patients rarely volunteer this information. Significant drug interactions may occur; for example, some herbal preparations can interact with anticoagulants.

Mind-body interventions such as tai chi, meditation, and yoga can improve psychological well-being, strength, balance, and pain level. Chiropractic and osteopathic manipulation as well as massage remain popular. Randomized controlled trials support the use of tai chi for arthritis; smaller trials suggest benefit from meditation techniques, yoga, massage, and manipulative medicine for various musculoskeletal problems.

Role of Surgery

Surgical procedures such as carpal tunnel release or rotator cuff tendon repair can address conditions that arise from repetitive trauma, injury, and degenerative changes in the soft tissue. Synovectomy of inflammatory pannus is occasionally employed when a single or limited number of joints in patients with RA do not respond to medications. Total joint arthroplasty, particularly of the knee or hip, can reduce or eliminate pain and restore function in patients with an inadequate response to medication and physical or occupational therapy.

KEY POINT

- Nonpharmacologic measures used in rheumatologic diseases include physical or occupational therapy, surgery, weight reduction, psychosocial support, and self-management programs.

Rheumatoid Arthritis

Pathophysiology and Risk Factors

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by a chronic inflammatory polyarthritis affecting large and small joints with a predilection for the small joints of the hands and feet. RA has a prevalence of 0.5% to 1% in the general population, with some specific populations having rates as high as 7%.

Genetic Factors

Genes provide 60% of the risk for RA. Among some 100 genetic loci currently recognized as associated with RA risk, the most important is the class II HLA group, especially HLA-D alleles. These risk alleles code for the shared epitope, a five amino acid sequence that binds and presents citrullinated peptide antigens important in the pathophysiology of RA. Because citrulline is an amino acid that does not normally occur in humans, citrullinated proteins are immunogenic, especially in people who also have the shared epitope.

Citrulline is formed by the action of the enzyme peptidylarginine deiminase (PADI), which is found at sites of inflammation and serves to deiminate arginine to form citrullinated peptides. Many of the genes associated with RA modify immune responses to provide a milieu for the development of autoantibodies.

Environmental Factors

Environmental factors provide 40% of the risk for RA. One of the most provocative environmental factors is smoking. Smoking can lead to lung inflammation, which activates enzymes such as PADI, and may promote citrullination. Patients who smoke and are at risk for RA because of family history must be counseled about smoking cessation.

Infectious Agents

A potential risk factor for the development of RA is periodontal disease. *Porphyromonas gingivalis*, a bacterium associated with periodontitis, produces PADI enzymes and provides a potential link to citrullinated peptide formation. Other infectious agents implicated include mycoplasma, Epstein-Barr virus, and parvovirus B19. However, a direct infectious cause of RA has not been identified. There is also interest in the role of the intestinal microbiome in RA. Gut dysbiosis has been postulated to promote early RA, possibly by activating proinflammatory lymphocytes.

Hormones

Women are two to three times as likely as men to develop RA. The role of estrogen and other gender-specific factors is incompletely understood but appears to promote a proinflammatory and/or proautoimmune milieu. Estrogen receptors are present on synovial fibroblasts and may lead to the production of cartilage-damaging metalloproteases. Stimulation of estrogen receptors on macrophages can increase tumor necrosis factor α production, a key RA inflammatory cytokine.

KEY POINT

- Potential risk factors for rheumatoid arthritis include genetic and environmental factors, infectious agents, and hormones; genes provide 60% of the risk.

Diagnosis

The 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria for RA are more sensitive but less specific than the prior 1987 criteria and emphasize early diagnosis and treatment to prevent the permanent consequences of chronic inflammation (**Table 13**).

Clinical Manifestations

RA is a chronic disorder, and onset of symptoms is usually gradual. Patients with RA typically report joint pain and inflammatory symptoms, including swelling and morning stiffness often lasting several hours. Stiffness is generally worse with rest but alleviated by ongoing activity. Joint swelling (softness or bogginess of the affected joint) is palpable on joint examination.

TABLE 13. The 2010 American College of Rheumatology/ European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

Criteria	Score[a]
Joint Involvement[b]	
1 large joint (shoulders, elbows, hips, knees, ankles)	0
2-10 large joints	1
1-3 small joints (MCPs, PIPs, wrists, 2-5 MTPs)	2
4-10 small joints	3
More than 10 small joints	5
Serology	
Negative RF or anti-CCP antibodies	0
Low-positive RF or anti-CCP antibodies (under 3 times the upper limit of normal)	2
High-level RF or anti-CCP antibodies (above 3 times the upper limit of normal)	3
Acute Phase Reactants	
Normal CRP or ESR	0
Abnormal CRP or ESR	1
Duration	
Less than 6 weeks	0
More than 6 weeks	1

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; RF = rheumatoid factor.

[a]Six points needed for classification as rheumatoid arthritis.

[b]At least one joint with definite clinical synovitis that is not better explained by another disease.

From Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81. doi: 10.1002/art.27584. [PMID: 20872595] Copyright 2010, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

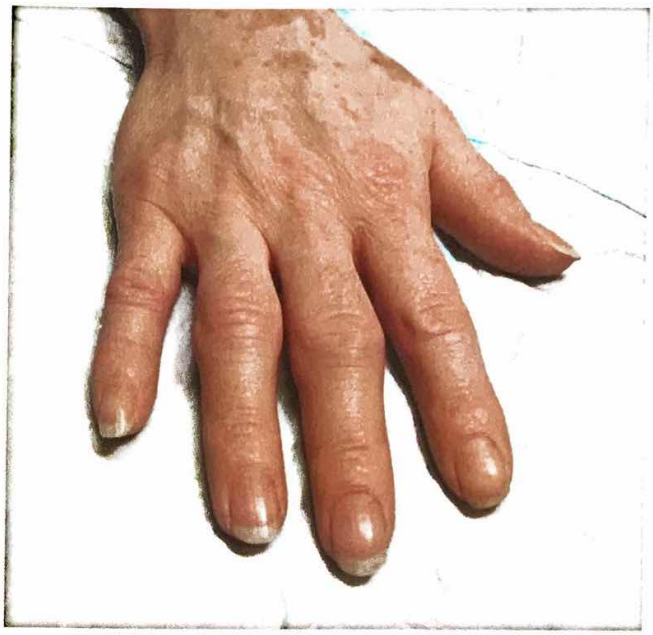

FIGURE 2. Early rheumatoid arthritis of the hands, with swelling in the third and fourth proximal interphalangeal joints.

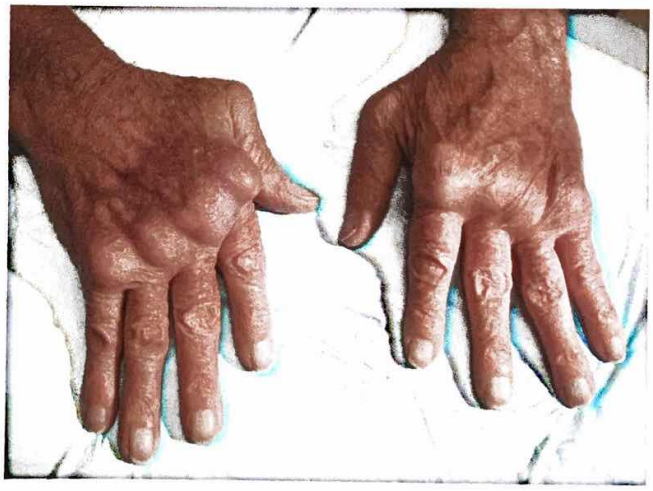

FIGURE 3. Severe rheumatoid arthritis of the hands, with ulnar deviation and subluxation at the metacarpophalangeal joints on both sides.

H The pattern of joint involvement is useful for diagnosing RA. RA characteristically affects the metacarpophalangeal joints, metatarsophalangeal joints, and proximal interphalangeal joints of the hands and feet but spares the distal interphalangeal joints of both the upper and lower extremities (**Figure 2** and **Figure 3**). Wrists, elbows, shoulders, hips, knees, and ankles also can be involved. RA affects joints symmetrically (that is, joints on both sides of the body are generally involved), but severity may be asymmetric. RA may occasionally present as persistent involvement in a single joint. RA spares the thoracic and lumbar spine but affects the cervical spine, especially the C1-C2 (atlantoaxial) articulation. See **Table 14** for more information. H

Laboratory Studies

The most useful laboratory studies to aid in the diagnosis of RA are rheumatoid factor and anti–cyclic citrullinated peptide (CCP) antibodies. Rheumatoid factor is found in approximately 70% of patients with RA and may be present at the time of disease onset. Because other diseases can be associated with rheumatoid factor, its specificity for RA is somewhat limited. Anti-CCP antibodies are also present in 70% of patients with RA but have a specificity of 95%. Anti-CCP antibodies are also more predictive than rheumatoid factor for erosive disease.

Approximately 10% to 20% of patients diagnosed with RA are seronegative (that is, neither rheumatoid factor nor anti-CCP antibodies is positive). Although categorized as having RA, these patients have somewhat different genetics and risk factors and generally have a better prognosis than those with seropositive RA.

TABLE 14. Consequences of Persistent Inflammation on Joints and Supporting Structures

Joint Area	Implications
C1-C2 articulation and transverse ligament	Laxity of the transverse ligament results in increased posterior motion of the dens on C2; with neck flexion, the dens can impact the midbrain and other vital neurologic structures
Shoulder and rotator cuff tendons	Restricted range of motion of the glenohumeral joint and rotator cuff tears
Elbow joint	Elbow contractures and difficulty with hand pronation and supination
Wrist carpal joints and finger tendons	Restricted range of motion of wrist; carpal tunnel syndrome; rupture of finger extensor tendons, especially the fourth and fifth
MCPs and surrounding structures	Ulnar deviation and subluxation of MCPs
PIPs and surrounding structures	Swan neck or boutonniere deformity due to inflammatory disruption of periarticular support structures
Hip joint	Axial migration of the femoral head in the acetabulum (protrusio acetabuli)
Knee joint	Tricompartmental joint-space narrowing
Ankle and mid-foot joints and tendons	Restricted range of motion of ankle; progressive pronated flat foot deformity
MTPs and surrounding structures	Fibular deviation of MTPs; cock-up deformities; skin ulceration underneath subluxed MTP heads

MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

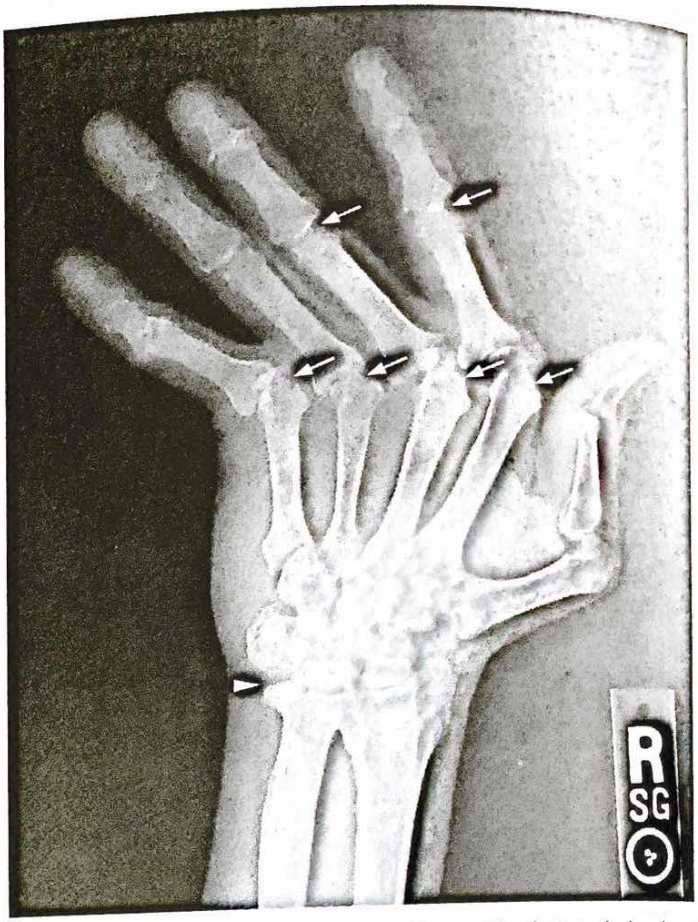

FIGURE 4. Radiograph showing advanced rheumatoid arthritis in the hand. There is ulnar deviation at the metacarpophalangeal joints; marginal erosions most prominently at the second through fourth metacarpophalangeal joints and the second and third proximal interphalangeal joints (*arrows*); and joint-space narrowing at the wrist, metacarpophalangeal, and proximal interphalangeal joints, which also represents erosive disease. Note the loss of the ulnar styloid (*arrowhead*), another common sign of bony erosion in rheumatoid arthritis.

Erythrocyte sedimentation rate and C-reactive protein are elevated in 75% of patients with RA and can be used to monitor treatment response. The systemic inflammation inherent to RA is commonly reflected by an anemia of inflammation and modest thrombocytosis.

Imaging Studies

Plain radiography of the hands and/or feet is a standard imaging study for RA and can aid in diagnosis and assessing progression, although early radiographs may be normal. Radiographic changes include periarticular osteopenia, marginal erosions, and joint-space narrowing (**Figure 4** and **Figure 5**). Radiography of the cervical spine with flexion/extension views is appropriate if C1-C2 subluxation is suspected.

MRI and ultrasonography are more sensitive than plain radiography and may have utility in following disease, assessing risk of progression, and determining response to therapy. Ultrasonography is becoming a standard tool for detecting joint fluid, synovial tissue thickening, early erosions, and increased vascularity. MRI is used for measuring bone marrow edema, synovitis, and erosions; it is also specifically indicated if atlantoaxial involvement is suspected.

KEY POINTS

- Clinical manifestations of classic rheumatoid arthritis typically include pain, swelling, and prolonged morning stiffness in symmetric small joints.
- The most useful laboratory studies to aid in the diagnosis of rheumatoid arthritis (RA) are rheumatoid factor and anti–cyclic citrullinated peptide (CCP) antibodies; anti-CCP antibodies have a specificity of 95% for RA. HVC
- Plain radiography of the hands and/or feet is a standard imaging study for rheumatoid arthritis; radiographic changes include periarticular osteopenia, marginal erosions, and joint-space narrowing, although early radiographs may be normal. HVC

Complications and Extra-Articular Manifestations

Joints

RA joint damage is a consequence of the development of synovitis within the joint. The synovial lining, normally only a few

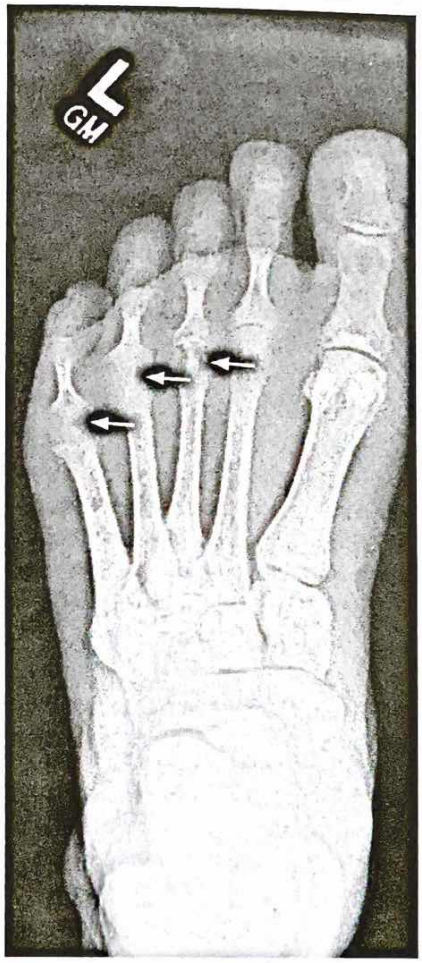

FIGURE 5. Radiograph of rheumatoid arthritis in the foot showing marginal erosions and joint-space narrowing at the third, fourth, and fifth metatarsophalangeal joints (*arrows*). Erosion at the fifth metatarsophalangeal joint is often the first radiographic sign of rheumatoid arthritis foot involvement.

cells thick, becomes significantly expanded and produces cartilage-damaging metalloproteases. Receptor activator of nuclear factor kappa B ligand (RANKL), produced by inflammatory cells, activates osteoclasts to erode bone. The metalloproteases and activated osteoclasts result in various irreversible changes to the joints (see Table 14).

Skin

The most common RA skin changes are rheumatoid nodules, present in up to 30% of patients. Nodules typically occur in the olecranon region and can be confused with gouty tophi, but can also occur over the hand and feet joints and even in the lungs. Nodulosis can rarely be induced by certain drugs (for example, methotrexate and leflunomide) but may respond to others (for example, hydroxychloroquine and colchicine). Patients with RA are also at an increased risk for neutrophilic dermatoses such as pyoderma gangrenosum or Sweet syndrome. Palpable purpura may result from small-vessel cutaneous vasculitis.

Eyes

The most common eye manifestation in RA is dry eye (keratoconjunctivitis sicca). It occurs in 10% to 15% of patients and can be severe. Most of these patients also have dry mouth and are classified as having secondary Sjögren syndrome. Less common (1%) are episcleritis (inflammation of the superficial scleral vessels) and scleritis (inflammation of deep scleral vessels). RA is one of the most common diseases associated with scleritis, which can be vision-threatening and lead to thinning of the sclera and perforation. Keratitis (corneal inflammation) can occur, which is ulcerative and occurs at the periphery of the cornea; severe keratitis is known as corneal melt. Both scleritis and keratitis require immediate referral to an ophthalmologist.

Lungs

Air trapping reflecting small airway disease occurs in up to 50% of patients with RA. Pleural disease occurs in up to 5%; pleural effusions are exudative and can be large. RA pleural effusions are characterized by low glucose and pH (mimicking bacterial or tubercular infection and malignancy) and low complement levels, as well as elevated levels of total protein, rheumatoid factor, and lactate dehydrogenase. Inflammatory cells in the RA effusion are characteristically mononuclear; a neutrophil-predominant effusion suggests infection. Interstitial lung disease contributes to excess mortality in RA and may develop in 50% of patients, but clinically significant disease is seen in 10%. Bronchiectasis and bronchiolitis occur, and the bronchiolitis can be obliterative/constrictive. Upper airway involvement from cricoarytenoid arthritis occurs rarely; symptoms include hoarseness, sore throat, dysphagia, and stridor. Cricoarytenoid arthritis can pose problems for endotracheal intubation.

Heart

Atherosclerotic heart disease remains the major cause of excess death in patients with RA, although recent data suggest that cardiovascular disease risk may be decreasing toward that of the general population. Nonetheless, patients with RA should be considered at high cardiovascular risk for purposes of perioperative evaluation, and cardiovascular disease risk factors such as dyslipidemia and hypertension should be addressed. Clinically significant pericarditis is rare. Granulomatous myocarditis, valvular disease (mainly mitral), conduction block, and aortitis are reported to occur in RA but are very rare.

Hematologic

Anemia of inflammation is the most common RA hematologic abnormality. Felty syndrome consists of neutropenia and splenomegaly and occurs in patients with long-standing, severe, seropositive RA. These patients are at risk for serious bacterial infection, lower extremity ulceration, lymphoma, and vasculitis. With current treatment, Felty syndrome has become rare.

CONT. Patients with RA can also have a large granular lymphocyte syndrome that can progress to large granular lymphocyte leukemia. Findings overlap with Felty syndrome and include neutropenia, anemia, thrombocytopenia, splenomegaly, and recurrent infections. Patients with RA are at increased risk for lymphomas (particularly large B-cell lymphomas), and risk is correlated with disease activity.

Blood Vessels

A small-vessel cutaneous vasculitis occurs in a small percentage of patients with RA, leading to palpable purpura or periungual infarcts. A very rare, larger-vessel vasculitis similar to polyarteritis nodosa can affect multiple organ systems; prior to current therapy, it had a 5-year mortality of 30% to 50%.

KEY POINT

- Extra-articular manifestations and complications of rheumatoid arthritis include rheumatoid nodules, rheumatoid vasculitis, dry eye, small airway disease, interstitial lung disease, pleural effusions, and anemia of inflammation.

Management

See Principles of Therapeutics for details on the uses, mechanisms of action, major toxicities, and/or monitoring requirements of the medications used in RA.

General Considerations

The 2015 ACR RA treatment guidelines (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis) advocate for early diagnosis and aggressive early therapy of RA to prevent irreversible cartilage and bone damage. The 2010 ACR RA classification criteria emphasize sensitivity to permit early diagnosis and institution of disease-modifying therapy (see Table 13). A key treatment goal is to treat to target, with the target being achievement of remission or low disease activity. Disease activity assessment involves making a measured determination using combinations of numbers of tender and swollen joints (typically utilizing 28 joints that exclude the feet), patient and physician impressions of disease activity, and, in some activity scoring systems, measurement of the erythrocyte sedimentation rate or C-reactive protein. These parameters are combined into a composite score, thus assigning a disease activity ranging from remission, to low, moderate, or high. The Clinical Disease Activity Index (CDAI) and Disease Activity Score 28 (DAS28) are two commonly used instruments to assess disease activity and response to treatment. Treating to target in RA results in less radiographic damage, reduced cardiovascular risk, and increased work productivity compared with conventional care.

The 2015 ACR RA treatment guidelines can assist in making initial treatment decisions in early RA. Treatment is typically advanced at 12-week intervals with the goal of reaching remission or low disease activity as rapidly as possible. Patients who remain in remission or a low disease activity state for 6 months or longer may be able to reduce treatment intensity. Treatment decisions for established RA are more complex. An initial approach to the treatment of both early and established RA is outlined in **Figure 6**.

Disease-Modifying Antirheumatic Drugs

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate is the anchor drug in RA, used in both monotherapy and combination therapy. It can be titrated to doses as high as 25 mg per week in partial responders; the treating physician should generally maximize methotrexate dosing before adding other agents. At doses greater than 15 mg weekly, methotrexate oral absorption approaches its effective limit; switching to subcutaneous administration allows for higher serum drug levels. Folic acid supplements minimize toxicity without diminishing efficacy. Of patients with RA taking methotrexate alone, 30% to 50% achieve remission or low disease activity.

Sulfasalazine, leflunomide, and hydroxychloroquine also can be used as monotherapy agents in RA. Leflunomide may

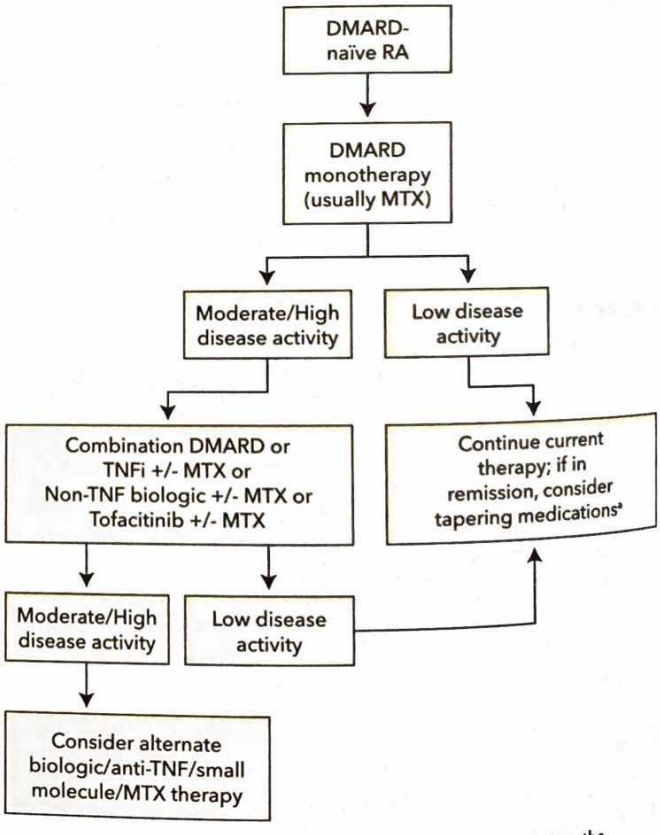

FIGURE 6. A simplified algorithm presenting an initial approach to the treatment of both early and established rheumatoid arthritis (RA). All patients with RA should receive a disease-modifying antirheumatic drug initially and be advanced to more aggressive and/or combination therapy as needed to control disease. Disease activity should be assessed, wherever possible, using a formal, validated, and consistent disease activity index. Refer to the American College of Rheumatology RA treatment guidelines for more complex algorithms accounting for differences between agents and patient-specific complexities. DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor.

[a]Do not discontinue all RA treatments.

be useful in those who cannot tolerate methotrexate. Hydroxychloroquine is the least potent agent but can be used in very early disease when the disease activity score is low. It is also used as part of triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine). Data suggest that triple therapy is comparable to methotrexate combined with a tumor necrosis factor α inhibitor, except in the area of radiographic progression.

Biologic Disease-Modifying Antirheumatic Drugs

Biologic DMARDs can be used as monotherapy but are typically added to methotrexate when moderate to high disease activity persists. Tumor necrosis factor (TNF)-α inhibitors are the most frequently used biologic DMARDs; these agents have a relatively rapid onset of action and demonstrate synergy with methotrexate. The combination of methotrexate and a TNF-α inhibitor has also been shown to have a "disconnect effect," meaning that even patients with continued clinical disease activity may demonstrate little to no damage to cartilage and bone. This effect also has been shown with rituximab or tocilizumab in combination with methotrexate. Other biologic DMARDs used in RA include abatacept (a selective T-cell costimulation modulator) and tofacitinib (a small-molecule Janus kinase inhibitor).

Until better data are available to guide therapeutic decisions, choice of a biologic DMARD remains empiric and based on patient characteristics, including what agents should be avoided due to patient comorbidity (for example, avoiding abatacept in a patient with COPD).

NSAIDs

NSAIDs were once the mainstay of therapy of RA. These agents are not disease modifying and do not prevent joint damage. They are used primarily to control symptoms while waiting for the full effect of DMARDs to be realized or in patients with postinflammatory osteoarthritis.

Glucocorticoids

Unlike NSAIDs, glucocorticoids may have a disease-modifying effect. A recent study tested 10 mg/d of prednisone versus placebo for 2 years in combination with methotrexate; the prednisone group had no more side effects than the placebo group but gained better control of disease activity, used less methotrexate, needed fewer additional medications, and had less radiographic damage. Low-dose prednisone (5-10 mg/d) can be used to rapidly improve RA symptoms while waiting for long-term medications to become effective, or they can be used short term for disease flares. Long-term therapy with glucocorticoids, however, may be associated with substantial adverse effects including osteoporosis, diabetes mellitus, and infection.

Surgery

Surgical therapy has become much less common in RA with current treatment strategies. However, some patients may require a synovectomy for a single persistently swollen joint, carpal tunnel release, repair of a ruptured tendon, total joint replacement (shoulder, metacarpophalangeal joints, hip, knee, or ankle), or joint fusion for a painful damaged joint (wrist or ankle). See MKSAP 18 General Internal Medicine for a discussion of perioperative RA medication management.

KEY POINTS

- In rheumatoid arthritis, treating to target of remission or low disease activity results in less radiographic damage, reduced cardiovascular risk, and increased work productivity compared with conventional care.
- Methotrexate is the anchor drug in rheumatoid arthritis; it is used as monotherapy and as a component of combination therapy. HVC
- Tumor necrosis factor α inhibitors are the most frequently used biologics to treat rheumatoid arthritis; they have a relatively rapid onset of action and demonstrate synergy with methotrexate.
- In rheumatoid arthritis, NSAIDs are not disease modifying and do not prevent joint damage; they are used primarily to control symptoms while waiting for the full effect of disease-modifying antirheumatic drugs to be realized or in patients with postinflammatory osteoarthritis. HVC
- Low-dose prednisone can be used in rheumatoid arthritis to rapidly improve symptoms until long-term medications become effective, or they can be used short term for disease flares.

Pregnancy

There is an increased risk for developing RA in the first year after a first pregnancy. Breastfeeding may decrease this risk. For women with established RA, two thirds will go into remission or low disease activity during pregnancy, and one third will not improve or will get worse. Medication management is a major issue, and pregnancy plans should be discussed with any woman of childbearing age who will be placed on therapy. A discussion of RA medications in pregnancy is located in Principles of Therapeutics.

KEY POINT

- There is an increased risk for developing rheumatoid arthritis (RA) in the first year after a first pregnancy; for women with established RA, two thirds will go into remission or achieve low disease activity during pregnancy, whereas one third will not improve or will get worse.

Osteoarthritis

Pathophysiology

Osteoarthritis (OA) is a chronic progressive multifactorial disorder of maladaptive cellular repair responses to joint stress.