pneumonitis,	SCr, CBC with	SCr, CBC with differential, AST, ALT, every 2–

	stomatitis, rash, GI perforation, diarrhea, thrombocytopenia, leukopenia	differential, AST, ALT, hepatitis B and C screening, tuberculosis screening	4 weeks for 3 months after starting or following a dose increase, then every 8–12 weeks during 3–6 months of therapy, and every 12 weeks after 6 months of therapy; signs of infection
Leflunomide	Hepatitis, diarrhea/nausea, alopecia, elevated BP	CBC with differential, SCr, ALT, AST, BP	CBC with differential, SCr, ALT, AST every 2–4 weeks for 3 months after starting or following a dose increase, then every 8–12 weeks during 3–6 months of therapy, and every 12 weeks after 6 months of therapy; BP periodically
Sulfasalazine	Rash, nausea, vomiting, diarrhea, photosensitivity, alopecia	CBC with differential, SCr, ALT, AST	CBC with differential, SCr, ALT, AST every 2–4 weeks for 3 months after starting or following a dose increase, then every 8–12 weeks during 3–6 months of therapy, and every 12 weeks after 6 months of therapy
Hydroxychloroquine	Retinal damage, rash, diarrhea	Ophthalmologic exam within 5 years of starting therapy	Ophthalmologic exam annually if risk factors for retinal damage present or annually beginning after 5 years of use if no risk factors
Etanercept, adalimumab, golimumab, certolizumab	Local injection-site reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential	Periodic skin examination, signs/symptoms of infection and malignancy, CBC with differential periodically
Infliximab	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential, LFTs	CBC with differential, LFTs, signs/symptoms of infection and malignancy
Abatacept	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening	Signs/symptoms of infection and malignancy
Sarilumab	Local injection-site reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential, LFTs, lipid panel	CBC with differential and LFTs 4–8 weeks after starting and then every 3 months, FLP 4–8 weeks after starting and every 6 months during therapy, signs/symptoms of infection and malignancy
Tocilizumab	Local injection-site reactions, infection, malignancy, GI	Tuberculosis	AST, ALT, CBC with differential every 4–8

	perforation, neutropenia, thrombocytopenia	screening, hepatitis B screening, CBC with differential, AST, ALT, FLP	weeks after starting then every 3 months; FLP after 4–8 weeks of starting then every 6 months; signs/symptoms of infection and malignancy
Baricitinib, tofacitinib, upadacitinib	Infection, malignancy, GI perforations, upper respiratory tract infections, headache, diarrhea, nasopharyngitis	Tuberculosis screening, hepatitis B screening, CBC with differential, Hgb, LFTs, FLP, HR, and BP	CBC with differential and Hgb after 4–8 weeks and every 3 months, FLP after 4–8 weeks and periodically, LFTs periodically, periodic skin examinations, HR and BP, signs/symptoms of infection and malignancy
Rituximab	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening, CBC with differential	CBC with differential prior to each treatment course and at 2- to 4-month intervals, signs/symptoms of infection
Anakinra	Local injection site reactions, infection, malignancy	CBC with differential, tuberculosis screening, SCr, hepatitis B screening	CBC with differential every 3 months up to 1 year, SCr periodically, signs/symptoms of infection and malignancy

ALT, alanine transaminase; AST, aspartate transaminase; BP, blood pressure; CBC, complete blood count; FLP, fasting lipid panel; GI, gastrointestinal; Hgb, hemoglobin; HPA, hypothalamic–pituitary–adrenal; HR, heart rate; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine.

Conventional DMARDs

- **Methotrexate** inhibits dihydrofolate reductase, thereby inhibiting DNA synthesis and repair and cellular replication. Injectable (subcutaneous [SC], intramuscular [IM]) methotrexate has higher bioavailability than oral methotrexate and thus provides superior clinical efficacy; it is typically better tolerated with less potential to cause gastrointestinal (GI) side effects as well. Oral methotrexate doses >15 mg weekly may not have significant added clinical benefit; changing to SC methotrexate may increase bioavailability and clinical benefit in this situation. Clinical benefit can be seen 3–6 weeks after starting therapy. Methotrexate has numerous adverse effects (**Table 4-2**); concomitant folic acid 1–5 mg/day may reduce some adverse effects without loss of efficacy. Methotrexate is teratogenic, and patients should use contraception and discontinue the drug if conception is planned. Methotrexate is contraindicated in pregnant and nursing women, chronic liver disease, immunodeficiency, and preexisting hematologic disorders (eg, leukopenia, thrombocytopenia). Methotrexate excretion is reduced in renal impairment and may require dose reduction or discontinuation in some cases.

- **Leflunomide** inhibits pyrimidine synthesis, which reduces lymphocyte proliferation and modulation of inflammation. It can be used as monotherapy or in combination with other DMARDs. Efficacy for RA is similar to that of methotrexate. A loading dose of 100 mg/day for 3 days may achieve steady state more rapidly but may increase the risk for toxicities. The usual maintenance dose of 20 mg/day may be lowered to 10 mg/day in cases of GI intolerance, alopecia, or other dose-related toxicity. Adverse effects are listed in **Table 4-2**. Leflunomide is teratogenic and should not be used in pregnant or nursing mothers or in patients with severe hepatic impairment.

- **Sulfasalazine** can be used as monotherapy or in combination with other DMARDs. Clinical benefit usually occurs in 4 weeks, but some patients

may require 12 weeks. Sulfasalazine use is limited by GI adverse effects (**Table 4-2**). Sulfasalazine crosses the placenta and is present in breast milk but can be used in pregnant and nursing mothers with caution.

- **Hydroxychloroquine** is typically used in combination with other DMARDs, but it can be used as monotherapy in mild cases. Clinical benefit is delayed and may take several weeks. Its main advantage is that it does not require frequent, routine laboratory monitoring because it is not generally associated with infection risk or hepatic, renal, or blood cell abnormalities. GI side effects can sometimes be mitigated by taking the medication with food or splitting the dose into two doses. Hydroxychloroquine can be continued during pregnancy because no studies have shown an increased risk of birth defects or ocular toxicities. Hydroxychloroquine is excreted into breast milk, and caution should be used in nursing mothers. Periodic ophthalmologic examinations are necessary for early detection of irreversible retinal toxicity (**Table 4-2**).

Biologic DMARDs

- Biologic agents are genetically engineered proteins that decrease inflammation by various mechanisms. They are categorized as either TNF inhibitors or non-TNF biologics. They may be effective when conventional DMARDs fail to achieve adequate disease control but are considerably more expensive.
- Biologic DMARDs are associated with an increased risk of infection due to immunosuppressive effects. A tuberculin skin test or interferon gamma release assay (IGRA) blood test should be obtained before starting a biologic to detect and treat latent or active tuberculosis. Patients should also be screened for hepatitis B before starting biologic therapy because of the risk for reactivation.
- Biologics can be used in combination with conventional DMARDs, but multiple biologics should not be used concomitantly due to additive immunosuppressive effects. In general, if patients are switched from one biologic to another, the new agent should be initiated when the patient is due for a dose of the previous biologic. Because of immunosuppressive effects, patients taking biologics should notify their providers if they are being treated for an infection or plan to undergo major surgery. Treatment may need to be held until appropriate postsurgical healing and/or resolution of infection can be confirmed. Live vaccines should not be given to patients taking biologic agents.
- *Biosimilars* are biologic products that have been verified to have no clinically meaningful differences compared to an FDA-approved reference biologic product. These agents can increase access to RA treatment because their costs are lower than the originator products. However, concerns that limit their use include lack of regulatory guidelines about switching from the original biologic product to the biosimilar and uncertainty about extrapolation of indications for biosimilars from the original biologic product.

TNF-α Inhibitors

- TNF inhibitors block the proinflammatory cytokine TNF-α. It may take several weeks for clinical benefit to be noted and up to 3 months to achieve full clinical benefit. These agents are typically used when disease activity remains moderate or high despite conventional DMARD therapy. TNF inhibitors are more expensive than conventional DMARDs.
- Selection of a particular TNF inhibitor depends on cost and patient preference for route and frequency of administration. They should not be used in patients with moderate-to-severe heart failure (New York Heart Association [NYHA] class III/IV) because new-onset and worsening heart failure have been reported. These agents increase the risk of serious infection and malignancies (eg, lymphoma, skin cancers), and new-onset or exacerbation of demyelinating disorders such as multiple sclerosis has been observed.
- See **Tables 4-1** and **4-2** for dosing and monitoring information.

  ✔ **Adalimumab** (Humira) binds to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF receptors. It is available as a prefilled syringe or pen for SC injection.

  ✔ **Certolizumab** (Cimzia) is a pegylated humanized antibody Fab fragment of TNF-α monoclonal antibody. Because it lacks the Fc region, it does not induce complement activation, antibody-dependent cell-mediated cytotoxicity, or apoptosis. Pegylation allows for delayed elimination and extended half-life. It is available as a prefilled syringe for SC injection.

  ✔ **Etanercept** (Enbrel) is a recombinant DNA-derived protein composed of TNF receptor linked to the Fc fragment of human IgG1. It is available as a prefilled syringe or pen for SC injection.

✔ **Golimumab** (Simponi) is a human monoclonal antibody that binds to human TNF-α. It is available as a prefilled syringe or pen for SC injection. It is also available as an intravenous (IV) product.

✔ **Infliximab** (Remicade) is a chimeric monoclonal antibody that binds to human TNF-α. It is administered as an IV infusion. To prevent formation of an antibody response to this foreign protein, methotrexate must be given orally in doses used to treat RA for as long as the patient continues infliximab. Premedication with an antihistamine, acetaminophen, and/or a glucocorticoid can decrease development of infusion-related reactions. Patients on infliximab plus methotrexate have been shown to have a better clinical response than patients treated with methotrexate alone.

Costimulation Modulator

- **Abatacept** (Orencia) inhibits T-cell activation by binding to CD80 and CD86, which blocks the interaction between T cells CD28, thus inhibiting the activation of T cells. Abatacept is indicated for moderate-to-severe RA and can be used as monotherapy or in conjunction with conventional DMARDs. Abatacept is typically initiated if disease activity persists after conventional DMARD monotherapy and can be an alternative to TNF inhibitors with or without methotrexate. It can also be initiated in patients who have failed or have had an inadequate response to TNF inhibitors. Abatacept plus methotrexate has similar efficacy and incidence of adverse events as adalimumab plus methotrexate in biologic-naive patients who had an incomplete response to methotrexate. Abatacept is available in a prefilled syringe or auto-injector for SC injection and as an IV infusion.

IL-6 Receptor Antagonists

- **Sarilumab** (Kevzara) is indicated for treatment of patients with moderate-to-severe RA who have had an incomplete response or intolerance to one or more DMARDs. It can be used as monotherapy or with conventional DMARDs. It is available as prefilled syringes for SC injection.
- **Tocilizumab** (Actemra) can be used for patients with moderate-to-severe RA who have had an incomplete response to one or more DMARDs. It can be used alone or in combination with conventional DMARDs. It is available as prefilled syringes for SC injection and as an IV infusion.

Anti-CD20 Monoclonal Antibody

- **Rituximab** (Rituxan) is a monoclonal antibody that binds the CD20 antigen on the surface of B cells. Binding of rituximab to B cells results in nearly complete depletion of peripheral B cells, with a gradual recovery over several months. Rituximab can be initiated in patients with moderate-to-severe RA who have had an incomplete response to one or more TNF inhibitors. Methotrexate should be given concurrently in the usual doses for RA to achieve optimal outcomes. An observational cohort study showed that patients who failed one TNF inhibitor had greater reductions in disease activity scores when treated with rituximab than with a second TNF inhibitor. Rituximab is given as two 1000-mg infusions separated by 2 weeks. Because recovery of B-cells can take several months, rituximab can be given every 24 weeks. The decision to re-dose should be based on the return of RA symptoms. Methylprednisolone 100 mg IV is recommended 30 minutes before each infusion as well as acetaminophen and an antihistamine to reduce the incidence and severity of infusion reactions.

IL-1 Receptor Antagonist

- **Anakinra** (Kineret) is an IL-1 receptor antagonist; it is less effective than other biologics, is used infrequently, and is not included in the current ACR treatment recommendations. However, it can be used in patients with moderate-to-severe RA who have failed one or more DMARDs. Anakinra can be used alone or in combination with DMARDs other than TNF-α inhibitors.

Janus-Kinase Inhibitors

- **Baricitinib** (Olumiant), **tofacitinib** (Xeljanz), and **upadacitinib** (Rinvoq) are oral, small-molecule, nonbiologic JAK inhibitors. Baricitinib is FDA approved for adults with moderately to severely active RA who have had an inadequate response to one or more TNF inhibitors; it may be used alone or in combination with methotrexate or other conventional DMARDs. Tofacitinib and upadacitinib have FDA approval for treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate; these drugs may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. JAK inhibitors should not be given concomitantly with biologic

agents.

- Labeling for all JAK inhibitors includes black-box warnings about serious infections, lymphomas, and other malignancies. Live vaccinations should not be given during treatment. Patients should be tested and treated for latent tuberculosis before starting therapy.

Nonsteroidal Anti-inflammatory Drugs

- NSAIDs inhibit prostaglandin synthesis, which is a small portion of the inflammatory cascade. They possess both analgesic and anti-inflammatory properties and reduce stiffness, but they do not slow disease progression or prevent bony erosions or joint deformity and should not be used as monotherapy for RA treatment. They have a more rapid onset of action than DMARDs and may be beneficial to “bridge” patients while DMARDs take effect. Common NSAID dosage regimens are shown in **Table 4-3**.

TABLE 4-3

Dosage Regimens for Nonsteroidal Anti-inflammatory Drugs

Recommended Total Daily Anti-inflammatory Dosage			
Drug	**Adult**	**Children**	**Dosing Schedule**
Aspirin	2.6–5.2 g	60–100 mg/kg	4 times daily
Celecoxib	200–400 mg	–	Once or twice daily
Diclofenac	150–200 mg	–	3 or 4 times daily; extended release: twice daily
Diflunisal	0.5–1.5 g	–	Twice daily
Etodolac	0.2–1.2 g (max. 20 mg/kg)	–	2–4 times daily
Fenoprofen	0.9–3 g	–	4 times daily
Flurbiprofen	200–300 mg	–	2–4 times daily
Ibuprofen	1.2–3.2 g	20–40 mg/kg	3 or 4 times daily
Indomethacin	50–200 mg	2–4 mg/kg (max. 200 mg)	2–4 times daily; extended release: once daily
Meclofenamate	200–400 mg	–	3–4 times daily
Meloxicam	7.5–15 mg	–	Once daily
Nabumetone	1–2 g	–	Once or twice daily
Naproxen	0.5–1 g	10 mg/kg	Twice daily; extended release: once daily
Naproxen sodium	0.55–1.1 g	–	Twice daily
Nonacetylated salicylates	1.2–4.8 g	–	2–6 times daily
Oxaprozin	0.6–1.8 g (max. 26 mg/kg)	–	1–3 times daily
Piroxicam	10–20 mg	–	Once daily
Sulindac	300–400 mg	–	Twice daily
Tolmetin	0.6–1.8 g	15–30 mg/kg	2–4 times daily

Glucocorticoids

- Glucocorticoids have anti-inflammatory and immunosuppressive properties; although they have been shown to slow RA progression, glucocorticoids should not be used as monotherapy for RA due to the potential for serious, long-term adverse effects (**Table 4-2**). They should be

used at the lowest effective dose for the shortest period of time. According to the ACR, short-term glucocorticoid therapy is defined as <3 months, and low-dose glucocorticoid is defined as prednisone ≤10 mg/day (or equivalent).

- Similar to NSAIDs, oral glucocorticoids (eg, **prednisone**, **methylprednisolone**) can be used to "bridge" patients while DMARDs take effect. They can also be used as adjuncts to DMARDs at the lowest dose possible in patients with refractory disease. High-dose, short-term bursts can be used as needed for acute flares of RA symptoms, followed by tapering to the lowest effective dose to control symptoms or until discontinued over several days.
- The IM route may be useful in nonadherent patients. Depot forms (**triamcinolone acetonide**, **triamcinolone hexacetonide**, and **methylprednisolone acetate**) provide 2–6 weeks of symptom control. Onset of effect may be delayed for several days. The depot effect provides a physiologic taper, avoiding hypothalamic–pituitary axis suppression.
- Intra-articular injections may be useful when only a few joints are involved. Injections should not be repeated more often than every 3 months because of the potential for accelerated loss of joint cartilage.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess disease activity at baseline and at each follow-up visit to evaluate therapeutic response. Clinical signs of improvement include reduction in joint pain, swelling, and tenderness; less morning stiffness; reduced fatigue; and improved ability to perform activities of daily living.
- Perform a physical examination at each visit to objectively evaluate the number of swollen and tender joints, joint mobility, and presence of deformity.
- Several assessment tools are available to measure RA disease activity, such as the Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS28), Patient Activity Scale (PAS), Routine Assessment of Patient Index Data 3 (RAPID-3), and Simplified Disease Activity Index (SDAI).
- Laboratory monitoring of acute phase reactants such as CRP and ESR can be useful in assessing inflammation.
- Obtain plain radiographs of the hands, wrists, and forefeet at baseline and every 2 years in patients with low disease activity or in remission. Little to no evidence of RA disease progression should be evident if drug therapy is effective. Imaging may be needed more frequently in patients with moderate or high disease activity. Drug therapy should be modified if patients have radiographic changes suggestive of disease progression (eg, periarticular osteopenia, bone erosions, joint space narrowing).
- It is important to monitor and assess for clinical and laboratory adverse effects of the medications used to treat RA (**Table 4-2**).

See Chapter 107, Rheumatoid Arthritis, authored by Stephanie Gruber, Bianca Lezcano, and Susan Hylland, for a detailed discussion of this topic.