ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

Chapter 111: Rheumatoid Arthritis

Stephanie Gruber; Bianca Harris; Susan Hylland

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 4, Rheumatoid Arthritis.

KEY CONCEPTS

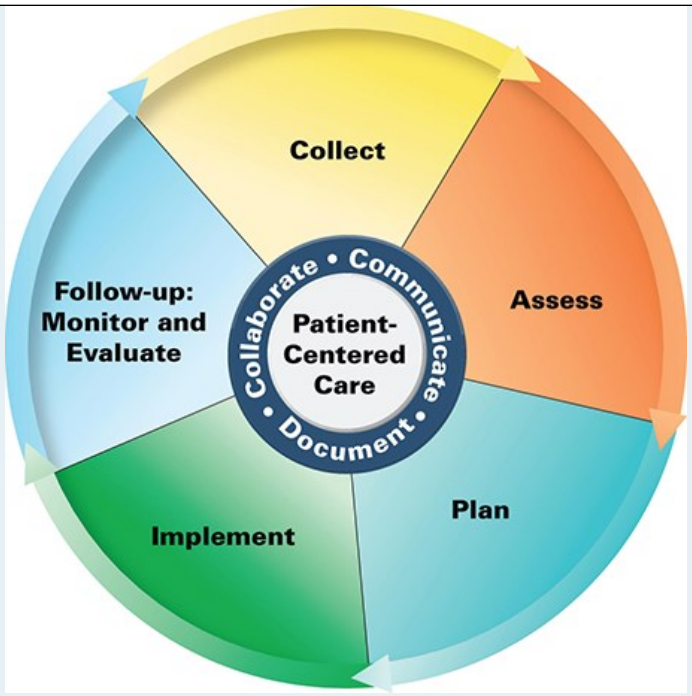
KEY CONCEPTS

1. The etiology of rheumatoid arthritis is unknown but is thought to result from a combination of genetic and environmental factors.
2. Rheumatoid arthritis is a systemic autoimmune condition in which inappropriate activation of innate and adaptive immune responses cause inflammation leading to bone, cartilage, and synovium erosion.
3. The primary goal of treatment includes targeting disease remission/low disease activity ultimately aiming at enhancing quality of life.
4. Care should be provided by a rheumatology-trained clinician.
5. Optimizing mental health and completing physical therapy are both crucial nonpharmacologic therapies in addition to providing comprehensive disease and treatment education.
6. Drug treatment should be started as soon as a diagnosis is established.
7. Choice of therapy depends on the level of disease activity, comorbid health conditions, patient preference, and often insurance coverage.
8. Nonsteroidal anti-inflammatory drugs, analgesics, and corticosteroids are used as adjunctive therapy to disease-modifying antirheumatic drug therapy.
9. Response to therapy is evaluated by patient subjective reports, physical examination, laboratory markers, and imaging.

PATIENT CARE PROCESS

Patient Care Process for Rheumatoid Arthritis

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility



Collect

- Patient characteristics (eg, age, sex, pregnancy status, insurance)
- Social history (eg, tobacco/alcohol use, activity)
- Patient medical history (eg, health conditions, immunizations, recent infections)
- Family medical history (eg, autoimmune conditions)
- Current medications
- Past RA medication trials
- Subjective symptom report
- Objective data such as blood pressure, labs (eg, ESR, CRP, CBC), imaging (eg, DEXA, x-ray films, ultrasound), physical examination (eg, number of tender/swollen joints)

Assess

- Patient subjective report (eg, pain score, duration of morning joint stiffness, adherence to therapy, injection technique/medication storage, side effects to drug therapy, disability, fatigue)
- Change in number of tender/swollen joints, labs, or imaging
- Cardiovascular risk factors
- Infection risk and upcoming procedures
- Patient treatment preference (utilize motivational interviewing as appropriate)

Plan*

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

- Drug therapy (see Table 111-2)
- Referrals when appropriate (eg, tobacco treatment clinic, podiatry, mental health, social work, physical and/or occupational therapy)
- Patient education (eg, dosing, side effects, infection risk management, symptom self-monitoring)
- Order follow-up labs based on therapy chosen (see Table 111-4)

Implement*

- Provide patient education regarding rationale for and follow-up of treatment plan
- Provide patient with written medication changes, time frame for follow-up, and clinic/emergency contact information
- Coordinate and schedule follow-up

Follow-up: Monitor and Evaluate

- Subjective symptom changes and impact on daily activities
- Presence of adverse effects and infections
- Laboratory results as indicated for therapy
- Patient adherence to treatment plan
- Time frame dependent on treatment plan (generally every 1-3 months)

**Collaborate with a rheumatologist.*

BEYOND THE BOOK

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

BEYOND THE BOOK

Direct-to-consumer advertising refers to the marketing of products to patients rather than healthcare professionals. This is a common marketing strategy, particularly for pharmaceutical products. Watch the following advertisements for tofacitinib and adalimumab:

- https://www.ispot.tv/ad/O1Z1/xeljanz-mornings-raking
- https://www.ispot.tv/ad/wrWz/humira-food-drive

Reflect on the promotional materials by considering the following questions:

- What is the general feeling generated by the commercials?
- What actions or activities do the commercials focus on?
- What additional concerns might one have after hearing about the possible side effects of this biologic product?

Watching the adalimumab commercial would lead patients to the product Website to do their own research: https://www.humira.com. Explore the Website and reflect on the following questions:

- How user-friendly is the Website? What resources are available for patients?
- What specifically is HUMIRA Complete?
- Where is the injection education video located on the Website?
- Would you direct patients to watch this video?
- What resources would you use from this Website, if any, for your patient education in clinic?

One of the counseling points for adalimumab is to contact your provider prior to having any surgeries or receiving any vaccinations. Make a chart of which immunizations a patient can and cannot receive while using this injectable medication.

INTRODUCTION

Autoimmune conditions cause the body to produce an inappropriate immune response against its own healthy tissue. Rheumatoid arthritis (RA) is a common, chronic, progressive autoimmune condition that primarily affects the joint and synovium but can also have detrimental effects on organ systems throughout the body. It can have substantial and devastating effects on one's ability to function and complete basic activities of daily living. The exact etiology of RA is unknown, but treatment options are numerous. Comprehensive treatment plans are developed under the guidance of a rheumatology specialist and through a process of shared decision making with the patient.

EPIDEMIOLOGY

RA is one of the more common autoimmune conditions. The annual incidence is about 40 individuals per 100,000. Worldwide disease prevalence is approximately 1% with some variance for race and geographic location.[1] This prevalence corresponds most closely with North American and Northern European countries; however, native American-Indian populations have the highest prevalence noted (approximately 5%-6%). Southern European, Eastern Asian, and African countries have a lower prevalence.[1] Women are twice as likely to develop the disease compared with men.[2]

RA generally presents in the fifth decade of life with increasing prevalence up to the eighth decade of life.[3] RA can affect children age 16 years or younger; in these patients, the condition is referred to as juvenile RA. This chapter focuses only on the clinical management of adult RA. Compared with the general population, individuals with RA have higher rates of disability claims and workplace limitations and lower rates of employment.[4] Loss of productivity has been associated with lower annual earnings.[2,4]

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

The mortality rate in patients with RA is higher than that of the general population. Cardiovascular (CV) disease is the leading cause of death in RA and presents the greatest concern. Patients with RA have a higher risk of major adverse CV events, and RA disease activity is a predictor of increased CV risk. The risk of death is also increased by infections, malignancy, depression, and pulmonary disease. The expected life expectancy of patients with RA is 3 to 10 years less than the general population.[5-7]

Despite advancements in therapy, mortality trends have not changed drastically, though one could argue additional time is required to detect changes in survival data. Other common comorbid autoimmune diseases include insulin-dependent diabetes mellitus and autoimmune thyroid disease.[6,7]

ETIOLOGY

1 The specific cause of RA is unknown. The disease results from a mix of genetic susceptibility and nongenetic factors combined with a triggering event. Genetic polymorphisms seem to play a large role based on descriptive epidemiologic studies. There is a thought that multiple genes are involved, specifically those of the human leukocyte antigen (HLA) system.[8] Genetics also seems to play a role based on familial studies. In studies of the development of RA in twins, monozygotic twins had a higher concordance than dizygotic twins.[9] Patients with a first-degree relative with RA are at a higher risk of having RA themselves when nongenetic factors are standardized.[10]

There is some variability regarding the role of hormonal regulation and the likelihood of RA development, particularly with estrogen. Evidence is conflicting as to whether pregnancy status affects the risk of RA. Pregnancy is often associated with disease remission in the last trimester, but flares commonly occur in the acute postpartum period.[8] There is also controversial evidence showing female oral contraceptives may protect against or postpone disease development. Testosterone may have a protective effect, as men with low testosterone levels are more likely to have RA.

Nongenetic or environmental factors possibly associated with RA include cigarette use, coffee consumption, and obesity.[8] Cigarette smoking has been tied to increased disease activity, increased biomarkers, and poor prognoses.[6] Ties are weaker for disease development with heavy coffee consumption and obesity.[11,12] Dietary choices have been reported by patients to both positively and negatively impact disease severity or progression.[13] Occupational hazards, such as exposure to silica, may also play a role in susceptibility to disease.[14]

Additional factors, aside from those mentioned above, are needed to trigger the disease itself. An infectious process is hypothesized to be the primary trigger. The Epstein–Barr virus and retroviruses are most commonly associated with the disease.[8] Infections of *Mycoplasma* spp. and *Porphyromonas gingivalis* have been suspected as bacterial triggers, but no true link has been found to show their causality.[15] Further studies are required to help uncover the exact etiology of RA.

PATHOPHYSIOLOGY

2 The role of the immune system is to detect foreign matter, build a response, and neutralize the threat. In RA, the immune system cannot discriminate between self and nonself. This results in cell proliferation, inflammation, and destruction of tissues and fluids throughout one's own body.

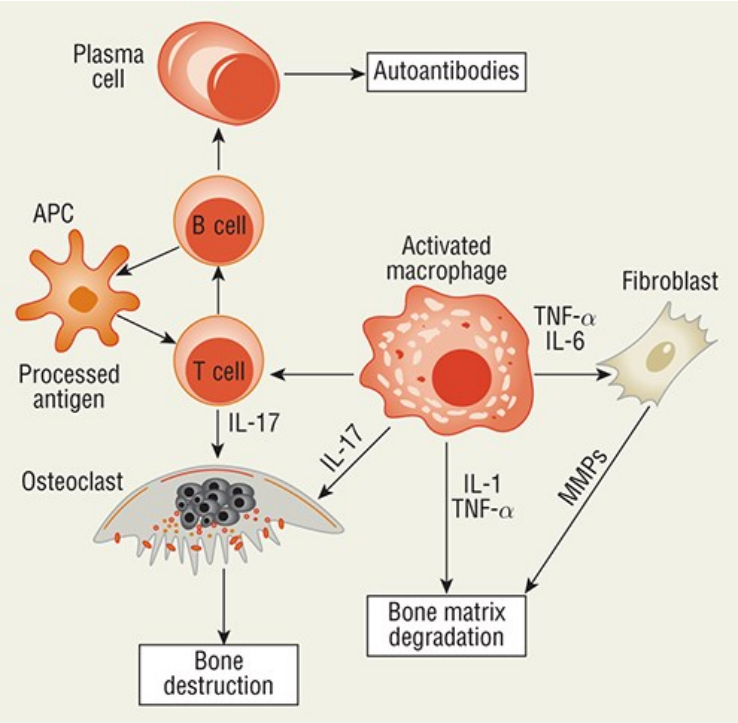
The immune cascade and inflammatory pathway dysregulation associated with RA is multifactorial (Fig. 111-1). Overstimulation of the innate immune system is thought to be one of the earliest histologic changes in RA. T cells display an activated surface phenotype with high allele expression of HLA and CD 27, increasing their affinity for lymphokines. Activated T cells stimulate B cells, causing production of autoantibodies. These autoantibodies form large complexes that deposit throughout the body. Antibodies to immunoglobulin G (IgG) have a strong correlation to the pathogenesis and poor prognosis of RA and are known as rheumatoid factor (RF). B cells also produce proinflammatory cytokines, including tumor necrosis factor (TNF) and the interleukin (IL) system, which are responsible for inducing expression of adhesion molecules on the endothelium, further enhancing T-cell proliferation and differentiation, encouraging cell migration, and regulating matrix modeling.[16-18]

FIGURE 111-1

Pathogenesis of the inflammatory response. Antigen-presenting cells process and present antigens to T cells, which may stimulate B cells to produce

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

antibodies and osteoclasts to destroy and remove bone. Macrophages stimulated by the immune response can stimulate T cells and osteoclasts to promote inflammation. They also can stimulate fibroblasts, which produce matrix metalloproteinases to degrade the bone matrix and produce proinflammatory cytokines. Activated T cells and macrophages release factors that promote tissue destruction, increase blood flow, and result in cellular invasion of synovial tissue and joint fluid. (APC, antigen-presenting cell; IL, interleukin; MMP, matrix metalloproteinase; TNF-α, tumor necrosis factor α.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

Other mechanisms of pathogenesis include overexpression of tumor suppressor gene *p53*, which prevents normal DNA repair and interferes with appropriate cell apoptosis (programmed cell death), and increased presence of anticitrullinated protein antibodies (ACPA). ACPA positivity is associated with a poorer prognosis in patients with RA.[19,20]

A variety of histological changes occur within the synovium, given the above pathological processes. Synovial tissue typically attaches to the skeletal tissues and the bone-cartilage joint cavity and provides a protective shield for the synovial interstitium and a nutrient-rich environment for cartilage. Migration of lymphocytes, macrophages, and mononuclear cells into the synovium and synovial cavity are some of the earliest histologic changes in RA. With the increased mass to the synovium comes hypertrophy and subsequently angiogenesis, which is needed to bring the necessary oxygen and nutrients to the environment. Angiogenesis is initiated by the proinflammatory cytokines and driven by factors such as IL-8, prostaglandins, vascular endothelial growth factor, and macrophage angiogenic factor. As the vessels develop, cytokines also stimulate further migration of both innate and adaptive immune systems into the synovium, causing inflammation. The inflamed, fibrotic synovium found in RA is known as a pannus. The pannus invades cartilage and bone around it, thereby promoting further destruction and dysregulation.[21-24]

Cytokines in the cartilage drive the generation of reactive nitrogen and oxygen species while increasing chondrocyte catabolism, inhibiting chondrocyte anabolism, and increasing extracellular matrix destruction. Proinflammatory cytokines travel to the bone, provide the source for receptor activator of NFkB ligand (RANKL), and enhance the differentiation and activity of osteoclasts leading to bone matrix destruction.[25-28]

Circulating immune complexes and T cells have been found in the extra-articular involvement of RA. Chronic inflammation in vascular endothelial and visceral, cutaneous, and pleural tissues leads to complications including vasculitis, fibrosis, anemia, and renal amyloidosis.[21,29]

CLINICAL PRESENTATION

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

CLINICAL PRESENTATION: Rheumatoid Arthritis

Joint Involvement

- Hands, wrists, ankles, and feet are most commonly affected, often bilaterally
- Presence of warmth and swelling with or without pain
- Prolonged morning stiffness, often for longer than 30 minutes in duration
- Decreased functionality
- Symptoms present for 6 weeks or more
- Subluxations and deformities possible with advanced disease

Extra-articular Involvement

- Generalized fatigue, weakness, and decreased mood are nonspecific implications of disease
- Rheumatoid nodules can be found on extensor or pleural lining surfaces
- Interstitial lung disease or pleural disease
- Vasculitis
- Keratoconjunctivitis sicca, scleritis, or Sjögren's syndrome
- Pericarditis, cardiac conduction abnormalities, or myocarditis
- Felty syndrome or anemia

Laboratory Findings

- Rheumatoid factor is detected in 70% to 80% of patients with RA with higher titers, which reflects increased sensitivity and more progressive disease
- Anticyclic citrullinated antibodies are more specific for disease, particularly early stage, and generally indicate more aggressive disease
- Erythrocyte sedimentation rate and C-reactive proteins may indicate the presence of a nonspecific inflammatory process
- Synovial fluid analysis through joint aspiration typically demonstrates a high white blood cell count in the absence of crystals or infection

Radiography

- In early stages of RA, it may show soft tissue swelling and joint space narrowing
- In late-stage disease, it may show joint subluxations, deviations, and secondary arthritis

Joint Involvement

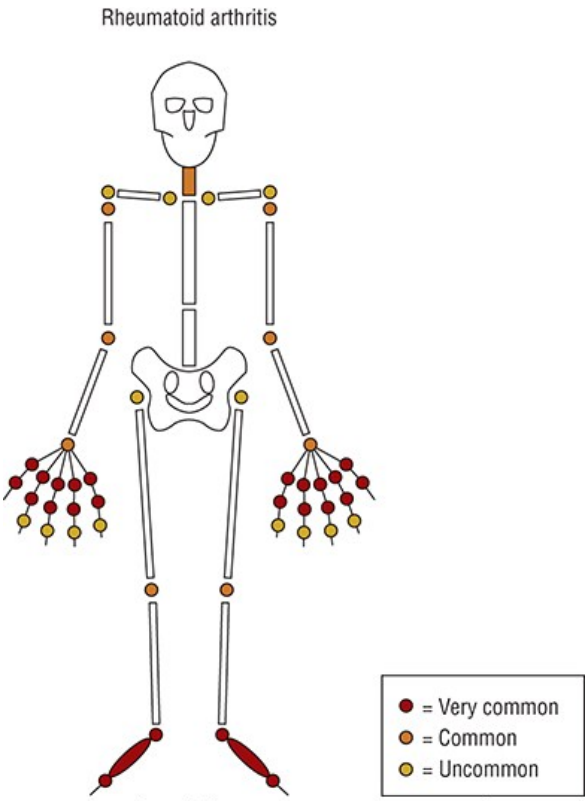
Patients with RA often present with involvement of synovial-lined peripheral joints, typically in a symmetrical fashion (Fig. 111-2). The joints of the hands, feet, wrists, and ankles are most commonly involved. Elbows, knees, shoulders, hips, cervical spine, and temporomandibular joints may also be affected.

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

FIGURE 111-2

Patterns of joint involvement in rheumatoid arthritis.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

Classic features of RA are the presence of swelling and prolonged morning stiffness, often for more than 30 minutes. Joint swelling is caused by proliferation of synovium or effusion within the joint capsule. On physical examination, joint swelling may be visible or detected by palpation of soft spongy tissue along joint lines. A swollen joint may appear erythematous, and the overlying skin may feel warmer than surrounding tissue. In contrast, the swelling associated with osteoarthritis is due to bony enlargement and not typically associated with signs of inflammation.

RA of the hands more specifically involves the metacarpophalangeal, proximal interphalangeal, and wrist joints, while sparing distal interphalangeal joints (Fig. 111-3). Pain and swelling commonly affect joint range of motion and grip strength. Wrist swelling may lead to focal nerve compression, causing symptoms of carpal tunnel syndrome. Untreated, long-term joint inflammation may lead to bony erosions, subluxations, and deformities (Figs. 111-4 and 111-5). These changes may alter the mechanics of hand function, reducing grip strength and making it difficult to perform usual daily activities.

FIGURE 111-3

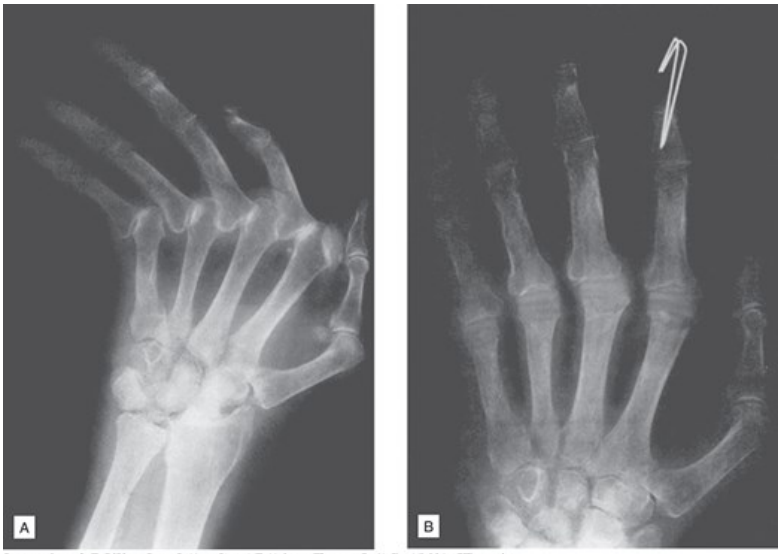
Typical hand deformities of rheumatoid arthritis showing ulnar deviation of the fingers and swelling of the metacarpophalangeal and proximal interphalangeal joints. *(Reproduced, with permission, from Brunicardi FC, Anderson DK, Billiar TR, et al. Schwartz's Principles of Surgery. 8th ed. New York: McGraw Hill; 2005.)*

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

FIGURE 111-4

Radiographs of hands of patient with rheumatoid arthritis showing erosions and subluxations of the metacarpophalangeal joints with ankylosis of the carpal bones of both wrists. *(Reproduced with permission from Papadopoulos DV, Bednar MS, Davidson A, Schmidt CC. Hand surgery. In: McMahon PJ, Skinner HB. eds. Current Diagnosis & Treatment in Orthopedics, 6th Edition. McGraw Hill; 2021.)*



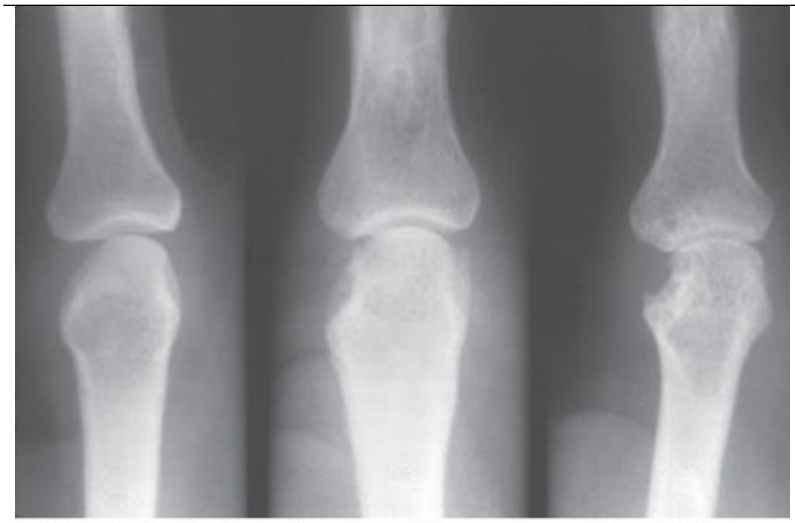
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

FIGURE 111-5

Radiograph showing soft tissue swelling, joint space narrowing, and erosions in the metacarpophalangeal joints. *(Reprinted, with permission, from Jonsson A, Borg A, Hannesson, et al. Film-screen vs digital radiography in rheumatoid arthritis of the hand: An ROC analysis. Acta Radiologica. 1994;35(4):312.)*

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

When patients with RA have involvement of the joints of the feet, walking may be difficult because of metatarsophalangeal, midfoot, and ankle joint inflammation. Untreated long-term inflammation may lead to subluxations of the metatarsal heads causing bunion formation, hammer toe deformities, or overlapping digits (Figs. 111-4 and 111-5). Affected joints are then subject to ulceration of the skin overlying joint deformities secondary to pressure caused by footwear.

Other parts of the body are also affected by pathophysiologic changes in RA. Pain and decreased range of motion in the elbow and shoulder joints may be the result of joint inflammation or inflammation of the tendons and bursae around the joints. Chronic synovial inflammation of the knee may lead to effusions, pain, and loss of range of motion. Synovitis of the knee may cause the formation of a fluid collection behind the knee called a popliteal (Baker) cyst. Eventually, chronic knee joint inflammation may lead to cartilage loss and muscle atrophy, which can result in laxity of the ligamentous structures that support the knee and ultimately instability. The hip joint, a large axial joint, is less commonly involved in RA, but may manifest with joint effusion and long-term accelerated cartilage loss.

Spinal involvement in RA, when present, occurs in the upper cervical vertebrae. Inflammation of the synovial-lined portions of the first and second cervical vertebrae (C1-C2) can lead to neck pain and stiffness. Long-term RA activity at this joint may lead to instability and subluxation, putting patients at risk for spinal cord compression, although this complication is rare.

The temporomandibular joint of the jaw is also a synovial lined joint and, when affected, patients with RA may experience malocclusion and difficulty chewing.

Extra-articular Involvement

Although joint involvement is the hallmark finding in RA, it is important to recognize that this is ultimately a multisystem inflammatory disease. Patients with high-titer RF or ACPA have a higher likelihood of extra-articular manifestations.

Rheumatoid Nodules

Rheumatoid nodules occur in 20% to 35% of patients with RA at some point during their disease course.[30] Rheumatoid nodules are subcutaneous collections of palisading macrophages surrounded by lymphocytes and fibroblasts, which can vary in size from several millimeters to several centimeters. They are most commonly found on the extensor surfaces of the elbows, forearms, and hands but also may be seen on the feet and at other pressure points. They also may develop in the lung or pleural lining of the lung. Rheumatoid nodules usually are asymptomatic and do not require any special intervention. They do not necessarily improve with treatments targeting RA activity and can accelerate in growth during treatment with methotrexate.[31]

Pulmonary Complications

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Interstitial lung disease (ILD) is the most common pulmonary manifestation of rheumatoid disease. Frequently ILD is not overtly clinically apparent, but it can be seen on high-resolution CT imaging in up to 33% of patients with RA without symptoms of cough or dyspnea.[32] The most frequent patterns of ILD seen in RA are the usual interstitial pneumonia and nonspecific interstitial pneumonia. Smoking increases the risk of this complication.[33]

Pleural disease is common in RA, and while most commonly asymptomatic, it may result in pleural effusion.[34] Rheumatoid nodules may also develop in lung tissue and may be difficult to distinguish from infection or malignancy on chest imaging. Interstitial pneumonitis is a rare but potentially life-threatening complication of RA. Treatments directed at treating articular manifestations of rheumatoid arthritis frequently do not control pulmonary manifestations.

Vasculitis

Rheumatoid vasculitis is a rare complication of RA seen in patients with long-standing seropositive disease. Invasion of arterial walls by inflammatory cells results in narrowing of the vessel lumen, producing tissue ischemia and infarct. Skin is the most common tissue involved, and infarcts of distal fingers or toes are usually of little consequence. Vasculitis may also involve skin in the lower extremities, producing ulcers that may first appear to be stasis ulcers but are painful due to the ischemic arterial component.

When more severe or visceral rheumatoid vasculitis is present, patients commonly show constitutional symptoms such as weight loss, fever, or failure to thrive. Infarction of vessels supplying blood to nerves can cause motor deficits, such as a foot drop. Renal involvement of vasculitis may lead to a necrotizing glomerulonephritis. Rarely, involvement of medium-sized vessels can result in life-threatening complications with visceral involvement similar to that seen in polyarteritis nodosa.

Rheumatoid vasculitis requires aggressive immunosuppressive therapy to prevent serious complications. Fortunately, the incidence of rheumatoid vasculitis has dramatically decreased with the advent of the routine use of disease-modifying antirheumatic drugs (DMARDs) and biologic therapies with the intent of treating patients with RA to target remission.[35]

Ocular Manifestations

Ocular manifestations of RA include keratoconjunctivitis sicca and inflammation of the sclera, episclera, cornea, and uveal tract. Inflammation and subsequent atrophy of the lacrimal glands may result in decreased tear formation, causing dry and itchy eyes, a condition usually termed *keratoconjunctivitis sicca*. When this condition is observed in association with RA, it is referred to as “secondary Sjögren’s syndrome.”

Inflammation of the superficial layers of the sclera is called *episcleritis* and is a generally self-limiting manifestation. *Scleritis* is a more serious vascular inflammation of the cornea, episclera, and uvea, as it is painful and threatens vision. Scleritis in RA is typically a sign of uncontrolled systemic inflammation and warrants prompt and aggressive immunosuppression to preserve vision.

Cardiac Involvement

RA is believed to be an independent risk factor for coronary artery disease and is associated with an increased risk of cardiovascular mortality. A meta-analysis published in 2008 concluded that the risk of cardiovascular mortality was 59% higher in patients with RA than in the general population.[36]

The risk for cardiovascular disease is higher in those with more active inflammation and is reduced with treatment, particularly with methotrexate.[37] Pericarditis may occur, although the development of clinically evident pericarditis with tamponade is a rare complication. Cardiac conduction abnormalities and aortic valve incompetence, caused by aortic root dilation, may occur. Myocarditis is a rare complication of RA.

Hematologic Involvement

A small subset of patients with more severe, long-standing, seropositive RA will go on to develop splenomegaly and neutropenia; this is known as *Felty syndrome*. Neutropenia leads to an increased susceptibility to recurrent bacterial infection. Treatment with immunosuppressive therapy, typically methotrexate, with the goal of reversing immune system dysfunction, will usually improve granulocyte counts.

Large granular lymphocyte leukemia (LGL) is an indolent leukemia characterized by a clonal proliferation of large granular lymphocytes. Often patients with LGL require no therapy, unless neutropenia is severe leading to recurrent infections. LGL is treated with immunosuppression. The majority of

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

experience has involved the use of methotrexate, cyclophosphamide, or cyclosporine.[38]

Other Complications

Lymphadenopathy may occur in patients with RA, and when present, it warrants a workup for infection or malignancy. Amyloidosis is a rare complication of longstanding RA and may lead to renal and gastrointestinal complications. Osteoporosis in patients with RA is almost two times higher than in patients without RA.[39]

Laboratory Findings

The complete blood count can be altered by RA or its treatment. A mild-to-moderate normocytic anemia is commonly due to anemia of chronic disease. It is important to differentiate anemia of chronic disease from anemia associated with complications of therapy, such as gastritis induced by nonsteroidal anti-inflammatory drugs (NSAIDs) or bone marrow suppression from immunosuppressive therapy. Thrombocytosis is a common finding with active RA since platelets are generally considered an acute phase reactant and tend to rise and fall in correlation with inflammation in many patients. Thrombocytopenia may also result as a side effect of immunosuppressive therapy. Neutropenia is associated with Felty syndrome and LGL, but it also may be a side effect of immunosuppressive drugs. Leukocytosis is seen commonly as a result of corticosteroid treatment.

The erythrocyte sedimentation rate (ESR) and C-reactive proteins (CRP) are nonspecific markers of inflammation that are usually elevated in patients with active RA. They may be used as an aid in following RA activity.

A positive RF is detected in 70% to 80% of patients with RA. In general, higher titers of RF increase the sensitivity and indicate a potentially more severe disease course. A positive RF (two times the upper limit of normal) in a patient with consistent clinical features of inflammatory arthritis is fairly specific for rheumatoid arthritis. However, a positive RF, especially with a low titer in a patient without clinical evidence of inflammatory arthritis, has low specificity for RA. Many patients with hepatitis C have a positive rheumatoid factor, as do many patients with Sjögren's syndrome, sarcoidosis, and certain infections.

Anticyclic citrullinated antibodies have a slightly lower sensitivity to the RF, being found in 57% (range, 12%-93%) of patients with RA, but ACPAs are more specific (96%) and may be detectable early in the disease.[40] The presence of ACPA, in general, predicts a more aggressive course of disease and increased risk of joint erosions. In contrast to RF, ACPAs are not typically present in patients with hepatitis C. Many rheumatologists order both tests in evaluating new patients.

Antinuclear antibodies (ANAs) are detected in 25% of patients with RA as a result of their disease. The presence of a positive ANA in a workup of polyarthritis may initially lead to a diagnostic challenge, since they are more commonly seen in systemic lupus erythematosus, systemic sclerosis, and mixed connective tissue disease, all of which can have arthritis as a presenting feature. However, patients with RA who have a positive ANA would not be expected to be positive for more specific antibodies for connective tissue disorders, including anti-ds DNA antibodies, anti-Smith antibodies, anti-SCL 70 antibodies, or anti-RNP antibodies.

Synovial fluid analysis may be performed during the initial diagnosis or follow-up in patients with RA to rule out crystalline disease or infection in swollen joints (especially joints that are swollen out of proportion to the rest of the clinical examination). Synovial fluid analysis of involved joints typically reveals white blood cell counts of 1,500 to 25,000/mm^3 (1.5×10^9 to 25×10^9/L) but may be higher in those with active RA.[41]

Plain radiographs in RA are often normal at the time of disease presentation. The earliest plain radiographic findings typically include soft tissue swelling and periarticular osteoporosis on hand and foot x-rays. As RA progresses, joint space narrowing occurs as a result of cartilage degradation, and marginal erosions (at the margins of the joint capsules) may occur, typically in the ulnar styloid, metacarpophalangeal and proximal interphalangeal joints of the hands (Fig. 111-5), and the metatarsophalangeal joints of the feet. In advanced stages of RA, radiographs may show deformities including joint subluxations, ulnar deviation of the metacarpophalangeal joints, and secondary osteoarthritis. Many DMARD and biologic therapies halt the progression of erosive changes in RA. Serial joint radiographs may be used in addition to clinical findings as a way of evaluating disease progression and adequacy of therapy.

DIAGNOSTIC CRITERIA

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

In 2010, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) updated their classification criteria for RA.[42] The revised criteria allow for identification of patients at an earlier stage of disease, such as synovitis of one small joint in the absence of an alternative diagnosis. Early identification of patients with RA may allow for earlier treatment geared toward preventing structural damage to joints.

The criteria use a scoring system which assigns points based upon the number and types (small and large) of joints involved. The presence of RF or ACPA and elevated acute phase reactants (CRP and ESR) result in additional points. A duration of symptoms of 6 weeks or more provides an additional point. A total score of 6 or more out of a possible total score of 10 is considered diagnostic for RA (Table 111-1).[42] Not all patients with RA will score 6 or greater initially but may evolve to higher scores over time.

TABLE 111-1

ACR/EULAR Rheumatoid Arthritis Classification Criteria

Criteria	Score
Low-positive RF or ACPA	2
High-positive RF or ACPA	3
High ESR or CRP	1
Duration of symptoms ≥6 weeks	1
Joint Involvement (at least one joint not explained by another disease)	
2-10 large joints	1
1-3 small joints (± large joint)	2
4-10 small joints (± large joint)	3
>10 joints (at least one small joint)	5

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; ACPA, anticitrullinated protein antibodies; CRP, C-reactive protein; ESR, eosinophil sedimentation rate; RF, rheumatoid factor.

Patients with inflammatory arthritis who have negative RF and ACPA may be diagnosed with RA if they fulfill further criteria otherwise characteristic of RA. In addition, a number of other inflammatory arthritic conditions are managed similarly to seropositive rheumatoid arthritis; these include psoriatic arthritis, reactive arthritis, ankylosing spondylitis, and arthritis associated with inflammatory bowel disease.

TREATMENT

Desired Outcomes

The ACR as well as the EULAR guidelines recommend a treat-to-target approach when treating patients with RA rather than a nontargeted treatment approach. If remission cannot be achieved, low disease activity is an acceptable alternative target. This treatment approach is supported by superior clinical outcomes compared with usual care. In general, RA treatment is directed toward reducing inflammation and symptoms, including joint pain and stiffness. Most of the therapies used to treat RA slow the disease progression and thus the progression of irreversible joint damage, which can help decrease disability and improve quality of life.[43]

General Approach to Treatment

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

3 4 Available pharmacologic therapies do not reverse joint damage that has already occurred. Therefore, early aggressive treatment of RA is imperative. Early treatment of RA results in improved outcomes. Patients with a shorter disease duration are more likely to respond to treatment.[44,45] Nonpharmacologic therapies also play a role in the management of RA and encourage patients to take an active role in managing their disease.[46] Therefore, the approach to the treatment of RA should include both pharmacologic and nonpharmacologic methodologies. Ultimately, care should be coordinated by a healthcare provider trained in rheumatology.

Nonpharmacologic Treatment

5 Nonpharmacologic approaches for the treatment of RA include referrals to occupational and physical therapy, mental health, social work, reviewing pain coping skills, and providing patient education. Both mental and physical health are important in patients with RA, as central neuroendocrine and dopaminergic pathways may be involved in both RA disease activity and physical and mental health. Patients with RA are also more likely to be affected by mood disorders and may benefit from referrals to specialty providers as appropriate.[47]

Patient education should involve disease state education as well as medication education related to potential adverse effects and how to appropriately administer injectable agents. Physical therapy is beneficial for reducing pain and inflammation while preserving joint function. The benefits of exercise and physical activity, including aerobic activity and muscle-strengthening exercises, have been demonstrated to improve RA-related disease outcomes. Assistive devices and orthoses such as braces and supports are useful to improve pain and function. Occupational therapy can be effective and provide several benefits such as exercises, appropriate footwear, and splinting.[46] Weight loss can help decrease the stress on joints. Surgical options, including joint replacements, are reserved for patients with more severe disease where there may have significant cartilage loss.

Pharmacologic Therapy

Currently available therapies used to treat RA and also slow the progression of the disease include conventional and biologic DMARDs and the small-molecule agents tofacitinib, baricitinib, and upadacitinib. Conventional DMARDs include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Biologic DMARDs fall into two categories: tissue necrosis factor (TNF) inhibitor biologics (adalimumab, etanercept, certolizumab, golimumab, and infliximab) and non-TNF biologics (abatacept, tocilizumab, rituximab, anakinra, and sarilumab). Tofacitinib, baricitinib, and upadacitinib are oral synthetic DMARDs that are also Janus Kinase (JAK) inhibitors. Many of the therapies used to treat RA are also indicated and used in the treatment of other conditions such as psoriatic arthritis and ankylosing spondylitis, conditions that are outside the scope of this chapter. Table 111-2 includes RA-indicated dosages for the agents discussed in this chapter.

TABLE 111-2

Usual Doses for Disease-Modifying Antirheumatic Drugs

Drugs	Brand Names	Routes of Administration	Starting Doses	Usual Ranges or Maintenance Doses	Comments
Methotrexate	• Rasuvo • Trexall • Otrexup (SubQ)	Oral, SubQ, IM	• Oral: 7.5 mg once weekly or 2.5 mg every 12 hours for 3 doses once weekly • SubQ/IM: 7.5 mg once weekly	7.5-20 mg once weekly	May be given with folic acid 1-5 mg/day to reduce adverse reactions
Leflunomide	Arava	Oral	Loading dose: 100 mg daily for 3 days, then 20 mg daily or 10-20 mg daily without loading	10-20 mg daily	Not recommended in liver disease (ALT >3 times ULN)

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

			dose		
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	1,000 mg twice daily (maximum dose is 3,000 mg/day if inadequate response after 12 weeks of 2,000 mg/day)	Not recommended in renal or hepatic impairment
Etanercept	Enbrel	SubQ	50 mg once weekly or 25 mg twice weekly	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 therapy; pretreat with methylprednisolone, acetaminophen, and antihistamine
Adalimumab	Humira	SubQ	40 mg every 2 weeks	40 mg every 2 weeks (may increase to 40 mg once weekly if not taking methotrexate)	
Certolizumab	Cimzia	SubQ	400 mg at 0, 2, 4 weeks	200 mg every other week or 400 mg every 4 weeks	
Golimumab	Simponi	SubQ	50 mg once monthly	Same as starting dose	
Rituximab	Rituxan	IV	1,000 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
Abatacept	Orencia	IV, SubQ	• IV: <60 kg: 500 mg, 60-100 kg: 750 mg, >100 kg: 1,000 mg at 0, 2, and 4 weeks or initial IV dose followed by 125 mg subcutaneously within 24 hours • SubQ: 125 mg weekly	• IV: dose based on weight every 4 weeks • SubQ: 125 mg weekly	
Tocilizumab	Actemra	IV, SubQ	IV: 4 mg/kg every 4 weeks SubQ: <100 kg:	• IV: 4-8 mg/kg every 4 weeks	Can increase the metabolism of CYP3A4 substrates

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

			162 mg every other week, >100 kg 162 mg weekly	(maximum 800 mg per infusion) • Subcutaneously: <100 kg: 162 mg every other week, followed by an increase to weekly injections if needed, >100 kg: 162 mg weekly	
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 daily	Same as starting dose	Use is not recommended in severe hepatic impairment.
Baricitinib	Olumiant	Oral	2 mg daily	Same as starting dose	eGFR 30-60 mL/min/1.73 m^2: 1 mg daily; use is not recommended with eGFR <30 mL/min/1.73 m^2; use is not recommended in severe hepatic impairment; dosage adjustment for concomitant strong organic anion transporter 3: 1 mg daily.
Anakinra	Kineret	SubQ	100 mg once daily	Same as starting dose	
Sarilumab	Kevzara	SubQ	200 mg every 2 weeks	Same as starting dose	

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

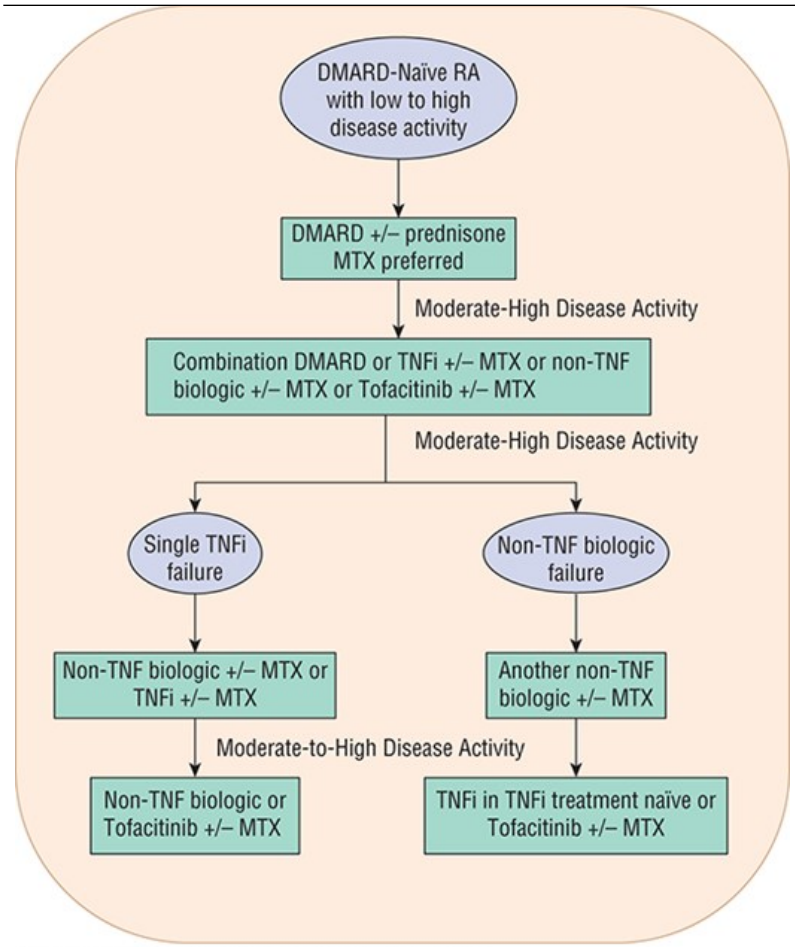
6 7 The current ACR guidelines for treatment of RA recommend initiation of conventional DMARDs irrespective of disease activity in treatment-naïve patients (Fig. 111-6) once a diagnosis is established. The preferred conventional DMARD is methotrexate unless a contraindication to its use exists.[48,49] In practice, choice of therapy may ultimately be dependent on level of disease activity, comorbid health conditions, patient preference, and often insurance coverage.

FIGURE 111-6

Treatment algorithm for rheumatoid arthritis based on the American College of Rheumatology guidelines. (DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumor necrosis factor.) *(Data from Reference 50.)*

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

The ACR guidelines recommend treatment with DMARD monotherapy for patients with early RA—defined as duration of disease/symptoms of less than 6 months—and low disease activity. Double or triple DMARD therapy is recommended if disease activity is moderate or high. A biologic agent can be used as monotherapy or with conventional DMARD(s) in patients with moderate or high disease activity. Tofacitinib would be an alternate option if disease activity remains moderate or high with combination conventional DMARDs. If disease activity remains moderate or high despite DMARD or biologic agents, a low-dose glucocorticoid can be added for the shortest duration of time necessary. Low-dose glucocorticoid is defined as prednisone 10 mg/day or less or an equivalent amount of another glucocorticoid. If patients achieve remission, DMARDs and biologic agents can be tapered; however, patients should remain on DMARD therapy at some level.

In patients with established RA—defined as duration of disease/symptoms for 6 months or more—treatment with DMARD monotherapy is recommended despite disease activity in DMARD-naïve patients. Combination conventional DMARDs or a biologic DMARD or tofacitinib can be used if disease activity remains moderate or high after an adequate trial with DMARD monotherapy. In patients who are on TNF inhibitor monotherapy with moderate or high disease activity, one or two 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. This is recommended over tofacitinib. Therapy can be switched to another non-TNF biologic if a single non-TNF biologic is unable to adequately control disease activity. If courses of two TNF inhibitors have not adequately controlled disease activity, a non-TNF biologic can be initiated. Tofacitinib can be initiated if disease activity persists despite multiple TNF inhibitors in patients for whom non-TNF biologics are not an option. Glucocorticoids can be added if disease flares occur or are inadequately controlled despite DMARD, TNF inhibitor, or non-TNF biologic therapy.[41] It is worth mentioning that the newer JAK inhibitors, baricitinib and upadacitinib, were not yet approved at the time of these ACR guidelines and, therefore, only tofacitinib is listed specifically.

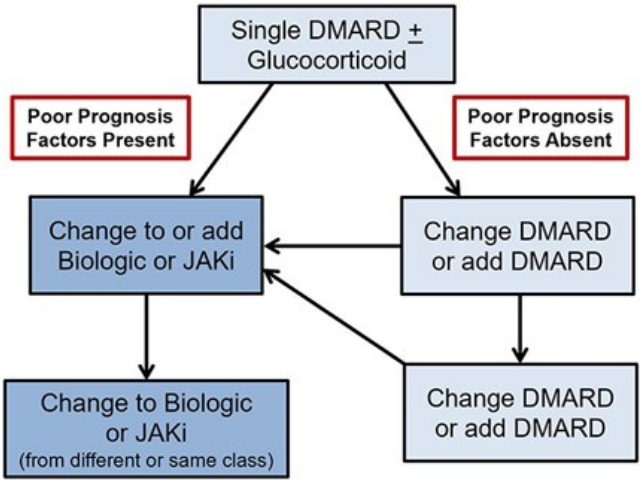
In contrast to the ACR guidelines, the 2019 EULAR guidelines delineates treatment recommendations based on past therapy, clinical response, and presence of poor prognostic factors (Fig. 111-7). Poor prognostic factors are defined as high disease activity, early joint damage, positive RF or ACPA,

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

and failure of >2 conventional DMARDs. Dosages and therapies should be reassessed no later than 3 months after the initiation or change. The algorithm also provides dose reduction recommendations for persistent disease remission of at least 6 months in duration, especially if having tapered glucocorticoid therapy. It is not recommended that all pharmacologic treatment be completely discontinued.[50]

FIGURE 111-7

Simplified treatment algorithm for rheumatoid arthritis based on the EULAR 2019 update. (DMARD, disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
Copyright © McGraw Hill. All rights reserved.

DMARDs can take weeks to months to take effect in patients with RA. NSAIDs and/or glucocorticoids, as well as other analgesics such as acetaminophen, can provide symptomatic relief and have a more rapid onset of action than DMARDs; they are often used as "bridge" therapy. NSAIDs do not impact disease progression, and corticosteroids have several side effects associated with their use, making both less desirable choices for long-term use.

Conventional Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate is the DMARD of choice for most patients unless its use is contraindicated. Methotrexate has been used in the treatment of RA for several decades and has a sustained clinical response over time and a glucocorticoid-sparing effect.[51] It can be taken as monotherapy or in combination with other DMARDs.

Methotrexate is a structural analogue of folic acid that inhibits dihydrofolate reductase. Dihydrofolate reductase is the enzyme responsible for reducing dihydrofolic acid to folinic acid, the active intracellular metabolite. Through this action, methotrexate inhibits DNA synthesis and repair and cellular replication.[52]

Methotrexate is taken once weekly and is typically given in either tablet form or as a subcutaneous injection. It is also available as an intramuscular injection. The absorption of oral methotrexate is highly variable. At low doses (≤30 mg/m^2), oral bioavailability is about 60%, and this decreases at higher doses. Methotrexate is about 50% protein bound and is excreted by the kidney, about 80% to 90% unchanged.[52] Injectable methotrexate has a higher bioavailability compared with oral methotrexate and thus provides superior clinical efficacy. Injectable methotrexate is typically better tolerated and has less potential to cause gastrointestinal side effects as well.[53] The doses used for the treatment of RA typically range from 7.5 to 20 mg weekly. Doses exceeding 20 mg weekly can increase the risk for toxicities.[52] At doses higher than 15 mg weekly, oral methotrexate may not have significant added clinical benefit; changing to subcutaneous methotrexate may increase bioavailability and clinical benefit.[8] Clinical benefit can be seen 3 to 6

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

weeks after starting methotrexate therapy.[52]

Methotrexate is teratogenic and is therefore contraindicated in pregnancy and breastfeeding. Additional contraindications include alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency, and preexisting hematologic disorders, such as leukopenia and thrombocytopenia. Methotrexate excretion is reduced in renal impairment and may require dose reduction or discontinuation in some cases. Excretion is also reduced in ascites or pleural effusions.[52]

Recommended laboratory monitoring prior to starting methotrexate includes a complete blood count (CBC) with differential, alanine transaminase (ALT), aspartate transaminase (AST), and renal function. These should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy.[5] A chest x-ray film can be considered before starting methotrexate in patients with underlying lung disease. Hepatitis B, hepatitis C, and tuberculosis screenings should be obtained at baseline in high-risk patients.[54]

Adverse effects of methotrexate include infection, pulmonary complications (eg, interstitial pneumonitis and chronic obstructive pulmonary disease [COPD]), gastrointestinal problems (eg, perforation and diarrhea), hematologic changes (eg, thrombocytopenia and leukopenia), and hepatic toxicities (eg, elevated liver enzymes and cirrhosis). Because methotrexate is a structural analogue of folic acid, it can cause folic acid deficiency; methotrexate should be given with folic acid 1 to 5 mg daily to reduce the incidence of toxicities associated with methotrexate.[52]

Leflunomide

Leflunomide, an oral DMARD that inhibits pyrimidine synthesis, can be used as monotherapy or in combination with other DMARDs to treat RA. Leflunomide reduces signs and symptoms of RA, inhibits structural damage, and improves physical function. It is significantly protein bound (>99.3%). The typical maintenance dose used to treat RA is 20 mg daily; the dose can be decreased to 10 mg daily if patients are unable to tolerate higher doses. A loading dose can be given of 100 mg for 3 days to achieve steady state more rapidly, but this may increase the risk for toxicities.

Leflunomide has a half-life of about 2 weeks and may require washout with cholestyramine if rapid elimination is required due to toxicity or incidental pregnancy. Leflunomide is excreted by the kidneys as well as through direct biliary excretion.[9] Baseline monitoring should include a tuberculosis screening, CBC with differential, ALT, AST, and renal function. These should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy.

Adverse reactions associated with leflunomide include diarrhea, elevated liver enzymes, alopecia, elevated blood pressure, and rash. If ALT is three times the upper limit of normal (ULN), leflunomide should be discontinued. Leflunomide should not be used in pregnant or nursing mothers or in patients with severe hepatic impairment.[55]

Sulfasalazine

Sulfasalazine is a prodrug with two metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine. The exact mechanism of action of sulfasalazine for the treatment of RA is unknown; however, it has immunomodulating and anti-inflammatory properties. Sulfasalazine can be used as monotherapy or in combination with other DMARDs to treat RA. The typical starting dose of sulfasalazine is 500 mg daily or 1 g daily in two divided doses; this can be increased weekly to 2 g daily in two divided doses to minimize the risk of adverse events. Clinical benefit can be seen in 4 weeks, but some individuals may need to be on sulfasalazine for 12 weeks before clinical benefit is achieved. If clinical benefit is not sufficient after 12 weeks of therapy, the dose can be further titrated to 3 g/day in evenly divided doses.

Sulfasalazine is primarily eliminated by the kidney and should be used with caution in renal impairment. Sulfasalazine is contraindicated in sulfonamide or salicylate allergy.[56] Baseline monitoring should include a CBC with differential, ALT, AST, and renal function.[56] These should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy. Glucose-6-phosphate dehydrogenase deficiency can cause hemolytic anemia; therefore, screening for this prior to initiation should be considered.[57]

Sulfasalazine use is limited by its potential to cause gastrointestinal adverse effects, including diarrhea, nausea, vomiting, and anorexia. Less common adverse effects associated with sulfasalazine include rash, urticaria, blood cell abnormalities (including leukopenia, anemia, and thrombocytopenia),

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

severe hypersensitivity reactions (including Stevens-Johnson syndrome), photosensitivity, elevated liver enzymes, and alopecia. Sulfasalazine can also cause urine and skin discoloration. Sulfasalazine crosses the placenta and is present in breast milk but can be used in pregnant and nursing mothers with caution.[56]

Hydroxychloroquine

Hydroxychloroquine is typically used in combination with other DMARDs in patients with RA, but it can be used as monotherapy in mild cases. The mechanism of action in the treatment of RA is not fully understood, but a proposed mechanism for its anti-inflammatory properties is its interference with antigen processing in macrophages and other antigen-presenting cells.[57] Hydroxychloroquine's oral absorption is incomplete and inconsistent, varying from 25% to 100%. It is about 40% protein bound and excreted predominately in the urine.[58]

The typical dose of hydroxychloroquine is 400 mg daily either as one dose or as two divided doses. Clinical benefit is delayed and may take several weeks. The main advantage of hydroxychloroquine use 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. The most common adverse effects with hydroxychloroquine are gastrointestinal side effects, including nausea, vomiting, and diarrhea; these can sometimes be mitigated by taking the medication with food or splitting the dose into two doses.[46]

Irreversible retinal damage can occur with hydroxychloroquine use. For patients with risk factors for developing retinal damage, such as low body weight and renal and hepatic impairment, ophthalmologic exams should be conducted annually throughout the treatment with this drug. If patients do not have risk factors for developing retinal damage, an ophthalmologic examination should be completed within 5 years of starting hydroxychloroquine and then repeated annually.[46,59]

Hydroxychloroquine can be continued during pregnancy as there is no increased risk of birth defects or ocular toxicities. Hydroxychloroquine is excreted into the breast milk, and caution should be exercised in nursing mothers.[60]

Biologic Disease-Modifying Antirheumatic Drugs

Biologics agents are genetically engineered protein molecules that have varying mechanisms by which they decrease inflammation. They can be separated into two groups: TNF inhibitor biologics including adalimumab, etanercept, certolizumab, golimumab, and infliximab; and non-TNF biologics including abatacept, tocilizumab, rituximab, anakinra, and sarilumab.

Biologic DMARDs are associated with an increased risk of infection due to their immunosuppressant 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.

Biologic agents 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 to avoid potential adverse effects. Because of the immunosuppressive effects of these agents, patients should notify their providers if they are being treated for an infection or plan to undergo major surgery while on a biologic or before starting a biologic. A patient's therapy may need to be held until appropriate postsurgical healing and/or resolution of infection can be confirmed.

TNF Inhibitor Biologics

TNF inhibitors block the proinflammatory cytokine TNF-α. Elevated levels of TNF-α are found in the synovial fluid of individuals with RA as well as other rheumatologic conditions. Adalimumab, etanercept, golimumab, certolizumab, and infliximab can take several weeks for clinical benefit to be noted and up to 3 months to achieve full clinical benefit.[61] The place in therapy for these agents is typically when disease activity remains moderate or high despite conventional DMARD therapy.

A major limitation to the use of TNF inhibitors is cost, as they are more expensive than conventional DMARDs. To optimize the use of TNF inhibitors, medication education should include site of administration, expected time to benefit, safe storage, proper disposal, and possible side effects.

Although these agents have similar side effect profile and contraindications, the TNF inhibitors all have differing structures, pharmacokinetics, and

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

dosing schemes. The selection of an agent depends on cost and patient preference for route and frequency of administration. TNF inhibitors should not be used in patients with moderate-to-severe heart failure (New York Heart Association [NYHA] class III/IV), as new-onset and worsening heart failure has been reported with TNF inhibitors. These agents increase the risk of serious infection and malignancies such as lymphoma and skin cancers.

New-onset or exacerbation of demyelinating disorders such as multiple sclerosis has been observed with TNF-α inhibitors. Therapy should be discontinued in patients who develop symptoms of demyelinating disorders, and caution should be exercised in using these agents in this patient population. Before starting TNF inhibitors, patients should be screened for tuberculosis and hepatitis B. During therapy, a CBC with differential should be monitored periodically as TNF inhibitors can cause blood cell disorders including pancytopenia. Other monitoring includes signs/symptoms of malignancy and serious infections.[61]

Certolizumab

Certolizumab is a pegylated humanized antibody Fab fragment of TNF-α monoclonal antibody. Because it is not a complete antibody and 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 subcutaneous injection. A loading dose of 400 mg at week 0, 2, and 4 can be given followed by a maintenance dose of 200 mg every other week or 400 mg every 4 weeks.

The most common adverse effects associated with certolizumab are upper respiratory tract infection, rash, and urinary tract infection. The safety and efficacy of certolizumab were evaluated in multiple studies that found that adult patients with moderate-to-severe RA treated with certolizumab had improved clinical response compared with placebo. Structural damage and RA progression was inhibited by certolizumab as compared with placebo plus methotrexate. Patients had improved function when treated with certolizumab compared with placebo.[62]

Adalimumab

Adalimumab 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 subcutaneous injection. Typical dosing for RA is 40 mg every 2 weeks when used with methotrexate. The dose can be increased to 40 mg weekly if it is not being used with methotrexate. Local injection site reactions are the most common adverse event and usually manifest as redness, itching, pain, and swelling.

Adalimumab has been studied as monotherapy, with methotrexate, or as combination therapy with other DMARDs in patients with RA. It improves clinical response, delays the progression of structural damage, and improves function.[61]

Etanercept

Etanercept 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 subcutaneous injection. Typical dosing for RA is 50 mg once weekly.[63]

The most common adverse effects associated with etanercept use include infections and injection site reactions. Patients treated with etanercept monotherapy and etanercept with methotrexate have improved clinical response. Clinical response was noted within 1 to 2 weeks of starting etanercept, but some patients required 3 months of therapy to demonstrate clinical response. Etanercept plus methotrexate decreased structural damage and progression of RA compared with monotherapy with etanercept or methotrexate. Function was also improved in patients treated with etanercept as compared with placebo.[63]

Golimumab

Golimumab is a human monoclonal antibody that binds to human TNF-α. It is available as a prefilled syringe or pen for subcutaneous injection and is typically dosed at 50 mg once monthly. It is also available as an intravenous product that dosed 2 mg/kg at weeks 0 and 4, and then every 8 weeks thereafter.

The most common adverse effects associated with golimumab use are upper respiratory tract infections and nasopharyngitis. Compared with methotrexate monotherapy, golimumab plus methotrexate improves clinical response in patients with RA. Golimumab also improves function in

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

patients as compared with placebo.[64]

Infliximab

Infliximab is a chimeric monoclonal antibody that binds to human TNF-α. Infliximab is administered as an IV infusion and typical dosing is 3 mg/kg at weeks 0, 2, and 6, followed by every 8 weeks.

The most common adverse effects associated with infliximab use are infections, infusion-related reactions, headache, and abdominal pain.[41] About 15% of patients develop antibodies to infliximab. Patients who develop these antibodies typically have a higher likelihood of developing an infusion reaction, have increased clearance of infliximab, and therefore decreased efficacy. An electrochemiluminescence immunoassay (ECLIA) can be used to measure infliximab antibodies if this is suspected. When infusion reactions occur with infliximab, they typically begin within 2 hours of infusion. Concomitant use with immunosuppressants such as methotrexate can lessen the likelihood of developing antibodies to infliximab. Premedication with an antihistamine, acetaminophen, and/or a glucocorticoid can help decrease the likelihood of patients developing infusion-related reactions. Patients on infliximab plus methotrexate have an improved clinical response as compared with patients on methotrexate alone. Structural damage and progression of RA was also delayed.[65]

Non-TNF Biologics

Abatacept

Abatacept is a selective co-stimulation modulator that inhibits T-cell activation by binding to CD80 and CD86. This binding blocks the interaction between T cells CD28, thus inhibiting the activation of T cells. Activated T cells are found in the synovial fluid of patients with rheumatologic conditions such as RA and are thought to play a role in the disease. Abatacept is indicated for moderate-to-severe RA and can be used as monotherapy or in conjunction with conventional DMARDs.[66]

Abatacept is typically initiated if disease activity persists in patients 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 compared with adalimumab plus methotrexate in biologic-naïve patients who had an incomplete response to methotrexate.[67]

Abatacept is available in a prefilled syringe or autoinjector for subcutaneous injection and is given at a dose of 125 mg once weekly. It is also available as a 30-minute IV infusion that is dosed according to body weight (<60 kg: 500 mg; 60-100 kg: 750 mg; >100 kg: 1,000 mg); it is given at 0, 2, and 4 weeks and every 4 weeks thereafter.[66]

The most common side effects associated with abatacept include headache, upper respiratory tract infection, nasopharyngitis, and nausea. Abatacept should be used with caution in patients with COPD; exacerbations have been observed in patients with both COPD and RA on abatacept. Like other biologics, abatacept has also been associated with serious infections and malignancy. Infusion reactions are rare but can include anaphylaxis, hypotension, dyspnea, and urticaria and can occur within 24 hours of intravenous administration.[66]

Tocilizumab

Tocilizumab is a monoclonal antibody that inhibits the binding of the proinflammatory cytokine IL-6 to its receptor. Tocilizumab can be used in patients with moderate-to-severe RA who have had an incomplete response to one or more conventional DMARDs and/or TNF inhibitor and can be used as monotherapy or in combination with DMARDs.[68] A study that included patients with severe RA who could not use methotrexate found that tocilizumab monotherapy was more effective in the symptom management of RA compared to adalimumab monotherapy.[69]

Tocilizumab is available as a prefilled syringe for subcutaneous injection with dosing dependent on weight (<100 kg: 162 mg every other week, followed by an increase to weekly injections if needed based on clinical response; >100 kg: 162 mg weekly). It is also available as a 1-hour intravenous infusion at a dose of 4 mg/kg every 4 weeks; the dose can be increased to 8 mg/kg every 4 weeks if needed based on clinical response.[68]

The most common side effects associated with tocilizumab include upper respiratory tract infections, nasopharyngitis, headache, hypertension,

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

increased liver enzymes, and injection site reactions. Infusion reactions can also occur, typically within 24 hours of infusion; these are manifest as headache, rash, pruritus, and urticaria. Tocilizumab can also cause gastrointestinal perforation, neutropenia, and thrombocytopenia as well as serious infections and malignancy. Baseline monitoring recommended should include neutrophils, platelets, lipid panel, AST, and ALT. Neutrophils, platelets, and liver enzymes should also be monitored 4 to 8 weeks after starting therapy and every 3 months thereafter. A lipid panel should be repeated after 4 to 8 weeks of treatment and every 6 months during treatment.[68]

Tocilizumab should not be initiated in patients with an absolute neutrophil count (ANC) of less than 2,000/mm^3 (2×10^9/L) or platelet count less than 100,000/mm^3 (100×10^9/L); treatment should be discontinued if ANC is less than 500/mm^3 (0.5×10^9/L) or platelet count is less than 50,000/mm^3 (50×10^9/L). Treatment should not be initiated if liver enzymes are greater than 1.5 times ULN and should be discontinued if liver enzymes are greater than five times ULN. Tocilizumab has the potential to increase the metabolism of drugs that are CYP450 substrates, particularly CYP3A4.[68]

Rituximab

Rituximab is a monoclonal antibody that binds the CD20 antigen found on the surface of B cells. Rituximab can be given as monotherapy or in combination with methotrexate and can be initiated in patients with moderate-to-severe RA who have had an incomplete response to one or more TNF inhibitors.[70] Patients who failed one TNF inhibitor had greater reductions in disease activity scores when treated with rituximab than with a second TNF inhibitor.[71]

Rituximab is available as an intravenous infusion and can be given as two 1,000-mg infusions separated by 2 weeks. The recovery of B cells can take several months; therefore, rituximab can be given every 24 weeks. Some patients may not need to receive another dose as often as every 24 weeks; the decision to re-dose should be based on the return of RA symptoms. Rituximab should not be given more frequently than every 16 weeks.[70]

Methylprednisolone 100 mg administered intravenously is recommended 30 minutes before each infusion as well as acetaminophen and an antihistamine to reduce the development and severity of infusion reactions. Side effects that could occur with rituximab treatment include upper respiratory tract infection, nasopharyngitis, urinary tract infection, serious infections, bronchitis, infusion reactions, bowel obstruction/perforation, blood cell disorders, and cardiovascular events.[70] A CBC with differential should be obtained before treatment, with each infusion, and every 2 to 4 months.

Anakinra

Anakinra inhibits IL-1, which is involved in inflammatory responses. It can be used in patients with moderate-to-severe RA who have failed one or more DMARDs; however, the ACR did not include this drug in its 2015 RA treatment recommendations due to its infrequent use for the treatment of RA and lack of new data to support its use since 2012. It is a once-daily subcutaneous injection dosed at 100 mg.[72]

Sarilumab

Sarilumab is an IL-6 receptor antagonist that is indicated in the treatment of patients with moderate-to-severe RA who have had an incomplete response to one or more DMARDs. The ACR did not include this drug in their RA treatment recommendations because it had been approved when the 2015 recommendations were issued. Sarilumab can be used as monotherapy or with conventional DMARDs. It is a subcutaneous injection of 200 mg administered every 2 weeks.[73]

The most common adverse effects with sarilumab include neutropenia, increased liver enzymes, injection site reactions, and upper respiratory and urinary tract infections. It can also be associated with gastrointestinal perforation and serious infections. Monitoring of this medication should include a baseline tuberculosis screening, CBC with differential, and liver enzymes at baseline, 4 to 8 weeks later, and every 3 months thereafter, and a lipid panel at baseline, 4 to 8 weeks after starting therapy, and then every 6 months. Sarilumab should not be initiated in patients with ANC less than 2,000/mm^3 (2×10^9/L), platelets less than 150,000/mm^3 (150×10^9/L), or liver enzymes greater than 1.5 times ULN.[73]

The MOBILITY study included patients treated with sarilumab plus methotrexate compared with methotrexate plus placebo; sarilumab plus methotrexate produced a decrease in symptoms, improvement in function, and less progression of RA compared with placebo plus methotrexate.[74] In the TARGET study, sarilumab plus a DMARD reduced the symptoms of RA and improved function compared with placebo plus DMARD.[75]

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Target-Specific DMARDs

Janus Kinase (JAK) Inhibitors

Tofacitinib and upadacitinib are oral (JAK) inhibitors approved for the treatment of moderate-to-severe rheumatoid arthritis with an inadequate response or intolerance to methotrexate. Baricitinib is a JAK inhibitor approved for the treatment of moderate-to-severe RA with an inadequate response to one or more TNFi therapies. Janus kinases function intracellularly in cell signaling for cytokine-activated receptors. JAK inhibitors bind to and modulate the catalytic activity of JAKs, thus blocking the messaging pathway of multiple pro-inflammatory cytokines and thereby exerting anti-inflammatory effects.[76,77]

JAK inhibitors can be used as monotherapy or in combination with conventional DMARDs and should not be used in combination with biologic DMARDs or other JAK inhibitors. These medications have black box warnings for serious infections including fungal, bacterial, and viral infections; malignancies, including lymphoma; and thrombosis, pulmonary embolism (PE), and deep vein thrombosis (DVT).[76,78,79]

Tofacitinib

Tofacitinib is available as a 5-mg immediate-release tablet and an 11-mg extended-release tablet. The recommended dosing is either 5 mg twice daily or 11 mg daily unless a dose reduction is recommended due to hepatic or renal impairment or if used concomitantly with CYP3A4 or CYP2C19 inhibitors.[76,78]

A common measure in studies of RA is *ACR 20* improvement, which is defined as at least a 20% improvement in seven ACR core measures of disease activity, including tender and swollen joints as well as patients' assessment of disease activity and physical function. It has been widely used to measure disease activity and response to therapy in clinical trials. Patients receiving tofacitinib with methotrexate had similar ACR 20 response after 6 months compared with adalimumab with methotrexate and a higher ACR 20 response compared to placebo with methotrexate.[80,81]

Adverse effects that can occur with tofacitinib include upper respiratory tract infection, cardiovascular effects, gastrointestinal perforation, serious infections, ILD, malignancy, nasopharyngitis, diarrhea, and headache. Because tofacitinib can be associated with bone marrow suppression, it should not be initiated when lymphocytes are less than 500 cells/mm^3 (0.5×10^9/L) or when ANC is less than 1,000 cells/mm^3 (1×10^9/L). Use should be avoided when hemoglobin is less than 9 g/dL (90 g/L; 5.59 mmol/L), and therapy should be interrupted if hemoglobin is less than 8 g/dL (80 g/L; 4.97 mmol/L) or decreases more than 2 g/dL (20 g/L; 1.24 mmol/L). Lymphocyte count should be monitored at baseline and every 3 months thereafter. ANA, platelet counts, and hemoglobin should be monitored at baseline, after 4 to 8 weeks of therapy, and every 3 months thereafter. Tofacitinib can also cause hyperlipidemia; lipids should be monitored 4 to 8 weeks after starting therapy and periodically thereafter. Hepatotoxicity can occur with treatment, and liver function test monitoring is recommended. Use in severe hepatic impairment is not recommended.[76]

An ongoing, open-label study evaluating the safety of tofacitinib 5 mg twice daily and 10 mg twice daily showed that patients with RA, who are 50 years or older with at least one cardiovascular risk factor, had a higher rate of all-cause mortality on tofacitinib 10 mg twice daily versus 5 mg twice daily on TNF inhibitors. These preliminary findings prompted a black box warning of mortality for tofacitinib. Of note, tofacitinib 10 mg twice daily is only FDA-approved for the treatment of ulcerative colitis.[82]

Upadacitinib

Upadacitinib is available as a 15-mg extended-release 24-hour oral tablet dosed once daily. No renal dose adjustment is recommended; however, upadacitinib has not been studied in end-stage renal disease (eGFR <15 mL/min/1.73 m^2). It can be utilized in mild-to-moderate hepatic impairment, but use is not recommended in severe hepatic dysfunction. Caution should be exercised when using upadacitinib in patients on strong CYP3A4 inhibitors, and use with strong CYP3A4 inducers is not recommended. Upadacitinib should not be started in patients with absolute lymphocyte count (ALC) less than 500 cells/mm^3 (0.5×10^9/L), absolute neutrophil count (ANC) less than 1,000 cells/mm^3 (1×10^9/L), or hemoglobin less than 8 g/dL (80 g/L; 4.97 mmol/L).[79]

A phase III, double-blind, randomized controlled trial evaluating the efficacy and safety of upadacitinib compared to placebo or adalimumab in patients with RA and a history of inadequate response to methotrexate showed that upadacitinib was superior to placebo and adalimumab in

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

improving signs, symptoms, and physical function in RA patients. Patients on upadacitinib had significantly less radiographic progression of RA compared to placebo. The safety profile of upadacitinib was similar to adalimumab, except for higher rates of herpes zoster and creatine phosphokinase (CPK) elevations in patients on upadacitinib.[83]

Adverse effects that may occur with upadacitinib include upper respiratory tract infections, neutropenia, lymphocytopenia, nausea, hepatotoxicity, CPK elevations, DVT, PE, increased cholesterol, and gastrointestinal perforation. Therapy should be interrupted if neutropenia, lymphopenia, or anemia occurs past the above ALC and ANC thresholds during treatment.

Recommended monitoring for upadacitinib includes lymphocyte count, ANC, hemoglobin, and liver function tests at baseline and periodically throughout treatment, lipids 12 weeks after initiation and periodically throughout treatment, hepatitis screenings prior to initiation and periodically thereafter, tuberculosis screening at baseline, signs and symptoms of infection during and after therapy, periodic skin examinations, and signs or symptoms of thrombosis throughout treatment.[79]

Baricitinib

Baricitinib is available as a 1-mg and 2-mg tablet and is typically dosed at 2 mg daily with eGFR greater than 60 mL/min/1.73 m^2. A dose reduction to 1 mg daily is recommended with eGFR 30 to 60 mL/min/1.73 m^2 and use is contraindicated with eGFR less than 30 mL/min/1.73 m^2. Use in severe hepatic impairment has not been studied and is therefore not recommended. A dose reduction to 1 mg daily is also recommended when used concomitantly with strong organic anion transporter 3 inhibitors, such as probenecid. Baricitinib should not be started in patients with ALC less than 500 cells/mm^3 (0.5×10^9/L), ANC less than 1,000 cells/mm^3 (1×10^9/L), or hemoglobin less than 8 g/dL (80 g/L; 4.97 mmol/L).[78]

A phase III, double-blind study comparing baricitinib to placebo in patients with RA and inadequate response or intolerance to one or more conventional DMARDs showed that patients on baricitinib had statistically significant improvements in signs and symptoms of RA, including morning stiffness and joint pain, and achieved an ACR20 response compared to placebo. Baricitinib also slowed radiographic progression of RA-related joint damage.[84]

Adverse effects that may occur with baricitinib use include upper respiratory tract infections, herpes zoster infection, hepatotoxicity, hematologic toxicities including anemia, gastrointestinal perforations, thrombosis, lymphocytopenia, neutropenia, increase in SCr and CPK. Therapy should be interrupted if neutropenia, lymphopenia, or anemia occurs past the above ALC and ANC thresholds during treatment.[84]

Recommended monitoring for baricitinib includes lymphocyte, ANC, platelet counts, hemoglobin, and LFTs at baseline and periodically throughout treatment, lipids 12 weeks after therapy and periodically throughout treatment, hepatitis B screening prior to starting therapy, signs and symptoms of infection, abdominal symptoms, and skin examinations periodically.[78]

Other Disease-Modifying Antirheumatic Drugs

Therapies such as azathioprine, cyclosporine, minocycline, and gold salts were previously used to treat RA. With the development of other DMARDs and biologics, they are now used infrequently and have no recent data to support their use.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs inhibit prostaglandin synthesis and can provide anti-inflammatory as well as analgesic effects. However, they do not slow disease progression and should not be used as monotherapy. NSAIDs can provide symptomatic relief from pain and stiffness and can be effective as adjuncts to DMARD therapy in patients with RA. They have a more rapid onset of action than DMARDs and may be beneficial to “bridge” patients while DMARDs take effect.

Although these agents are available without prescription, they still possess potentially serious risks to use. In the United States, NSAIDs carry a Boxed Warning because they increase the risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke.[85] Their use is also associated with serious gastrointestinal bleeding and ulcerations. For more details on NSAIDs, see Chapter 110, “Osteoarthritis.”

Glucocorticoids

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Glucocorticoids have been used in the treatment of RA for their anti-inflammatory and immune-modulating effects.[84] Although these agents slow the progression of RA, glucocorticoids should not be used as monotherapy in the treatment of RA, particularly due to the potential for serious, long-term adverse effects. Therefore, they should be used at the lowest effective dose for the shortest period of time. According to the ACR, short-term glucocorticoid is defined as less than 3 months of therapy and low-dose glucocorticoid is defined as prednisone 10 mg/day or less or its equivalent.

Glucocorticoids can be administered orally or intramuscularly. They act systemically to decrease inflammation and pain. Intra-articular injections administered directly into joints can provide a local decrease in inflammation and pain relief. The intra-articular route is associated with fewer systemic adverse effects because of the limited systemic action. Intra-articular injections should not be repeated more often than every 3 months because of the potential for accelerated loss of cartilage in the joint. Oral glucocorticoids are absorbed almost completely in the gastrointestinal tract, metabolized in the liver, and eliminated in the urine. Typically, oral glucocorticoids, such as prednisone, are taken once daily. Intramuscular glucocorticoids such as triamcinolone acetonide and methylprednisolone acetate can be administered instead of oral steroids based on patient preference or in patients who may not adhere to daily oral therapy. This can also be used in place of an intra-articular injection when multiple joints are involved. To avoid withdrawal associated with hypothalamus–pituitary–adrenal (HPA) axis suppression, glucocorticoids should not be stopped abruptly but should be tapered, especially when used for long term or at high doses. Intramuscular glucocorticoids provide patients with a physiologic taper.

Similar to NSAIDs, glucocorticoids 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.[86]

Use of long-term glucocorticoids is limited by adverse effects, which include 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, and cataracts.[87,88] The lowest effective dose for the shortest period of time should be used to minimize the potential for these adverse effects. Patients with RA are at a higher risk of developing osteoporosis, and the use of long-term glucocorticoids doubles this risk. In a study of prednisone 7.5mg daily, patients lost an average of 9.5% of bone in the spine over 20 weeks of treatment.[88] For more information on glucocorticoid-induced bone loss, see Chapter 112, “Osteoporosis.”

Special Populations

Pregnancy and Lactation

Data on the safety of a majority of the medications used to treat RA during pregnancy and breastfeeding are limited, and a majority of medications with available safety data in this population have been associated with adverse effects. The potential risks of becoming pregnant should be discussed with women of childbearing age who are being treated for RA, and contraception counseling should be discussed for those not planning on becoming pregnant. Approximately 20% to 40% of patients with RA achieve remission during the third trimester of pregnancy and remission is more common in women with RF-negative RA.[89]

Because of risks associated with paternal exposure to DMARDs, family planning for male patients should also be taken into account when developing treatment plans.[89]

In women who want to become pregnant, therapies that are contraindicated in pregnancy such as methotrexate and leflunomide should be discontinued. Medications that are unsafe during pregnancy or have inadequate data to determine safety, such as abatacept, tocilizumab, rituximab, tofacitinib, and anakinra, should also be discontinued. Disease activity should then be monitored. For symptom control, NSAIDs, acetaminophen, and glucocorticoids can be considered. DMARDs that can be used during pregnancy include hydroxychloroquine and sulfasalazine.[89] Newer medications including upadacitinib, baricitinib, and sarilumab do not have sufficient data available to determine safety during pregnancy.[73,78,79]

There is no increase in congenital malformations with use of TNF inhibitors and therefore they may be considered for use during the first part of pregnancy.[89,90] Specifically, etanercept and certolizumab may be continued throughout pregnancy.[90]

For women who are breastfeeding, methotrexate and leflunomide are contraindicated. NSAIDs, acetaminophen, hydroxychloroquine, sulfasalazine, and glucocorticoids are preferred. TNF inhibitors, anakinra, abatacept, rituximab, tocilizumab, tofacitinib, sarilumab, baricitinib, and upadacitinib do

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

not have sufficient evidence to recommend safe use during breastfeeding.[79,89] Since TNF inhibitors are large protein molecules, little to no drug is likely to be found in breastmilk.[90]

For male patients with RA, methotrexate should be held for 3 months before conception, and sulfasalazine may need to be held if the patient is having difficulty with fertility. There is limited data on adverse outcomes with leflunomide. TNF inhibitors can disrupt spermatogenesis, but use could be considered. Adverse outcomes have been reported with rituximab and abatacept.[89]

Serious Infections

In patients with a history of serious infections, combination DMARDs are recommended over TNF inhibitors. Abatacept can be considered over TNF inhibitors; in a study of patients hospitalized for an infection while on TNF inhibitors, abatacept was associated with the lowest risk of a subsequent infection compared with other biologics.[43]

In patients who screen positive for tuberculosis via either a tuberculin skin test or IGRA, a chest x-ray film should be obtained to determine if the patient has latent or active tuberculosis infection. If the chest x-ray film is positive, a sputum for acid-fast bacillus (AFB) can be collected to rule out active tuberculosis. If this is negative, then the patient likely has latent tuberculosis and a biologic DMARD or tofacitinib can be started or resumed after completing at least 1 month of treatment for latent tuberculosis. If the test is positive, then the patient likely has active tuberculosis and a biologic DMARD or tofacitinib can be started or resumed after the patient has completed treatment for active tuberculosis.[43]

Hepatitis

In patients with hepatitis B infection who are receiving treatment for hepatitis B, treatment of RA should be the same as in patients without a history of hepatitis. In patients with prior exposure to hepatitis B, RA treatment should be the same as unexposed patients, with monitoring of viral load every 6 to 12 months. In patients with history of untreated hepatitis B, treatment of hepatitis B should be considered prior to initiating immunosuppressive therapies.

Patients who are being treated for hepatitis C should not be treated differently than patients without hepatitis C. TNF inhibitors can be used in patients with hepatitis C when they are being treated for this viral infection. In patients with untreated hepatitis C, DMARDs are recommended over TNF inhibitors. Methotrexate and leflunomide should be avoided due to potential effects on the liver; instead, hydroxychloroquine or sulfasalazine should be considered.[43]

Malignancy

In patients with previous melanoma and nonmelanoma skin cancer, DMARDs are preferred over biologic agents and tofacitinib. DMARDs are less immunosuppressive than biologics, decreasing the risk of skin cancer with DMARDs compared with other RA therapies. However, in patients with low-grade skin cancer with history of prior treatment, biologics could be considered with close monitoring of the skin by a dermatologist.

In patients with previously treated lymphoproliferative disorders, rituximab use is recommended over TNF inhibitors because of the known increased risk of lymphoma with TNF inhibitors. Also, rituximab is an FDA-approved treatment for some lymphoproliferative disorders. Combination DMARDs, abatacept, or tocilizumab can be considered over TNF inhibitors. Patients with a history of previously treated solid organ malignancy should be treated as patients without this history.[43]

Heart Failure

TNF inhibitors should be avoided in patients with NYHA II, III, or IV heart failure because of the potential for TNF inhibitors to worsen heart failure or cause new-onset heart failure. If patients develop signs of worsening heart failure on TNF inhibitors, this therapy should be discontinued. Combination DMARDs, non-TNF biologics, or tofacitinib would be recommended as alternative therapies.[43]

Comorbidity Management

Cardiovascular Risk Reduction

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

RA poses as a risk factor for CV disease; this is likely the result of multiple factors present in patients with RA, including chronic inflammation. Therefore, part of RA management is to also manage cardiovascular disease risk. To lower CV disease risk, RA disease activity should be as low as possible. Lifestyle recommendations should be discussed with patients including smoking cessation, regular exercise, and healthy diet.

Other factors that contribute to CV disease—such as hypertension, hyperlipidemia, and diabetes—should be screened for and treated appropriately. NSAIDs should be used with caution, especially in patients with established CVD. Glucocorticoid use should be minimized and tapered to the lowest possible dose due to their potential ill effects on blood glucose and blood pressure.[91]

Osteoporosis

RA is associated with an increased incidence of osteoporosis, falls, and fractures. Glucocorticoid use can increase the potential for these risks. Published recommendations for osteoporosis screening in patients with RA vary greatly. The American Association of Clinical Endocrinologists recommends screening all postmenopausal women with an increased risk of secondary osteoporosis, including those with RA. Canadian recommendations include osteoporosis screening for all patients older than 50 years of age who have RA.[92]

In patients with RA who have low bone mineral density, treatment should be considered based on estimated 10-year probability of a major osteoporotic fracture or hip fracture risk.[92] Vitamin D supplementation and calcium intake should also be assessed and optimized.

According to the ACR, patients on long-term glucocorticoids who are 40 years of age or older should have bone mineral density testing at least within 6 months of initiating glucocorticoids, and fracture risk should be estimated using FRAX. In patients younger than 40 years of age, bone mineral density testing should be considered at least within 6 months of initiating glucocorticoids if the patient has a history of an osteoporotic fracture or has significant risk factors for developing osteoporosis.[93]

Immunizations

Live vaccines should not be given during treatment with biologics but instead should be given before starting therapy when possible and avoided for at least 3 months after immunosuppressants are discontinued.[6] This is because of the inability of the immunocompromised patient to mount an appropriate immune response to the vaccine. Live vaccines can be given to patients on methotrexate (the doses used in RA typically do not produce enough immunosuppression to cause concern), leflunomide, sulfasalazine, and hydroxychloroquine. Inactivated vaccines can be administered while patients are on conventional DMARDs, TNF and non-TNF biologics, and JAK inhibitors; however, efficacy of the vaccine may be reduced if the patient is on methotrexate or biologic agents.[43]

Several influenza vaccines are available, including inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), and the intranasal live-attenuated influenza vaccine (LAIV). Patients with RA should receive the influenza vaccine yearly before initiating and during therapy. The IIV and RIV can be administered to all patients on conventional DMARDs, TNF inhibitors, non-TNF biologics, and JAK inhibitors and who do not have other contraindications to the vaccine. The high-dose inactivated influenza vaccine that is licensed for individuals 65 years of age or older can be given to RA patients regardless of concomitant RA drug therapy.

The available hepatitis B vaccines—either a three-dose series over 6 months (Recombivax HB, Engerix-B), a newer recombinant product (Heplisav-B) that is given in two doses 1 month apart, or a three-dose series in combination with hepatitis A protection (Twinrix)—are licensed for use in adults. These can be given before initiating or while on therapy for RA, but patients on immunosuppressive agents may have a reduced response to the vaccine. The series can be completed as directed in product labeling without regard for RA therapy. The Centers for Disease Control and Prevention (CDC) immunization schedule states that Heplisav-B can be used as a substitute for a dose of a three-dose series hepatitis B vaccine; however, two doses of Heplisav-B still need to be given at least 4 weeks between doses in order for the series to be complete.

Tetanus, diphtheria, acellular pertussis (Tdap) is an inactivated vaccine that should be given to adults who have not received a dose of Tdap as an adult or child. A dose of Td or Tdap is then recommended every 10 years.

The two inactivated pneumococcal vaccines, the pneumococcal polysaccharide vaccine (PPSV, Pneumovax 23) and the pneumococcal conjugated vaccine (PCV, Prevnar 13), should be administered to patients with acquired immunodeficiencies, including patients with RA who are receiving biologic therapy. PCV13 is administered to such patients who are 19 to 64 years of age followed by PPSV23 at least a year later. Another dose of PPSV23 should

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

be given 5 years later. At age 65 or older, an additional dose of PPSV23 should be given at least 5 years after the most recent dose of PPSV23.[94,95]

The Advisory Committee on Immunization Practices (ACIP) no longer recommends routine PCV13 use for all adults >65 years old. Instead, shared clinical decision making for PCV13 use is recommended for adults age 65 years and older who do not have an immunocompromising condition. Due to the nature of RA and its immunocompromising therapies, the updated recommendation does not change immunization practices with respect to this health condition.[96]

A recombinant, adjuvant zoster vaccine to prevent herpes zoster was approved in 2017 (Shingrix) and is recommended for adults aged 50 years and older. It is administered as two doses at 0 and 2 to 6 months. The safety of this vaccine in patients with certain comorbid conditions, including RA, still needs to be determined.[97,98] An older zoster vaccine, Zostavax, is a live vaccine that is contraindicated in patients with RA who are on immunosuppressive therapies; Shingrix is now the preferred vaccine over Zostavax, according to the CDC.[9]

EVALUATION OF THERAPEUTIC OUTCOMES

9 An assessment of disease activity should be conducted at baseline and at each follow-up visit for patients with RA to evaluate disease control and therapeutic response. The evaluation of therapeutic outcomes should be based largely on the patient's subjective improvement of RA symptoms with respect to joint pain, swelling and tenderness, morning stiffness, and fatigue, as well as on a patient's ability to perform activities of daily living. A physical examination should also be conducted at each visit to evaluate the number of swollen and/or tender joints to obtain objective data. This can also help clinicians evaluate loss of joint mobility and deformity. As detailed in Table 111-3, several useful tools can guide clinicians in the objective measurement of disease activity.

TABLE 111-3

Assessment Tools to Measure Rheumatoid Arthritis Disease Activity

Assessment Tool	Scale	High Disease Activity	Moderate Disease Activity	Low Disease Activity	Remission
Clinical Disease Activity Index (CDAI)	0 to 76	>22	>10 to 22	>2.8 to 10	≤2.8
Disease Activity Score (DAS28)	0 to 9.4	>5.1	≥3.2 to ≤5.1	≥2.6 to <3.2	<2.6
Patient Activity Scale (PAS) or PASII	0 to 10	≥8.0	>3.7 to <8.0	>2.5 to 3.7	0 to 2.5
Routine Assessment of Patient Index Data 3 (RAPID-3)	0 to 10	>4.0 to 10	>2 to 4	>1.0 to 2.0	0 to 1.0
Simplified Disease Activity Index (SDAI)	0 to 86	>26	>11 to ≤26	>3.3 to ≤11.0	≤3.3

Laboratory monitoring of acute phase reactants such as CRP and ESR can be useful in assessing inflammation. Plain radiographs of the hands, wrists, and forefeet should be obtained at baseline as well as every 2 years in patients with low disease activity or in remission. Little-to-no evidence of RA disease progression should be evident on this imaging if drug therapy is effective. Imaging may be needed more frequently in patients with moderate or high disease activity. If patients have radiographic changes on imaging that indicate RA disease progression—such as periarticular osteopenia, bone erosions, or joint space narrowing—drug therapy should be modified.[98]

It is also important to monitor and assess for adverse effects of the medications used to treat RA as detailed in Table 111-4.

TABLE 111-4

Adverse Drug Reactions and Monitoring Recommended for Disease-Modifying Antirheumatic Drugs

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Drugs	Adverse Drug Reactions	Initial Monitoring	Maintenance Monitoring
NSAIDs	GI ulceration, bleeding, and 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, blood pressure every 3-6 months	Same as initial
Hydroxychloroquine	Retinal damage, rash, diarrhea	Ophthalmologic exam (fundus examination plus visual fields and spectral-domain optical coherence tomography if maculopathy present) 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
Methotrexate	Infection, hepatic fibrosis, cirrhosis, interstitial pneumonitis, stomatitis, rash, GI perforation, diarrhea, thrombocytopenia, leukopenia	SCr, CBC with differential, AST, ALT, hepatitis B and C screening, tuberculosis screening	SCr, CBC with differential, AST, ALT, 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, signs of infection
Leflunomide	Hepatitis, diarrhea/nausea, alopecia, elevated blood pressure	CBC with differential, SCr, ALT, AST, blood pressure	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; blood pressure 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
Tocilizumab	Local injection-site reactions, infection, malignancy, GI perforation, neutropenia, thrombocytopenia	Tuberculosis screening, hepatitis B screening, CBC with differential, AST, ALT, FLP	AST, ALT, CBC with differential every 4-8 weeks after starting then every 3 months; FLP after 4-8 weeks of starting then every 6 months, signs/symptoms of infection and malignancy

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

Upadacitinib	Infection, malignancy, GI perforations, upper respiratory tract infections, neutropenia, lymphocytopenia, nausea, hepatotoxicity, CPK elevation, thrombosis, increased cholesterol	Tuberculosis screening, hepatitis screening, CBC with differential, LFTs, FLP	CBC with differential, FLP, LFTs, hepatitis screening periodically
Baricitinib	Infection, malignancy, upper respiratory tract infections, herpes zoster infection, hepatotoxicity, hematologic toxicities including anemia, gastrointestinal perforations, thrombosis, lymphocytopenia, neutropenia, increase in SCr and CPK	CBC with differential, LFTs, FLP, tuberculosis, and hepatitis screening	CBC with differential, LFTs, FLP periodically
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
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
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
Abatacept	Immune reactions, infection, malignancy	Tuberculosis screening, hepatitis B screening	Signs/symptoms of infection and malignancy
Tofacitinib	Infection, malignancy, GI perforations, upper respiratory tract infections, headache, diarrhea, nasopharyngitis	Tuberculosis screening, hepatitis B screening, CBC with differential, Hgb, LFTs, FLP, HR, and blood pressure	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 blood pressure, 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

ALT, alanine transaminase; AST, aspartate transaminase; CBC, complete blood count; CPK, creatine phosphokinase; FLP, fasting lipid panel; GI, gastrointestinal; HPA, hypothalamic–pituitary–adrenal; LFTs, liver function tests; SCr, serum creatinine.

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

CONCLUSION

Rheumatoid arthritis is an autoimmune condition that impacts approximately 1% of the population. It is a systemic, progressive disease that can lead to disability and decreased quality of life. The course of therapy is variable but includes both nonpharmacologic and pharmacologic therapies. A patient-centered, comprehensive treatment plan should be initiated as soon as a diagnosis is established to target disease remission or low disease activity. Though a treatment plan should be created with a trained rheumatologist, other clinicians should be utilized for their expertise, such as social work, mental health, and physical/occupational therapy. Chosen pharmacologic treatment is dependent on level of disease activity, past medication trials, comorbidities, and patient-preference. Though the etiology of RA is unclear, we can expect further research to be conducted to determine its cause to help design additional targeted therapies, including expansion of the role of biosimilars.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ACPA	anticitrullinated protein antibodies
ACR	American College of Rheumatology
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANTI-CCP	anti-citrullinated C protein
BID	twice daily
CBC	complete blood count
CPK	creatine phosphokinase
CRP	C-reactive protein
CT	computed tomography
CYP450	cytochrome P450
DEXA	dual-energy x-ray absorptiometry
DMARDs	disease-modifying antirheumatic drugs
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

EULAR	European League Against Rheumatism
EX	extended release
FDA	Food and Drug Administration
GI	gastrointestinal
HLA	human leukocyte antigen
Hgb	hemoglobin
HPA	hypothalamic–pituitary–adrenal
IgG	immunoglobulin G
IL	interleukin
IM	intramuscular
IR	immediate release
IV	intravenous
ILD	interstitial lung disease
JAK	Janus kinase
LFTs	liver function tests (includes AST/ALT, T bilirubin, Alkaline Phosphatase)
LGL	large granular lymphocyte leukemia
MO	month
MTX	methotrexate
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
PBM	pharmacy benefit managers
RA	rheumatoid arthritis
RANKL	receptor activator of NFkB ligand
RF	rheumatoid factor
SCr	serum creatinine
SubQ	subcutaneous

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

TNF	tumor necrosis factor
ULN	upper limit of normal
US	ultrasound

REFERENCES

1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: Estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73(7):1316–1322. [PubMed: 24550173]

2. Sullivan P, Ghushchyan V, Huang X, Globe D. Influence of rheumatoid arthritis on employment, function, and productivity in a nationally representative sample in the United States. *J Rheumatol.* 2010;37(3):544–549. [PubMed: 20080920]

3. Silman AJ, Hochberg MC. Descriptive epidemiology of rheumatoid arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH eds. *Rheumatoid Arthritis*. Philadelphia, PA: Mosby Elsevier; 2009;15–22.

4. Martikainen JA, Kautiainen H, Rantalaiho V, Puolakka K. Long-term work productivity costs due to absenteeism and permanent work disability in patients with early rheumatoid arthritis: A Nationwide Register Study of 7831 Patients. *J Rheumatol.* 2016;34(26):2101–2015.

5. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *Am J Manag Care*. 2012;18:S295–S302. [PubMed: 23327517]

6. Myasoedova E, Davis J III, Crowson C, Gabriel S. Epidemiology of rheumatoid arthritis: Rheumatoid arthritis and mortality. *Curr Rheumatol Rep.* 2010;12:379–385. [PubMed: 20645137]

7. Carmona L, Cross M, Williams B et al. Rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2010;24:733–745. [PubMed: 21665122]

8. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res Ther.* 2002;4(3):S265.

9. Silman AJ, MacGregor AJ, Thomson W et al. Twin concordance rates for rheumatoid arthritis: Results from a nationwide study. *Br J Rheumatol.* 1993;32(10):903. [PubMed: 8402000]

10. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. *Arthritis Rheum.* 2009;60(3):661. [PubMed: 19248111]

11. Bridges SL Jr, White DW, Worthing AB, et al. The science behind biosimilars: Entering a new era of biologic therapy. *Arthritis Rheumatol.* 2018;70(3):334–344. [PubMed: 29411547]

12. Pedersen M, Jacobsen S, Garred P et al. Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: A nationwide case-control study in Denmark. *Arthritis Rheum.* 2007;56(5):1446. [PubMed: 17469102]

13. Tedeschi SK, Frits M, Cui J, et al. Diet and rheumatoid arthritis symptoms: Survey results from a rheumatoid arthritis registry. *Arthritis Care Res (Hoboken)*. 2017;69(12):1920–1925. [PubMed: 28217907]

14. Khuder SA, Peshimam AZ, Agraharam S. Environmental risk factors for rheumatoid arthritis. *Rev Environ Health*. 2002;17(4):307. [PubMed: 12611472]

15. Wegner N, Lundberg K, Kinloch A et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis.

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Immunol Rev. 2010;233(1):34. [PubMed: 20192991]

16. Jiang H, Chess L. Regulation of immune response by T cells. *N Engl J Med.* 2006;354:1166–1176. [PubMed: 16540617]

17. Youinou P, Taher TE, Pers J-O et al. B lymphocyte cytokines and rheumatoid autoimmune disease. *Arthritis Rheum.* 2009;60:1873–1880. [PubMed: 19565509]

18. Uesugi M, Hayashi T, Jasin HE. Covalent cross-linking of immune complexes by oxygen radicals and nitrite. *J Immunol.* 1998;161:1422. [PubMed: 9686606]

19. Firestein GS, Echeverri F, Yeo M et al. Somatic mutations in the p53 tumor suppressor gene in rheumatoid arthritis synovium. *Proc Natl Acad Sci USA.* 1997;94:10895.

20. Huizinga TW, Amos CI, van der Helm-van Mil AH et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins. *Arthritis Rheum.* 2005;52:3433. [PubMed: 16255021]

21. John Hopkins Arthritis Center. RA Pathophysiology. Available at: https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-pathophysiology-2/. Last accessed, September 14, 2018.

22. Deane KD, O'Donnell CI, Hueber W et al. The number of elevated cytokines and chemokines in preclinical seropositive rheumatoid arthritis predicts time to diagnosis in an age-dependent manner. *Arthritis Rheum.* 2010;62:3161. [PubMed: 20597112]

23. Hill JA, Southwood S, Sette A et al. Cutting edge: The conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. *J Immunol.* 2003;171:538. [PubMed: 12847215]

24. Hitchon CA, El-Gabalawy HS. The synovium in rheumatoid arthritis. *Open Rheumatol J.* 2011;5(1:M3):107–114. [PubMed: 22279509]

25. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest.* 2008;118:3537–3545. [PubMed: 18982160]

26. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med.* 2001;344(12):907–916. [PubMed: 11259725]

27. Catrina AI, af Klint E, Ernestam S et al. Anti-tumor necrosis factor therapy increases synovial osteoprotegerin expression in rheumatoid arthritis. *Arthritis Rheum.* 2006;54:76. [PubMed: 16385498]

28. Gravallese EM. Bone destruction in arthritis. *Ann Rheum Dis.* 2002;61(S2):ii84–ii86. [PubMed: 12379632]

29. Jasin HE, Taurog JD. Mechanisms of disruption of the articular cartilage surface in inflammation. Neutrophil elastase increases availability of collagen type II epitopes for binding with antibody on the surface of articular cartilage. *J Clin Invest.* 1991;87:1531. [PubMed: 1708782]

30. Turesson C, Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol.* 2004;33(2):65. [PubMed: 15163106]

31. Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. *Pharmacotherapy*. 2002;22(9):1157. [PubMed: 12222551]

32. Gochuico BR, Avila NA, Chow CK et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med.* 2008;168(2):159. [PubMed: 18227362]

33. Lake F, Proudman S. Rheumatoid arthritis and lung disease: From mechanisms to a practical approach. *Semin Respir Crit Care Med.* 2014;35(2):222–238. [PubMed: 24668537]

34. Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. Rheumatoid pleural effusion. *Semin Arthritis Rheum.* 2006;35(6):368. [PubMed:

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

16765714]

35. Bartels C, Bell C, Rosenthal A, Shinki K, Bridges A. Decline in rheumatoid vasculitis prevalence among US veterans: A retrospective cross-sectional study. *Arthritis Rheum.* 2009;60(9):2553. [PubMed: 19714622]

36. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. *Arthritis Rheum.* 2008;59(12):1690. [PubMed: 19035419]

37. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol.* 1999;26(12):2562–2571. [PubMed: 10606363]

38. Lamy T, Loughran TP Jr. How I treat LGL leukemia. *Blood*. 2011;117(10):2764. [PubMed: 21190991]

39. Hauser B, Riches PL, Wilson JF, Horne AE, Ralston SH. Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53(10):1759. [PubMed: 24764264]

40. Whiting PF, Smidt N, Sterne JA et al. Systematic review: Accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. *Ann Intern Med.* 2010;152(7):456. [PubMed: 20368651]

41. Dougados M. Synovial fluid cell analysis. *Baillieres Clin Rheumatol.* 1996;10(3):519. [PubMed: 8876957]

42. Aletaha D, Neogi T, Silman AJ et al. Arthritis 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Rheum.* 2010;62(9):2569.

43. Solomon DH, Bitton A, Katz JN et al. Treat to Target in rheumatoid arthritis: Fact, fiction or hypothesis? *Arthritis Rheumatol.* 2014;66(4):775–782. [PubMed: 24757129]

44. Demoruelle MK, Deane KD. Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid Arthritis. *Curr Rheumatol Rep.* 2012;14(5):472–480. [PubMed: 22773387]

45. Anderson JJ, Wells G, Verhoeven AC et al. Factors predicting response to treatment in rheumatoid arthritis: The importance of disease duration. *Arthritis Rheum.* 2000;43:22–29. [PubMed: 10643696]

46. Vliet Vlieland TP, Van Den Ende CH. Nonpharmacological treatment of rheumatoid arthritis. *Curr Opin Rheumatol.* 2011; 23(3):259–264. [PubMed: 21346575]

47. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: Psychological and disease-related pathways. *Nat Rev Rheumatol.* 2016;12(9):532. [PubMed: 27411910]

48. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685–699. [PubMed: 31969328] .

49. Weinblatt ME. Efficacy of methotrexate in rheumatoid arthritis. *Br J Rheumatol.* 1995;34(Suppl 2):43–48. [PubMed: 8535649]

50. Methotrexate [package insert]. Huntsville, AL: DAVA Pharmaceuticals, Inc; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf.

51. Bianchi G, Caporali R, Todoerti M et al. Methotrexate and rheumatoid arthritis: Current evidence regarding subcutaneous versus oral routes of administration. *Adv Ther.* 2016;33:369–378. [PubMed: 26846283]

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

52. Kremer JM, Alarcon GS, Lightfoot RW Jr et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. *Arthritis Rheum.* 1994;37(3):316–328. [PubMed: 8129787]

53. Arava [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2011, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020905s022lbl.pdf.

54. Azulfidine [package insert]. New York, NY: Pfizer; 2012, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/007073s125lbl.pdf.

55. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rhem.* 1993;23(2 Suppl 1):82–91.

56. Tett SE, Day RO, Cutler DJ. Concentration-effect relationship of hydroxychloroquine in rheumatoid arthritis: A cross sectional study. *J Rheumatol.* 1993;20(11):1874–1879. [PubMed: 8308772]

57. Marmor MF, Kellner U, Lai TY et al. American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123(6):1386–1394. [PubMed: 26992838]

58. Plaquenil [package insert]. St. Michael, Barbados: Concordia Pharmaceuticals; January 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.

59. Humira [package insert]. North Chicago, IL: Abbvie: August 2018. Available at: https://www.rxabbvie.com/pdf/humira.pdf.

60. Cimzia [package insert]. Smyrna, GA: UCB; May 2018, https://www.cimzia.com/sites/default/files/docs/CIMZIA_full_prescribing_information.pdf.

61. Enbrel [package insert]. Thousand Oaks, CA: Immunex Corporation; December 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf.

62. Simponi [package insert]. Horsham, PA: Janssen Biotech; August 2011, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125289s0064lbl.pdf.

63. Remicade [package insert]. Horsham, PA: Janssen Biotech; November 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf.

64. Orencia [package insert]. Princeton, NJ: Bristol-Meyers Squibb; March 2017. Available at: https://packageinserts.bms.com/pi/pi_orencia.pdf.

65. Weinblatt ME, Schiff M, Valente R et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum.* 2013;65(1):28–38. [PubMed: 23169319]

66. Actemra [package insert]. South San Francisco, CA: Genentech; May 2018. Available at: https://www.gene.com/download/pdf/actemra_prescribing.pdf.

67. Gabay C, Emery P, van Vollenhoven R et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): A randomised, double-blind, controlled phase 4 trial. *Lancet*. 2013;381(9877):1541–1550. [PubMed: 23515142]

68. Rituxan [package insert]. South San Francisco, CA: Genentech; June 2018. Available at: https://www.gene.com/download/pdf/rituxan_prescribing.pdf.

69. Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. *Stand J Rheumatol.* 2013;42(3):190–195.

70. Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf.

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

71. Kevzara [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S.; May 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf.

72. Genovese MC, Fleischmann R, Kivitz AJ et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: Results of a phase III study. *Arthritis Rheumatol.* 2015;67(6):1424–1437. [PubMed: 25733246]

73. Strand V, Really M, Chen CI et al. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumor necrosis factor inhibitors. *RMD Open*. 2017;3:e000416. [PubMed: 28326189]

74. Xeljanz [package insert]. New York, NY: Pfizer; May 2018. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=959.

75. Dowty ME, Lin TH, Jesson MI, et al. Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition. *Pharmacol Res Perspect*. 2019;7(6):e00537–e00537. [PubMed: 31832202]

76. Olumiant [package insert]. Indianapolis, IN: Eli Lilly; May 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf.

77. Rinvoq [package insert]. North Chicago, IL: AbbVie Inc; August 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf.

78. van Vollenhoven RF, Fleischmann R, Cohen S et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med.* 2012;367(6):508–519. [PubMed: 22873531]

79. Felson DT, LaValley MP. The ACR20 and defining a threshold for response in rheumatic disease: Too much of a good thing. *Arthritis Res Ther.* 2017;16(1):101.

80. Xeljanz XR (tofacitinib): Drug safety communication—due to an increased risk of blood clots and death with higher dose. Available at: https://www.fda.gov/safety/medical-product-safety-information/xeljanz-xeljanz-xr-tofacitinib-drug-safety-communication-due-increased-risk-blood-clots-and-death.

81. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a Phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol.* 2019;71(11):1788–1800. [PubMed: 31287230]

82. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: Results from the RA-BUILD study. *Ann Rheum Dis.* 2017;76(1):88–95. [PubMed: 27689735]

83. Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf.

84. Kavanaugh A, Wells AF. Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53(10):1742–1751. [PubMed: 24729402]

85. Rayos [package insert]. Deerfield, IL: Horizon Pharma USA; July 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000lbl.pdf.

86. Da Silva JAP, Jacobs JWG, Kirwan JR et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: Published evidence and prospective trial date. *Ann Rheum Dis.* 2006;65(3):285–293. [PubMed: 16107513]

87. Krause ML, Makes A. Management of rheumatoid arthritis during pregnancy: Challenges and solutions. *Open Access Rheumatol.* 2016;8:23–26.

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

[PubMed: 27843367]

88. Skorpen CG, Hoeltzenbein M, Tincani A et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016;75:795–810. [PubMed: 26888948]

89. Agca R, Heslinga SC, Rollefstad S et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 Update. *Ann Rheum Dis.* 2016;0:1–12.

90. Jeremiah MP, Unwin BK, Greenawald MH et al. Diagnosis and management of osteoporosis. *Am Fam Physician*. 2015;92(4):261–268. [PubMed: 26280231]

91. Buckley L, Guyana G, Fink HA et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol.* 2017;69(8):1521–1537. [PubMed: 28585373]

92. Centers for Disease Control and Prevention. Recommended immunization schedule for adults aged 19 years or older, United States, 2018. Available at: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Last assessed, September 10, 2018.

93. Centers for Disease Control and Prevention. Pneumococcal vaccine timing for adults. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf. Last assessed, September 10, 2018.

94. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2019;68(46):1069–1075. [PubMed: 31751323]

95. Shingrix [package insert]. Research Triangle Park, NC: GlaxoSmithKline Biologicals; October 2017. Available at: https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Shingrix/pdf/SHINGRIX.PDF.

96. Khanna D, Ranganath VK, Fitzgerald J et al. Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage. *Arthritis Rheum.* 2005;52(8):2284. [PubMed: 16052588]

97. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2021;73(7):924–939. [PubMed: 34101387]

98. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685–699. [PubMed: 31969328]

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements about rheumatoid arthritis is true?

   A. Men are twice as likely to have rheumatoid arthritis compared with women.

   B. Rheumatoid arthritis generally presents in the third decade of life.

   C. The mortality rate of rheumatoid arthritis is increased compared to the general population.

   D. Cigarette smoking has not been shown to impact disease activity.

2. Which of the following signs/symptoms are consistent with the clinical presentation of rheumatoid arthritis?

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

A. Red, swollen bilateral phalangeal joints

B. Joint stiffness present only in the evenings

C. Unilateral joint pain present in the left knee

D. Bony enlargements

3. Which of the following is a routinely recommended nonpharmacologic therapy for rheumatoid arthritis?

A. Sodium restriction

B. Increased physical activity

C. Protein restriction

D. Increased vitamin B intake

4. Which of the following is considered a treatment goal for rheumatoid arthritis management?

A. Increase social involvement

B. Decrease disability

C. Low disease activity/disease remission

D. All the above

5. Which of the following is *not* a TNF inhibitor?

A. Adalimumab (Humira)

B. Golimumab (Simponi)

C. Certolizumab (Cimzia)

D. Tocilizumab (Actemra)

6. Which of the following biologics is manufactured as an intravenous (IV) infusion?

A. Etanercept (Enbrel)

B. Adalimumab (Humira)

C. Infliximab (Remicade)

D. Golimumab (Simponi)

7. Which of the following is an appropriate patient-counseling point for methotrexate?

A. It is important to complete all laboratory follow-up as instructed by your provider.

B. This medication should be taken daily.

C. You may continue this medication if you become pregnant.

D. This medication can cause macular damage.

8. Which of the following therapies for rheumatoid arthritis has the lowest pregnancy risk?

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

A. Methotrexate (Rheumatrex)

B. Sulfasalazine (Azulfidine)

C. Leflunomide (Arava)

D. Rituximab (Rituxin)

9. Which of the following vaccinations should be avoided in a patient being treated with a biologic agent for rheumatoid arthritis?

A. Intranasal influenza

B. Intramuscular influenza

C. Hepatitis B

D. Tetanus, diphtheria, acellular pertussis

10. Which of the following therapies for rheumatoid arthritis should be avoided in a patient with advanced heart failure?

A. Abatacept (Orencia)

B. Tocilizumab (Actemra)

C. Golimumab (Simponi)

D. Tofacitinib (Xeljanz)

11. Rapid elimination of leflunomide can be completed with which of the following therapies?

A. Carbidopa

B. Chlorambucil

C. Cholestyramine

D. Cholecalciferol

12. Which of the following would be an appropriate counseling point for adalimumab (Humira)?

A. This medication can cause high blood pressure.

B. This medication should not be interrupted for any reason.

C. This medication should be administered monthly.

D. This medication can be given with methotrexate.

13. RT is a 66-year-old man with well-controlled rheumatoid arthritis on tocilizumab therapy. His primary care provider inquires about appropriate immunizations. What do you recommend?

A. Influenza IM (Fluzone), hepatitis B (Recombivax), PCV 13 (Prevnar)

B. Influenza intranasal (Flumist), PPSV 23 (Pneumovax)

C. Influenza IM (Fluzone), herpes zoster (Zostavax)

D. The patient should not receive any immunizations while taking tocilizumab

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

14. BG is a 57-year-old woman with newly diagnosed rheumatoid arthritis. After shared decision making, she will be starting methotrexate and enrolling in a physical therapy program. What laboratory monitoring needs to be completed while she is on therapy?

    A. CBC, TSH, SCr + eGFR

    B. TSH, SCr + eGFR, AST/ALT

    C. CBC, A1c, TSH

    D. CBC, SCr + eGFR, AST/ALT

15. TK is 69-year-old woman with type 2 diabetes, chronic obstructive pulmonary disease, inflammatory bowel disease, and established rheumatoid arthritis. She has an allergy to sulfa drugs and penicillin. Her disease activity scores remain elevated despite optimized methotrexate therapy. What would be an appropriate therapeutic intervention to help her achieve her goal of low disease activity?

    A. Add sulfasalazine to methotrexate.

    B. Add adalimumab to methotrexate.

    C. Stop methotrexate and add abatacept.

    D. Add abatacept to methotrexate.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** The mortality rate in patients with rheumatoid arthritis is increased compared with the general population, with 3 to 10 fewer years of expected life in those with this disease. Rheumatoid arthritis affects women twice as often as men and typically presents in the fifth decade of life. Cigarette smoking has also been tied to increased disease activity, increased biomarkers, and poor prognoses. See "Epidemiology" and "Etiology" sections of this chapter for additional information.

2. **A.** Rheumatoid arthritis typically involves bilateral, multiple small joints. Joint stiffness typically starts in the morning and can last throughout the day. Boney enlargements are typically seen with osteoarthritis. See "Clinical Presentation" section of this chapter for additional information.

3. **B.** Increased physical activity is recommended in patients with rheumatoid arthritis; the other options are not applicable to management of this condition. See "Treatment" section of this chapter for additional information.

4. **D.** All the options are reasonable goal of care. Other goals include decrease joint pain/stiffness and decreased disability. See "Treatment" section of this chapter for additional information.

5. **D.** Tocilizumab is a monoclonal antibody that inhibits the binding of the proinflammatory cytokine IL-6 to its receptor. All other options are TNF inhibitors. See "Treatment" section of this chapter for additional information.

6. **C.** Only infliximab (Remicade) is administered IV. All other options are manufactured as subcutaneous injections administered using pens or syringes. See "Treatment" section of this chapter or Table 111-2 for additional information.

7. **A.** Methotrexate requires routine laboratory work that is important for monitoring therapy. See "Treatment" section of this chapter for required blood work and time frames. Methotrexate is dosed weekly, not daily, for its rheumatoid arthritis indication. It is contraindicated in pregnancy. Option D is a counseling point for hydroxychloroquine and is not relevant for methotrexate.

8. **B.** Sulfasalazine crosses the placenta and is present in breast milk but can be used in pregnant and nursing mothers with caution. Methotrexate and leflunomide are contraindicated in pregnancy, and rituximab is one of several agents considered potentially unsafe to use during pregnancy. See "Treatment" section of this chapter for more information.

9. **A.** The intranasal influenza vaccine is a live-attenuated influenza product, and live vaccines should not be administered to patients taking biologic

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

therapy. If possible, live vaccines should be administered to patients before starting therapy. None of the other options are live vaccines. See "Treatment" section of this chapter for more information.

10. **C.** Golimumab is a TNF inhibitor, and TNF inhibitors as a class should be avoided in patients with advanced heart failure. The other options are not TNF inhibitors and thus can be used for rheumatoid arthritis management in this patient population. See "Treatment" section of this chapter for more information.

11. **C.** Cholestyramine is a bile acid sequestrant that can be used to bind leflunomide and remove it from the body in the case of elevated laboratory values or incidental pregnancy. This is useful as leflunomide otherwise has a long half-life. The other options are dopaminergic, antineoplastic, and vitamin supplement therapies. See "Treatment" section of this chapter for more information.

12. **D.** Adalimumab (Humira) can be given with or without methotrexate. It is dosed weekly or biweekly. Biologics should be held periprocedurally and during an acute infection. This medication most commonly causes injection site reactions (itching, bruising, minor bleeding, redness) and headache. See "Treatment" section for more information and the postclass learning activity in this chapter for additional guidance.

13. **A.** Influenza IM (Fluzone), hepatitis B (Recombivax), and PCV 13 (Prevnar) are all killed vaccines that can be administered before or during biologic therapy treatment. Influenza intranasal vaccine (Flumist) and the older herpes zoster product (Zostavax) are live-attenuated vaccines that should not be given to immunocompromised patients on biologics; in addition, Flumist is licensed by the FDA for use in patients ages 2 through 49 years. See "Treatment" section of this chapter for additional information.

14. **D.** CBC with differential, hepatic enzymes, and renal function should be monitored every 2 to 4 weeks for 3 months after initiation or following a dose increase, then every 8 to 12 weeks during 3 to 6 months of therapy, and every 12 weeks after 6 months of therapy. TSH and A1c are not routine labs required for methotrexate monitoring. See "Treatment" section of this chapter for additional information.

15. **B.** Adalimumab can be used with or without methotrexate and may provide dual treatment for both inflammatory bowel disease and rheumatoid arthritis. Sulfasalazine should not be recommended in patients with a sulfa allergy. Abatacept should not be recommended in patients with chronic obstructive pulmonary disease. See "Treatment" section of this chapter for additional information.

Downloaded 2024-1-30 12:26 A Your IP is 130.194.219.239
Chapter 111: Rheumatoid Arthritis, Stephanie Gruber; Bianca Harris; Susan Hylland
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility