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myeloproliferative disorders, hypercholesterolemia, or other causes of thrombophilia. Diagnosis of CAPS should be considered in patients with mainly microvascular thrombotic disease involving multiple organs in a short time period. A patient is classified as definite CAPS if all four of the following criteria are fulfilled and as probable CAPS when a combination of these criteria is present: (1) thrombosis in three or more organs/ systems; (2) development in less than a week; (3) histologic evidence of small-vessel thrombosis in at least one organ; and (4) aPL presence. Because thrombotic microangiopathy (microangiopathic hemolytic anemia and severe thrombocytopenia) is a typical finding in CAPS, the differential diagnosis includes thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, and heparin-induced thrombocytopenia.

TREATMENT Antiphospholipid Syndrome It has been increasingly appreciated that the risk of thrombotic and obstetric events is closely related to the underlying aPL profile. The latter depends on the type of autoantibodies (IgG high risk vs IgM low risk), the number of aPL antibodies (simultaneous presence of two or three classical autoantibodies vs a single antibody denotes a higher risk profile), their titer (moderate-high titer vs low), and the persistence of aPL positivity in repeated measurements. Following the first thrombotic event, APS patients should be placed on vitamin K antagonists (VKAs) for life, aiming to achieve an international normalized ratio (INR) ranging from 2.0 to 3.0 in case of an unprovoked venous thrombosis. For patients with arterial thrombosis, the corresponding INR target should be 3.0–4.0 or 2.0–3.0 with or without low-dose aspirin (LDA, 75–100 mg daily), depending on the thrombotic/hemorrhagic patient profile. Administration of direct oral anticoagulants (DOACs) recently has been shown to increase the risk of arterial events, especially in patients with triple positivity or previous arterial thrombosis. A recent meta-analysis of four open-label randomized controlled trials showed that prior thrombosis type (arterial vs venous) did not affect the increased odds of arterial thrombosis associated with DOACs compared to VKAs in APS. In pregnant women with a history of obstetric APS, combination treatment with LDA and prophylactic dose of low-molecular-weight heparin (LMWH) is recommended, whereas in cases of thrombotic APS, LDA plus therapeutic LMWH dose should be administered. When recurrent obstetric complications occur despite standard treatment, increasing the LMWH dose (from prophylactic to therapeutic) or administering oral hydroxychloroquine 400 mg/d or low-dose prednisolone in the first trimester are alternative options. For asymptomatic individuals or SLE patients with a high-risk aPL profile and no evidence of a previous thrombotic event or pregnancy morbidity, prophylactic treatment with LDA is recommended. In nonpregnant women with a history of APS-related obstetric complications, independently of the presence of

underlying SLE diagnosis, treatment with LDA seems to reduce the risk of a subsequent thrombotic event. Patients with CAPS should be treated with combination therapy including glucocorticoids, heparin, and plasma exchange or intra venous immunoglobulin (IVIG) together with appropriate management of triggering events such as infections. For refractory CAPS, B-cell depletion (e.g., with rituximab) or complement inhibition (e.g., with eculizumab) therapies are alternative options.

■ ■ FURTHER READING Barbhuiya M et al: 2023 ACR/EULAR antiphospholipid syndrome classification criteria. *Arthritis Rheumatol* 75:1687, 2023. Knight JS et al: Antiphospholipid syndrome: Advances in diagnosis, pathogenesis, and management. *BMJ* 380:e069717, 2023. Tektonidou MG et al: EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 78:1296, 2019.

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Rheumatoid Arthritis CHAPTER 370 INTRODUCTION Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by a symmetric, erosive polyarthritis. It is the most common form of chronic inflammatory arthritis. Since persistently active RA often results in articular cartilage and bone destruction and functional disability, it is vital to diagnose and treat this disease early and aggressively before damage ensues. Although predominately affecting joints, RA is a systemic disease that may lead to a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities. Rheumatoid Arthritis Insights gained over the past two decades have revolutionized the contemporary paradigms for the diagnosis and management of RA. Testing for serum antibodies to anti-citrullinated protein antibodies (ACPA) and rheumatoid factor continues to be valuable in the diagnostic evaluation of patients with suspected RA, and these autoantibodies serve as biomarkers of prognostic significance. Advances in imaging modalities assist clinical decision-making by improving the detection of joint inflammation and monitoring the progression of damage. The science of RA has taken major leaps forward by illuminating new disease-related genes, environmental interactions, and the molecular components and pathways of disease pathogenesis. The relative contribution of these cellular and inflammatory mediators in disease pathogenesis has been further brought to light by the efficacy of the approved biologic and targeted synthetic disease-modifying therapies. Despite these major strides, incomplete understanding of the initiating events of RA and the factors perpetuating the chronic inflammatory response remains a barrier to finding a cure. The past 20 years have witnessed a remarkable improvement in the outcomes of RA. The crippling arthritis of years past is encountered much less frequently today. Much of this progress can be traced to the expanded therapeutic armamentarium and the renewed sense of urgency to identify patients earlier in the disease process, enabling prompt treatment intervention. This shift in treatment strategy dictates a new mindset for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for confirmation of the diagnosis and initiation of disease-modifying therapy, since delays in starting effective treatment are associated with worse outcomes. Reaching a clinical state of low disease activity and remission is now an achievable goal for most patients.

CLINICAL FEATURES The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. The presenting symptoms are typically related to inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting >1 h that eases with physical activity. The earliest involved joints are mostly the small joints of the hands and feet. The initial pattern of joint involvement may be monoarticular,

oligoarticular (≤ 4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis. Those with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or ACPA, and have higher scores for physical disability. In established RA, the most frequently involved joints are the wrists and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints (Fig. 370-1). Distal interphalangeal (DIP) joint involvement may occur in patients with RA, but it is usually due to coexistent osteoarthritis. Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength,

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Metacarpophalangeal joint swelling and subluxation. (Reproduced with permission from RP Usatine, MA Smith, EJ Mayeaux: *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. New York, McGraw Hill, 2019; Fig. 97.5.) and “trigger” fingers. Flexor tendon involvement may also lead to tendon rupture, most commonly the flexor pollicis longus. Progressive destruction of the joints and soft tissues may result in chronic, irreversible deformities. Ulnar deviation is a common deformity of long-standing RA that is caused by subluxation of the MCP joints, with subluxation, or partial dislocation, of the proximal phalanx to the volar side of the hand. Hyperextension of the PIP joint with flexion of the DIP joint (“swan-neck deformity”), flexion of the PIP joint with hyperextension of the DIP joint (“boutonnière deformity”), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint (“Z-line deformity”) also may result from damage to the tendons, joint capsule, and other soft tissues. Inflammation about the ulnar styloid and tenosynovitis of the extensor carpi ulnaris may cause subluxation of the distal ulna, resulting in a “piano-key movement” of the ulnar styloid. Although metatarsophalangeal (MTP) joint involvement is an early feature of disease, chronic inflammation of the ankle and midtarsal regions usually comes later and may lead to pes planovalgus (“flat feet”). Large joints, including the knees and shoulders, are often affected in established disease and may remain asymptomatic for many years after onset. Atlantoaxial involvement of the cervical spine is clinically noteworthy because of its potential to cause compressive myelopathy and neurologic dysfunction. Neurologic manifestations are rarely a presenting sign or symptom of atlantoaxial disease, but they may slowly evolve over time with progressive instability of C1 on C2. The prevalence of atlantoaxial subluxation has been declining in recent years and occurs now in $<10\%$ of patients. Unlike the spondyloarthritides (Chap. 374), RA rarely affects the thoracic and lumbar spine. Extraarticular manifestations may develop during the clinical course of RA in up to 40% of patients, even prior to the onset of arthritis (Fig. 370-2). Patients most likely to develop extraarticular disease have a history of cigarette smoking, have early onset of significant physical disability, and test positive for serum RF or ACPA. Subcutaneous nodules, Sjögren’s disease, interstitial lung disease (ILD), pulmonary nodules, and anemia are among the most frequently observed extraarticular manifestations. Recent studies have shown a decrease in the incidence and severity of at least some extraarticular manifestations, particularly Felty’s syndrome and vasculitis. The most common systemic and extraarticular features of RA are described in more detail in the sections below. ■ ■

CONSTITUTIONAL These signs and symptoms include weight loss, fever, fatigue, malaise, depression, and in the most severe cases, cachexia; they generally reflect a high degree of inflammation and may even precede the onset of joint symptoms. In general, the presence of a fever of $>38.3^{\circ}\text{C}$

(101°F) at any time during the clinical course should raise suspicion of systemic vasculitis (see below) or infection. ■ ■ **NODULES** Subcutaneous nodules have been reported to occur in 30–40% of patients and more commonly in those with the highest levels of disease activity, who carry the disease-related shared epitope (SE) (see below), who have a positive test for serum RF, and who show radiographic evidence of joint erosions. However, more recent cohort studies suggest a declining prevalence of subcutaneous nodules, perhaps related to early and more aggressive disease-modifying therapy. When palpated, the nodules are generally firm; nontender; and adherent to periosteum, tendons, or bursae; they develop in areas of the skeleton subject to repeated trauma or irritation such as the forearm, sacral prominences, and Achilles tendon. They may also occur in the lungs, pleura, pericardium, and peritoneum. Nodules are typically benign, although they can be associated with infection, ulceration, and gangrene. Accelerated growth of smaller nodules may occur in up to 10% of patients taking long-term methotrexate, although the mechanisms behind this phenomenon are unclear. ■ ■ **SJÖGREN'S SYNDROME** Secondary Sjögren's syndrome, or Sjögren's disease (Chap. 373), is defined by the presence of either keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth) in association with another connective tissue disease, such as RA. Approximately 10% of patients with RA have secondary Sjögren's syndrome. ■ ■ **PULMONARY** Pleuritis, the most common pulmonary manifestation of RA, may result in pleuritic chest pain and dyspnea, as well as a finding of a pleural friction rub and radiographic evidence of a pleural effusion. Pleural effusions tend to be exudative with increased numbers of monocytes and neutrophils. ILD may also occur in patients with RA and is heralded by symptoms of dry cough and progressive shortness of breath. ILD can be associated with cigarette smoking and is generally found in patients with higher disease activity, although it may be diagnosed in up to 3.5% of patients prior to the onset of joint symptoms. Recent studies have shown the overall prevalence of ILD in RA to be as high as 12%. Diagnosis is readily made by high-resolution chest computed tomography (CT) scan, which shows infiltrative opacification, or ground-glass opacities, in the periphery of both lungs. Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the main histologic and radiologic patterns of ILD. UIP causes progressive scarring of the lungs that, on chest CT scan, produces honeycomb changes in the periphery and lower portions of the lungs. In contrast, the most common radiographic changes in NSIP are relatively symmetric and bilateral ground-glass opacities with associated fine reticulations, volume loss, and traction bronchiectasis. In both cases, pulmonary function testing shows a restrictive pattern (e.g., reduced total lung capacity) and a reduced diffusing capacity for carbon monoxide (DLCO). The presence of ILD confers a poor prognosis. The prognosis of ILD in RA, however, is not quite as poor as that of idiopathic pulmonary fibrosis (e.g., usual interstitial pneumonitis) and responds better to immunosuppressive therapy (Chap. 304). Pulmonary nodules are also common in patients with RA and may be solitary or multiple. Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure. Less commonly, RA may be associated with respiratory bronchiolitis and bronchiectasis. ■ ■ **CARDIAC** The most frequent site of cardiac involvement in RA is the pericardium. However, clinical manifestations of pericarditis occur in <10% of patients with RA despite pericardial involvement being detectable in nearly one-half of cases by echocardiogram or at autopsy. Up to 20% of patients with RA may have asymptomatic pericardial effusions on echocardiography. Cardiomyopathy, another clinically important manifestation of RA, may result from necrotizing or granulomatous myocarditis, coronary artery disease, or diastolic dysfunction. This

Ocular: Keratoconjunctivitis sicca, episcleritis, scleritis Neurologic: Cervical myelopathy Hematologic: Anemia of chronic disease, neutropenia, splenomegaly, Felty's syndrome, large granular lymphocyte leukemia, lymphoma GI: Vasculitis Skeletal: Osteoporosis

FIGURE 370-2 Extraarticular manifestations of rheumatoid arthritis. Involvement, too, may be subclinical and only identified by echocardiography or cardiac magnetic resonance imaging (MRI). Rarely, the heart muscle may contain rheumatoid nodules or be infiltrated with amyloid.

■ **VASCULITIS** Rheumatoid vasculitis (Chap. 375) typically occurs in patients with long-standing disease, a positive test for serum RF or ACPA, and hypo complementemia. The overall incidence has decreased significantly in the past decade to <1% of patients. The cutaneous signs vary and include petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, painful lower extremity ulcerations. Vascular ulcers, which may be difficult to distinguish from those caused by venous insufficiency, may be treated successfully with immunosuppressive agents including cytotoxic treatment and skin grafting in severe cases. Sensorimotor polyneuropathies, such as mononeuritis multiplex, may occur in association with systemic rheumatoid vasculitis; they usually present with new onset of numbness, tingling, or focal muscle weakness.

■ **HEMATOLOGIC** A normochromic, normocytic anemia often develops in patients with RA and is the most common hematologic abnormality. The degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Platelet counts may also be elevated in RA as an acute-phase reactant; immune-mediated thrombocytopenia is rare.

CHAPTER 370 Oral: Xerostomia, periodontitis Pulmonary: Pleural effusions, pulmonary nodules, interstitial lung disease, pulmonary vasculitis, organizing pneumonia Rheumatoid Arthritis Cardiac: Pericarditis, ischemic heart disease, myocarditis, cardiomyopathy, arrhythmia, mitral regurgitation Renal: Membranous nephropathy, secondary amyloidosis Endocrine: Hypoandrogenism Skin: Rheumatoid nodules, purpura, pyoderma gangrenosum Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA and is seen in <1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease. It typically occurs in the late stages of severe RA and is more common in whites than other racial groups. T-cell large granular lymphocyte leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA. T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly. As opposed to Felty's syndrome, T-LGL may develop early in the course of RA. Leukopenia apart from these disorders is uncommon and most often a side effect of drug therapy.

■ **LYMPHOMA** Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population. The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma. The risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

■ **ASSOCIATED CONDITIONS** In addition to extraarticular manifestations, several conditions associated with RA contribute to disease morbidity and mortality rates. They are worthy of mention because they affect chronic disease management. Cardiovascular Disease The most common cause of death in patients with RA is cardiovascular disease. The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking. Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in

RA than in the general population. The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Osteoporosis Osteoporosis is more common in patients with RA than an age- and sex-matched population, with an incidence rate of nearly double that of the healthy population and a prevalence of approximately one-third in postmenopausal women with RA. There is also an increased risk of fragility fracture, with a greater risk among women. The inflammatory milieu of the joint promotes generalized bone loss by activating osteoclasts. Both trabecular and cortical bone are affected by the inflammatory response, with cortical sites more susceptible to bone loss. Chronic use of glucocorticoids and disability-related immobility also contribute to osteoporosis. Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

EPIDEMIOLOGY RA affects ~0.5–1% of the adult population worldwide, although the majority of epidemiologic studies have been done in Western countries. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. The incidence and prevalence of RA vary based on geographic location, both globally and among certain ethnic groups within a country (Fig. 370-3). For example, the indigenous Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates in some studies of nearly 7%. In contrast, many population studies from Africa and Asia show lower prevalence rates for RA in the range of 0.2–0.4%. Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2–3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1. Given this preponderance of females, various theories have been proposed to explain the possible role of estrogen in disease pathogenesis. Broadly speaking, most of the theories center on the role of estrogens and androgens in enhancing and suppressing the immune

European ancestry: HLA-DRB1: *0401 *0404 *0301 *0101 PTPN22: European US: 0.7–1.3% STAT4: North American TNFAIP3: North American TRAF1/CF: North American CTLA4: European Asian ancestry: HLA-DRB1: Brazil: 0.4–1.4% *0401 (East Asian) *0405 *0901 (Japanese, Malaysian, Korean) PADI4 CD244 Other: CD40

FIGURE 370-3 Global prevalence rates of rheumatoid arthritis (RA) with genetic associations. Listed are the major genetic alleles associated with RA. Although human leukocyte antigen (HLA)-DRB1 mutations are found globally, some alleles have been associated with RA in only certain ethnic groups.

response, respectively. However, estrogens have both stimulatory and inhibitory effects on the immune system, and their role, if any, on the development of RA is unknown.

GENETIC CONSIDERATIONS It has been recognized for >30 years that genetic factors contribute to the occurrence of RA as well as to its severity. The likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2–10 times greater than in the general population. There remains, however, some uncertainty in the extent to which genetics plays a role in the causative mechanisms of RA. Heritability estimates range from 40 to 60%, although this may be higher in ACPA-positive patients compared to those without ACPA. The estimate of genetic influence has varied across studies, probably due to gene–environment interactions. The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC) and, in particular, those encoding the MHC class II molecules. MHC class II molecules are typically expressed on antigen-presenting cells and are comprised of α and β chains. Most, but probably not

all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β -chain molecule. The disease-associated HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β -chain, termed the shared epitope (SE). These amino acids are located in the antigen-binding groove within the hypervariable regions of the HLA-DR β 1 molecule. These hypervariable regions are important not only for determining antigen recognition but also for binding of the MHC-peptide complex to the T-cell receptor (TCR). Peptides derived from posttranslationally modified proteins (via citrullination, acetylation, or carbamylation, for example) may bind with greater avidity to the SE, providing a potential explanation for increased disease risk at a molecular level. The risk of RA is four times higher in persons carrying a single SE allele and eight times higher in those carrying two alleles compared to SE-negative individuals. Carriership of the SE alleles is associated with production of ACPAs and worse disease outcomes. Some HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, 0404, 1001, and 0901). Over 90% of patients with RA express at least one of these variants. Interestingly, HLA-DRB1*1301 and to a lesser extent HLA-DRB1*1302 confer protection from ACPA-positive RA. Additionally, there is geographic variation in disease susceptibility and the identity of the HLA-DRB1 risk alleles. In Greece, for example, Norway: 0.4% Bulgaria: 0.2–0.6% UK: 0.8–1.1% Iraq: 0.4–1.5% India: 0.1–0.4% Japan: 0.2–0.3% Spain: 0.2–0.8% Greece: 0.3–1% Jamaica: 1.9–2.2% Hong Kong: 0.1–0.5% Saudi Arabia: 0.1–0.2% Liberia: 2–3% Java: 0.1–0.2% Lesotho: 1.7–4.5% South Africa: 2.5–3.6%

where RA tends to be milder than in western European countries, RA susceptibility has been associated with the *0101 SE allele. By comparison, the *0401 or *0404 alleles are found in ~50–70% of northern Europeans and are the predominant risk alleles in this group. The most common disease susceptibility SE alleles in Asians, namely the Japanese, Koreans, and Chinese, are *0405 and *0901. Lastly, disease susceptibility of Native American populations such as the Pima and Tlingit Indians, where the prevalence of RA can be as high as 7%, is associated with the SE allele *1042. The risk of RA conferred by these SE alleles is less in African and Hispanic Americans than in individuals of European ancestry. Genome-wide association studies (GWAS) have made possible the identification of several non-MHC-related genes that contribute to RA susceptibility. GWASs are based on the detection of single nucleotide polymorphisms (SNPs), which allow for examination of the genetic architecture of complex diseases such as RA. Overall, several themes have emerged from GWAS in RA. First, among the >100 non-MHC loci identified as risk alleles for RA, they individually have only a modest effect on risk; they also contribute to the risk for developing other autoimmune diseases, such as type 1 diabetes mellitus, systemic lupus erythematosus, and multiple sclerosis. Second, although most of the non-HLA associations are described in patients with ACPA-positive disease, there are several risk loci that are unique to ACPA-negative disease. Third, risk alleles vary among ethnic groups. And fourth, the risk loci mostly reside in genes encoding proteins involved in the regulation of the immune response. However, the risk alleles identified by GWAS only account at present for ~5% of the genetic risk, suggesting that rare variants or other classes of DNA variants, such as variants in copy number, may be yet found that significantly contribute to the overall risk model. Among the best examples of the non-MHC genes contributing to the risk of RA is the gene encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22). This gene varies in frequency among patients from different parts of Europe (e.g., 3–10%) but is absent in patients of East Asian ancestry. PTPN22 encodes lymphoid tyrosine phosphatase, a protein that regulates T- and B-cell function. Inheritance of the risk allele for PTPN22 produces a gain-of-function in the protein that is hypothesized to result in the abnormal

thymic selection of autoreactive T and B cells and appears to be associated exclusively with ACPA-positive disease. The peptidyl arginine deiminase type IV (PADI4) gene is another risk allele that encodes an enzyme involved in the conversion of arginine to citrulline and is postulated to play a role in the development of antibodies to citrullinated antigens. A polymorphism in PADI4 has been associated with a twofold increase in the risk of RA, primarily in those of East Asian descent. Recently, polymorphisms in apolipoprotein M (APOM) in an East Asian population were found confer an increased risk for RA as well as risk for dyslipidemia, independent of RA disease activity. Epigenetics is the study of heritable traits that affect gene expression but do not modify DNA sequence. Epigenetic mechanisms are theoretically involved in three important aspects of RA: contribution to disease etiology, perpetuation of chronic inflammatory responses, and disease severity. The best-studied epigenetic mechanisms are those regulating posttranslational histone modifications and DNA methylation. DNA methylation patterns have been shown to differ between RA patients and healthy controls, including monozygotic twins, as well as from patients with osteoarthritis. Epigenetics may also offer a mechanistic explanation for how cigarette smoking confers an increased risk for ACPA-positive RA (see below) as those patients with the SE have higher levels of DNA methylation compared to nonsmokers. MicroRNAs, which are noncoding RNAs that function as posttranscriptional regulators of gene expression, represent an additional epigenetic mechanism that may potentially influence cellular responses.

ENVIRONMENTAL FACTORS In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA. The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case-control studies have demonstrated that smoking confers a

relative risk for developing RA of 1.5–3.5 times. Smoking-related risk interacts in a synergistic manner with MHC risk alleles. The classic SE alleles alone increase the likelihood of developing RA by four- to sixfold; however, this risk increases to 20- to 40-fold when combined with smoking. In particular, women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after smoking cessation. A twin who smokes will have a significantly higher risk for RA than their monozygotic co-twin, theoretically with the same genetic risk, who does not smoke. Interestingly, the risk from smoking is almost exclusively related to RF and ACPA-positive disease. However, it has not been shown that smoking cessation, while having many health benefits, reduces the severity or extent of joint inflammation. Inhalant-related occupations and silica inhalants also may increase RA risk. These observations have led to the theory that subclinical lung disease may play a critical early role in the initial development of autoreactive immune cells and account for the occurrence of autoantibodies more than a decade prior to the clinical development of joint disease.

CHAPTER 370 Rheumatoid Arthritis Researchers began to aggressively seek an infectious etiology for RA after the discovery in 1931 that sera from patients with this disease could agglutinate strains of streptococci. Certain viruses such as Epstein-Barr virus (EBV) have garnered the most interest over the past 30 years given their ubiquity, ability to persist for many years in the host, and frequent association with arthritic complaints. For example, titers of IgG antibodies against EBV antigens in the peripheral blood and saliva are significantly higher in patients with RA than in the general population. EBV DNA has also been found in synovial fluid and synovial cells of RA patients. Because the evidence for these links is largely circumstantial, it has not been possible to directly implicate infection as a causative factor in RA. An attractive hypothesis raised by newer

studies is that microbial dysbiosis of the oral or gut microbiome may predispose to the development of RA. Recent work suggests that periodontitis in the oral cavity may play a role in disease mechanisms. Multiple studies provide evidence for a link between ACPA-positive RA and cigarette smoking, periodontal disease, and the oral microbiome, specifically *Porphyromonas gingivalis*. It has been hypothesized that the immune response to

P. gingivalis may trigger the development of RA and the bacterial enzyme peptidyl arginine deiminase (PAD) induces ACPA by catalyzing the citrullination of arginine residues on the stimulating autoantigens. Interestingly, *P. gingivalis* is the only oral bacterial species known to harbor this enzyme. Some studies have shown a relationship between the presence of circulating antibodies to *P. gingivalis* and RA, as well as with first-degree relatives at risk for this disease. However, it remains unproven whether the observed dysbiosis in the oral cavity precedes the development of disease. There are also limited data suggesting a role for the gut microbiome in the etiology of RA. Some studies have found that the gut microbiome is different in patients with early RA compared with controls. In particular, *Prevotella copri* was reported to be enriched in early untreated RA as well as in an “at-risk” population. On the other hand, a common dysbiotic signature does not seem to predominate in patients with RA, and evidence is lacking for a direct immune-modulating effect. PATHOLOGY RA affects the synovial lining tissue of the diarthrodial joints and the underlying cartilage and bone. The synovial membrane, which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue. In joints, it faces the bone and cartilage, bridging the opposing bony surfaces and inserting at periosteal regions close to the articular cartilage. It consists primarily of two cell types— type A synoviocytes (macrophage-derived) and type B synoviocytes (fibroblast-derived). The synovial fibroblasts are the most abundant and produce the structural components of joints, including collagen, fibronectin, and laminin, as well as other extracellular constituents of the synovial matrix. The sublining layer consists of blood vessels and a sparse population of mononuclear cells within a loose network of connective tissue. Synovial fluid, an ultrafiltrate of blood, diffuses through the subsynovial lining tissue across the synovial membrane

and into the joint cavity. Its main constituents are hyaluronan and lubricin. Hyaluronan is a glycosaminoglycan that contributes to the viscous nature of synovial fluid, which, along with lubricin, lubricates the surface of the articular cartilage.

The pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. Chronic inflammation leads to synovial lining hyperplasia and the formation of pannus, a thickened cellular membrane consisting of multiple layers of fibroblast-like synoviocytes and granulation-reactive fibrovascular tissue that has a propensity for invading underlying cartilage and bone. The inflammatory infiltrate is made up of no less than six cell types: T cells, B cells, plasma cells, dendritic cells, mast cells, and, to a lesser extent, granulocytes. The T cells compose 30–50% of the infiltrate, with the other cells accounting for the remainder. The topographical organization of these cells is complex and may vary among individuals with RA. Most often, the lymphocytes are diffusely organized among the tissue resident cells; however, in some cases, the B cells, T cells, and dendritic cells may form higher levels of organization, such as lymphoid follicles and germinal center-like structures. Growth factors secreted by synovial fibroblasts and macrophages promote the formation of new blood vessels in the synovial sublining that supply the increasing demands for oxygenation and nutrition required by the infiltrating

leukocytes and expanding synovial tissue. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders The structural damage to the mineralized cartilage and subchondral bone is mediated by the osteoclast. Osteoclasts are multinucleated giant cells that appear at the pannus-bone interface where they eventually form resorption lacunae. These lesions typically localize where the synovial membrane inserts into the periosteal surface at the edges of bone close to the rim of articular cartilage and at the attachment sites of ligaments and tendon sheaths. This process most likely explains why bone erosions usually develop at the radial sites of the MCP joints juxtaposed to the insertion sites of the tendons, collateral ligaments, and synovial membrane. Periarticular osteopenia, another form of bone loss, occurs in joints with active inflammation. It is associated with substantial thinning of the bony trabeculae along the metaphyses of bones from inflammation of the bone marrow cavity. These lesions can be visualized on MRI scans, where they appear as signal alterations in the bone marrow adjacent to inflamed joints. Their signal characteristics show they are water-rich with a low-fat content and are consistent with highly vascularized inflammatory tissue. These bone marrow lesions are often the forerunner of bone erosions. The cortical bone layer that separates the bone marrow from the invading pannus is relatively thin and susceptible to penetration by the inflamed synovium. The bone marrow lesions visualized on MRI scans are associated with an endosteal bone response characterized by the accumulation of osteoblasts and deposition of osteoid. Finally, generalized osteoporosis, which results in the thinning of trabecular bone throughout the body, is a third form of bone loss found in patients with RA and can lead to fragility fractures. Articular cartilage is an avascular tissue comprised of a specialized matrix of collagens, proteoglycans, and other proteins. It is organized in four distinct regions (superficial, middle, deep, and calcified cartilage zones)—chondrocytes constitute the unique cellular component in these layers. Originally, cartilage was considered to be an inert tissue, but it is now known to be a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which, in turn, alter the balance between cartilage anabolism and catabolism. In RA, the initial areas of cartilage degradation are juxtaposed to the synovial pannus. The cartilage matrix is characterized by a generalized loss of proteoglycan, most evident in the superficial zones adjacent to the synovial fluid. Degradation of cartilage may also take place in the perichondrocytic zone and in regions adjacent to the subchondral bone. PATHOGENESIS The pathogenic mechanisms of synovial inflammation are likely the result of a complex interplay of genetic, environmental, and immunologic factors that cause immune system dysregulation and a breakdown in self-tolerance (Fig. 370-4). Precisely what triggers these initiating events and what genetic and environmental factors disrupt the immune

system remains a mystery. However, a detailed molecular picture is emerging of the mechanisms underlying the chronic inflammatory response and the resulting destruction of the articular cartilage and bone. In RA, the preclinical stage appears to be characterized by a breakdown in self-tolerance. This idea is supported by the finding that autoantibodies, such as RF and ACPA, may be found in sera from patients many years before onset of clinical disease. However, the antigenic targets of ACPA and RF are not restricted to the joint. ACPAs are directed against deaminated peptides, which result from posttranslational modification by the enzyme PAD14. They recognize citrulline-containing regions of several different matrix proteins, including filaggrin, keratin, fibrinogen, and vimentin, and are present at higher levels in the joint fluid compared to the serum. Antibodies binding to carbamylated peptides and mutant citrullinated vimentin, as well as the 14-3-3 family of proteins, have also been detected in a minority of RA patients. In theory, environmental triggers may synergize with other factors to bring about inflammation in RA. People

who smoke display higher citrullination of proteins in bronchoalveolar fluid than those who do not smoke. Thus, it has been speculated that long-term exposure to tobacco smoke might induce citrullination of cellular proteins via increased PADI expression in the lung and generate a neoepitope capable of inducing self-reactivity, which in turn, leads to formation of immune complexes that trigger joint inflammation and joint damage. Microbiota may also be involved in the initiating events of RA. The immune system is alerted to the presence of microbial infections when pathogen-associated molecular patterns (PAMPs) on their surface bind to Toll-like receptors (TLRs) on host cells. There are 10 TLRs in humans that recognize a variety of microbial products, including bacterial cell-surface lipopolysaccharides and heat-shock proteins (TLR4), lipoproteins (TLR2), double-strand RNA viruses (TLR3), and unmethylated CpG DNA from bacteria (TLR9). TLR2, 3, and 4 are abundantly expressed by synovial fibroblasts in early RA and, when bound by their ligands, upregulate the cell's production of proinflammatory cytokines. Although TLR ligands may theoretically amplify inflammatory pathways in RA, their specific role in disease pathogenesis remains uncertain. The pathogenesis of RA is built upon the concept that self-reactive T cells drive the chronic inflammatory response. In theory, self-reactive T cells might arise in RA from abnormal central (thymic) selection or intrinsic defects lowering the threshold in the periphery for T-cell activation. Either mechanism might result in abnormal expansion of a self-reactive T-cell repertoire and a breakdown in T-cell tolerance. The support for these ideas comes mainly from studies of arthritis in mouse models. It has not been shown that patients with RA have abnormal thymic selection of T cells or defective apoptotic pathways regulating cell death. At least some antigen stimulation inside the joint seems likely, owing to the fact that T cells in the synovium express a cell-surface phenotype indicating prior antigen exposure and show evidence of clonal expansion. There is substantial evidence of a role for CD4⁺ T cells in the pathogenesis of RA. First, the co-receptor CD4 on the surface of T cells binds to invariant sites on MHC class II molecules, stabilizing the MHC-peptide-T-cell receptor complex during T-cell activation. Because the SE on MHC class II molecules is a risk factor for RA, it follows that CD4⁺ T-cell activation plays a role in the pathogenesis of this disease. Second, CD4⁺ memory T cells are enriched in the synovial tissue from patients with RA and therefore are implicated through "guilt by association." Third, CD4⁺ T cells have been shown to be important in the initiation of arthritis in animal models. Fourth, some, but not all, T cell-directed therapies have shown clinical efficacy in this disease. Taken together, these lines of evidence suggest that CD4⁺ T cells play an important role in orchestrating the chronic inflammatory response in RA. However, other cell types, such as CD8⁺ T cells, natural killer (NK) cells, and B cells are present in synovial tissue and may also influence pathogenic responses. In the rheumatoid joint, by mechanisms of cell-cell contact and release of soluble mediators, activated T cells stimulate macrophages and fibroblast-like synoviocytes to generate proinflammatory

Genetics Environment TLR APC MHC II TCR TH1 IFN- γ , TNF- α lymphotoxin- β TH CD40L CD40 IFN- γ , IL17 IL15, GM-CSF, TNF- α B M RF, Anti-CCP Ab Pre-OB OB

FIGURE 370-4 Pathophysiologic mechanisms of inflammation and joint destruction. Genetic predisposition along with environmental factors may trigger the development of rheumatoid arthritis (RA), with subsequent synovial T-cell activation. CD4⁺ T cells become activated by antigen-presenting cells (APCs) through interactions between the T-cell receptor and class II MHC-peptide antigen (signal 1) with co-stimulation through the CD28-CD80/86 pathway, as well as other pathways (signal 2). In theory, ligands binding Toll-like receptors (TLRs) may further stimulate activation of APCs inside the joint. Synovial CD4⁺ T cells differentiate into TH1 and TH17 cells, each with their distinctive cytokine

profile. CD4⁺ TH cells in turn activate B cells, some of which are destined to differentiate into autoantibody-producing plasma cells. Immune complexes, possibly comprised of rheumatoid factors (RFs) and anti-cyclic citrullinated peptides (CCP) antibodies, may form inside the joint, activating the complement pathway and amplifying inflammation. T effector cells stimulate synovial macrophages (M) and fibroblasts (SF) to secrete proinflammatory mediators, among which is tumor necrosis factor α (TNF- α). TNF- α upregulates adhesion molecules on endothelial cells, promoting leukocyte influx into the joint. It also stimulates the production of other inflammatory mediators, such as interleukin 1 (IL-1), IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). TNF- α has a critically important function in regulating the balance between bone destruction and formation. It upregulates the expression of dickkopf-1 (DKK-1), which can then internalize Wnt receptors on osteoblast precursors. Wnt is a soluble mediator that promotes osteoblastogenesis and bone formation. In RA, bone formation is inhibited through the Wnt pathway, presumably due to the action of elevated levels of DKK-1. In addition to inhibiting bone formation, TNF- α stimulates osteoclastogenesis. However, it is not sufficient by itself to induce the differentiation of osteoclast precursors (Pre-OC) into activated osteoclasts capable of eroding bone. Osteoclast differentiation requires the presence of macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor- κ B (RANK) ligand (RANKL), which binds to RANK on the surface of Pre-OC. Inside the joint, RANKL is mainly derived from stromal cells, synovial fibroblasts, and T cells. Osteoprotegerin (OPG) acts as a decoy receptor for RANKL, thereby inhibiting osteoclastogenesis and bone loss. FGF, fibroblast growth factor; IFN, interferon; MMP, matrix metalloproteinase; TGF, transforming growth factor.

CHAPTER 370 Rheumatoid Arthritis CD80 CD28 T TH17 IL-17A, IL-17F, TNF- α , IL-6, GM-CSF Teff Teff SF IL-6, IL-8 FGF, TGF- β IL-1, IL-6, IL-18 TNF- α MMP + Wnt TH + St Dkk-1 OPG RANK-L + RANK OC Pre-OC Cathepsin K

mediators and proteases that drive the synovial inflammatory response and destroy the cartilage and bone. CD4⁺ T-cell activation is dependent on two signals: (1) T-cell receptor binding to peptide-MHC on antigen-presenting cells; and (2) CD28 binding to CD80/86 on antigen-presenting cells. This interaction then leads to downstream signals that differentiate CD4⁺ T cells into effector and memory cell populations, as well as activate CD8⁺ T cells. Certain subsets of CD4⁺ T cells, called T helper cells, enable B cells to differentiate into antibody-secreting cells. An earlier T cell-centric model for the pathogenesis of RA was based on a TH1-driven paradigm, which came from studies indicating that CD4⁺ T helper (TH) cells differentiated into TH1 and TH2 subsets, each with their distinctive cytokine profiles. TH1 cells were found to mainly produce interferon γ (IFN- γ), lymphotoxin β , and tumor necrosis factor (TNF)- α , whereas TH2 cells predominately secreted interleukin (IL)-4, IL-5, IL-6, IL-10, and IL-13. In humans, naïve T cells may also be induced to differentiate into TH17 cells by exposure to transforming growth factor β (TGF- β), IL-1, IL-6, and IL-23. Upon activation, TH17 cells secrete a variety of proinflammatory mediators such as IL-17, IL-21, IL-22, TNF- α , IL-26, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Substantial evidence now exists from studies in both animal models and humans that IL-17 plays an important role not only in promoting joint inflammation but also in destroying cartilage and subchondral bone. However, therapeutic antibodies that interfere with the IL-17/IL-17 receptor pathway were not particularly effective in clinical trials for reducing joint inflammation in RA.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders The immune system has evolved mechanisms to counterbalance the potentially harmful immune-mediated inflammatory responses provoked by infectious agents and other triggers. Among these negative regulators are regulatory T (Treg) cells, which are produced in the thymus and induced in the periphery to suppress immune-mediated inflammation. They are characterized by the surface expression of CD25 and the expression of the transcription factor forkhead box P3 (FOXP3). Tregs orchestrate dominant tolerance through contact with other immune cells and secretion of inhibitory cytokines, such as TGF- β , IL-10, and IL-35. They are heterogeneous and capable of suppressing distinct classes (TH1, TH2, TH17) of the immune response, although data supporting their role in suppressing inflammation in RA are inconclusive. Cytokines, chemokines, antibodies, and endogenous danger signals bind to receptors on the surface of immune cells and stimulate a cascade of intracellular signaling events that can amplify the inflammatory response. Examples of signaling molecules in these critical inflammatory pathways include Janus kinase (JAK)/signal transducers and activators of transcription (STAT), spleen tyrosine kinase (Syk), mitogen-activated protein kinases (MAPKs), and nuclear factor- κ B (NF- κ B). These pathways exhibit significant crosstalk and are found in many cell types. Some signal transducers, such as the JAKs, are expressed in hematopoietic cells and play an important role in the inflammatory response in RA. Activated, autoreactive B cells are also important players in the chronic inflammatory process. B cells give rise to plasma cells, which, in turn, produce antibodies, including RF and ACPA. RFs may form large immune complexes inside the joint that contribute to the pathogenic process by fixing complement and promoting the release of proinflammatory cytokines and chemokines. In mouse models of arthritis, RF-containing immune complexes and ACPA-containing immune complexes synergize with other mechanisms to exacerbate the synovial inflammatory response. RA is often considered to be a macrophage-driven disease because this cell type is the predominant source of proinflammatory cytokines inside the joint. Key proinflammatory cytokines released by macrophage-like synoviocytes include TNF- α , IL-1, IL-6, IL-12, IL-15, IL-18, and IL-23. Synovial fibroblasts, the other major cell type in this microenvironment, produce the cytokines IL-1 and IL-6 as well as TNF- α . TNF- α is a pivotal cytokine in the pathobiology of synovial inflammation and has many proinflammatory effects. It upregulates adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment; activates synovial

fibroblasts; stimulates angiogenesis; promotes pain receptor sensitizing pathways; and drives osteoclastogenesis. Fibroblasts secrete matrix metalloproteinases (MMPs) as well as other proteases that are chiefly responsible for the breakdown of articular cartilage; they also promote inflammation and synovial proliferation by secreting cytokines such as IL-6, IL-1, IL-18, and GM-CSF, chemokines, and vascular endothelial growth factor. Recent studies of synovial tissue samples from patients with RA have combined histology and single-cell RNA expression data to identify distinct cell populations that drive joint inflammation. These studies reveal that synovial tissue samples can be distinguished among patients with RA by the relative abundance of myeloid cells, T cells, B cells, synovial fibroblasts, and endothelial cells and hence can be divided into different subsets. Thus far, these data highlight the importance of IFN- γ -secreting granzyme K⁺ CD8⁺ T cells, peripheral helper CD4⁺ T cells, activated stromal fibroblasts, and proinflammatory monocytes as key mediators of joint inflammation. In these studies, most of the synovial tissue samples were found to be populated by T cells, fibroblasts, and myeloid cells and had cellular phenotypes classified as predominately myeloid, T and B cell, and T cell and myeloid, while others had a paucity of immune cells and were dominated by endothelial cells and fibroblasts. Further research

along these lines will enrich our understanding of the active immune pathways in RA and may help to determine in the future if knowledge of these cellular phenotypes can be used to guide a personalized treatment approach. Osteoclast activation at the site of the pannus is closely tied to the presence of focal bone erosion. Receptor activator of nuclear factor- κ B ligand (RANKL) is expressed by stromal cells, synovial fibroblasts, and T cells. Upon binding to its receptor RANK on osteoclast progenitors, RANKL stimulates osteoclast differentiation and bone resorption. RANKL activity is regulated by osteoprotegerin (OPG), a decoy receptor of RANKL that blocks osteoclast formation. Monocytic cells in the synovium serve as the precursors of osteoclasts and, when exposed to macrophage colony-stimulating factor (M-CSF) and RANKL, fuse to form polykaryons termed preosteoclasts. These precursor cells undergo further differentiation into osteoclasts with a characteristic ruffled membrane. Cytokines such as TNF- α , IL-1, IL-6, and IL-17 can promote osteoclastogenesis by increasing the expression of RANKL inside the joint. Osteoclasts also secrete cathepsin K, a cysteine protease that degrades the bone matrix by cleaving collagen and thus contributes to generalized bone loss and osteoporosis. Increased bone loss is only part of the story in RA, as decreased bone formation plays a crucial role in bone remodeling at sites of inflammation. Recent evidence shows that inflammation suppresses bone formation. TNF- α plays a key role in actively suppressing bone formation by enhancing the expression of dickkopf-1 (DKK-1). DKK-1 is an important inhibitor of the Wnt pathway, which acts to promote osteoblast differentiation and bone formation. The Wnt system is a family of soluble glycoproteins that binds to cell-surface receptors known as frizzled (fz) and low-density lipoprotein (LDL) receptor-related proteins (LRPs) and promotes cell growth. In animal models, increased levels of DKK-1 are associated with decreased bone formation, whereas inhibition of DKK-1 protects against structural damage in the joint. Wnt proteins also induce the formation of OPG and thereby shut down bone resorption, emphasizing their key role in tightly regulating the balance between bone resorption and formation.

DIAGNOSIS The clinical diagnosis of RA is largely made by recognizing the signs and symptoms of a chronic inflammatory arthritis and the typical pattern of joint involvement, with laboratory and radiographic results providing important corroborating information. In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy (Table 370-1). The items in the newly revised criteria yield a score of 0–10, with a score of ≥ 6 fulfilling the requirements for definite RA. The new classification

TABLE 370-1 Classification Criteria for Rheumatoid Arthritis

SCORE	Joint involvement
1	large joint (shoulder, elbow, hip, knee, ankle)
2–10	large joints
1–3	small joints (MCP, PIP, thumb IP, MTP, wrists)
4–10	small joints

“ 10 joints (at least 1 small joint) Serology Negative RF and negative ACPA Low-positive RF or low-positive anti-CCP antibodies (≤ 3 times ULN) High-positive RF or high-positive anti-CCP antibodies (> 3 times ULN) Acute-phase reactants Normal CRP and normal ESR Abnormal CRP or abnormal ESR Duration of symptoms < 6 weeks ≥ 6 weeks Note: These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical

synovitis that is not better explained by another disease. A score of ≥ 6 fulfills requirements for definite RA. Abbreviations: ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal. Source: Reproduced with permission from D Aletaha et al: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 62:2569, 2010.

criteria differ in several ways from the older criteria sets. Previous classification schemes required symptoms to be present for >6 weeks. There are several conditions, including virus-related syndromes, that may cause a polyarthritis mimicking RA and be associated with transient production of RF. Such conditions usually last only 2–3 weeks. The 2010 criteria, however, do not mandate symptoms be present for >6 weeks. They also include as an item a positive test for serum ACPA, which carries greater specificity for the diagnosis of RA than a positive test for RF. About three-fourths of patients with the clinical and radiographic features of RA test positive for RF and/or ACPA (seropositive), while the remaining one-fourth of patients with RA test negative for RF and/or ACPA (seronegative). The presence of rheumatoid nodules or radiographic joint damage as items were not included as they occur only rarely in early RA. It is important to emphasize that the 2010 ACR-EULAR criteria are “classification criteria” as opposed to “diagnostic criteria” and serve to distinguish patients at the onset of disease who have a high likelihood of evolution to chronic disease with persistent synovitis and joint damage. The presence of radiographic joint erosions or subcutaneous nodules may inform the diagnosis in the later stages of the disease. The differential diagnosis for RA includes all types of acute and chronic inflammatory arthritides, many of which may be differentiated from RA based on the clinical course, pattern of joint involvement, the presence of disease in other organ systems, and ancillary laboratory studies. Patients with primary Sjögren’s syndrome whose predominate clinical manifestations are dry eyes and dry mouth often also have symptoms of polyarthralgia and may show a mild inflammatory synovitis similar to RA. Moreover, 50% of patients with primary Sjögren’s syndrome test positive for RF and, therefore, may be confused with early RA. However, most patients with primary Sjögren’s syndrome test positive for ANA and approximately two-thirds have detectable anti-Ro/SSA antibodies. Spondyloarthropathies, such as psoriatic arthritis or enteropathy-associated arthritis, may present similarly to RA and may be distinguished by the presence of sacroiliitis, other enthesopathic features, and the presence of psoriasis or inflammatory bowel disease, respectively. In elderly patients, seronegative RA may be difficult at times to distinguish from polymyalgia rheumatica (PMR), a chronic inflammatory condition of the elderly characterized by neck/shoulder girdle and lower back/hip girdle pain and stiffness (Chap. 375). While PMR may occasionally feature distal limb involvement, RA

predominately affects the wrists/hands and ankles/feet, especially at disease onset. Similarly, the relatively rare condition called remitting seronegative symmetrical synovitis with pitting edema (RS3PE) and paraneoplastic syndromes may also be confused with early RA. RS3PE is typically characterized by prominent distal limb pitting edema, which is unusual in RA, and responds promptly to treatment with low doses of prednisone. Chronic tophaceous gout may mimic severe RA in some cases, and tophi may be confused with rheumatoid nodules. Hepatitis C-related arthropathy often involves the small joints of the hands and is associated in half the cases with a positive RF, but generally not ACPA.

CHAPTER 370

Rheumatoid Arthritis LABORATORY FEATURES Patients with systemic inflammatory diseases such as RA will often present with elevated nonspecific inflammatory markers such as an ESR or CRP. Testing for serum RF and anti-cyclic citrullinated peptide (CCP) antibodies is important in differentiating RA from other poly articular diseases, although RF lacks diagnostic specificity and may be found in association with other chronic inflammatory diseases in which arthritis figures in the clinical manifestations.

IgM, IgG, and IgA isotypes of RF occur in sera from patients with RA, although the IgM isotype is the one most frequently measured by commercial laboratories. Serum IgM RF has been found in 75% of patients with RA; therefore, a negative result does not exclude the presence of this disease. It is also found in other connective tissue diseases, such as primary Sjögren's syndrome, systemic lupus erythematosus, and type II mixed essential cryoglobulinemia, as well as chronic infections such as subacute bacterial endocarditis and hepatitis B and C. Serum RF, mostly at low levels, may also be detected in 1–5% of the healthy population. The presence of serum anti-CCP antibodies has about the same sensitivity as serum RF for the diagnosis of RA. However, its diagnostic specificity approaches 95%, so a positive test for anti-CCP antibodies in the setting of an early inflammatory arthritis is useful for distinguishing RA from other forms of arthritis. There is some incremental value in testing for the presence of both RF and anti-CCP, as some patients with RA are positive for RF but negative for anti-CCP and vice versa. The presence of RF or anti-CCP antibodies also has prognostic significance, with anti-CCP antibodies showing the most value for predicting worse outcomes. Patients with RA may also have other antibodies associated with autoimmune disease. Approximately 30% of patients with RA test positive for antinuclear antibodies (ANAs), and some sera from some patients contain antineutrophil cytoplasmic antibodies (ANCA; particularly p-ANCA). However, patients with RA would not be expected to test positive for anti-MPO or anti-PR3 antibodies as they would if they had an ANCA-associated vasculitis. ■ ■ **SYNOVIAL FLUID ANALYSIS** Typically, the cellular composition of synovial fluid from patients with RA reflects an acute inflammatory state. Synovial fluid white blood cell (WBC) counts can vary widely but generally range between 5000 and 50,000 WBC/ μ L, compared with <2000 WBC/ μ L for a noninflammatory condition such as osteoarthritis. In contrast to the synovial tissue, the overwhelming cell type in the synovial fluid is the neutrophil. Clinically, the analysis of synovial fluid is most useful for confirming an inflammatory arthritis (as opposed to osteoarthritis), while at the same time excluding infection or a crystal-induced arthritis such as gout or pseudogout (Chap. 384). ■ ■ **JOINT IMAGING** Joint imaging is a valuable tool not only for diagnosing RA but also for tracking progression of any joint damage. Plain x-ray is the most common imaging modality, but it is limited to visualization of the bony structures and inferences about the state of the articular cartilage based on the amount of

joint space narrowing. MRI and ultra sound techniques offer the added value of detecting changes in the soft tissues such as synovitis, tenosynovitis, and effusions, as well as providing greater sensitivity for identifying bony abnormalities. Plain

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders FIGURE 370-5 X-ray of the right hand demonstrating features of advanced rheumatoid arthritis. This x-ray is notable for carpal crowding of the wrist (yellow arrow), loss of joint space and subluxation of the fifth metacarpophalangeal joint (green arrow), and an erosion of the fourth proximal interphalangeal joint (red arrow). radiographs are usually relied upon in clinical practice for the purpose of diagnosis and monitoring affected joints. However, in selected cases, MRI and ultrasound can provide additional diagnostic information that may guide clinical decision-making. Musculoskeletal ultrasound with power Doppler is increasingly used in rheumatology clinical practice for detecting synovitis and bone erosion. Plain Radiography Classically in RA, the initial radiographic finding is periarticular osteopenia. Practically speaking, however, this finding is difficult to appreciate on plain films and particularly their digitalized images. Other findings on plain radiographs include soft tissue swelling, symmetric joint space loss, and juxtaarticular and subchondral erosions, most frequently in the wrists and hands (MCPs and PIPs) and the feet (MTPs). In the feet, the lateral aspect of the fifth MTP is often targeted first, but other MTP joints may be involved at the same time. X-ray imaging of advanced RA may reveal signs of severe destruction, including joint subluxation and collapse (Fig. 370-5). MRI MRI offers the greatest sensitivity for detecting synovitis and joint effusions, as well as early bone and bone marrow changes. These soft tissue abnormalities often occur before osseous changes are noted on x-ray. Presence of bone marrow edema has been recognized to be an early sign of inflammatory joint disease and can predict the subsequent development of erosions on plain radiographs as well as MRI scans. Cost and availability of MRI are the main factors limiting its routine clinical use. Ultrasound Ultrasound, including power color Doppler, can detect more erosions than plain radiography, especially in easily accessible joints. It can also reliably detect synovitis, including increased joint vascularity indicative of inflammation. The usefulness of ultrasound is dependent on the experience of the sonographer; however, it does offer the advantages of portability, lack of radiation, and low expense relative to MRI, factors that make it attractive as a clinical tool (Fig. 370-6). See Videos 370-1, 370-2, and 370-3. CLINICAL COURSE The natural history of RA is complex and affected by a number of factors including age of onset, gender, genotype, phenotype (i.e., extraarticular manifestations or variants of RA), and comorbid conditions, which make for a truly heterogeneous disease. It is important to realize

FIGURE 370-6 Ultrasound demonstrating an effusion (arrow) within the metacarpophalangeal joint. (Courtesy of Dr. Ryan Jessee.) that as many as 10% of patients with inflammatory arthritis fulfilling ACR classification criteria for RA will undergo a spontaneous remission within 6 months (particularly seronegative patients). However, the vast majority of patients will exhibit a pattern of persistent and progressive disease activity that waxes and wanes in intensity over time. A minority of patients will show intermittent and recurrent explosive attacks of inflammatory arthritis interspersed with periods of disease quiescence. Finally, an aggressive form of RA may occur in an unfortunate few with inexorable progression of severe erosive joint disease, although this highly destructive course is less common in the modern treatment era. Disability, as measured by the Health Assessment Questionnaire (HAQ), shows gradual worsening over time in the face of poorly controlled disease activity and disease progression. Disability may result from both a disease

activity-related component that is potentially reversible with therapy and a joint damage-related component owing to the cumulative and largely irreversible effects of soft tissue, cartilage, and bone breakdown. Early in the course of disease, the extent of joint inflammation is the primary determinant of disability, while in the later stages of disease, the amount of joint damage is the dominant contributing factor. Previous studies have shown that more than one-half of patients with RA are unable to work 10 years after the onset of their disease; however, increased employability and less work absenteeism have been reported recently with the use of newer therapies and earlier treatment intervention. The overall mortality rate in RA is two times greater than in the general population. In particular, patients are at significantly increased risk for death due to respiratory illness, cardiovascular disease, and infection. Median life expectancy is shortened by an average of 7 years for men and 3 years for women compared with control populations. Patients at higher risk for shortened survival are those with systemic extraarticular involvement, low functional capacity, low socioeconomic status, low education, and chronic prednisone use.

TREATMENT Rheumatoid Arthritis

The amount of clinical disease activity in patients with RA reflects the overall burden of inflammation and is the variable that most influences treatment decisions. Joint inflammation is the main driver of joint damage and is the most important cause of functional disability in the early stages of disease. Several composite indices have been developed to assess clinical disease activity. The ACR 20, 50, and 70 improvement criteria (which correspond to a 20, 50, and 70% improvement, respectively, in joint counts, physician/ patient assessment of disease severity, pain scale, serum levels of

acute-phase reactants [ESR or CRP], and a functional assessment of disability using a self-administered patient questionnaire) are a composite index with a dichotomous response variable. The ACR improvement criteria are commonly used in clinical trials as an endpoint for comparing the proportion of responders between treatment groups. In contrast, the Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), and the Routine Assessment of Patient Index Data 3 (RAPID3) are continuous measures of disease activity that are used in clinical practice for tracking disease status and documenting treatment response. The identification of genetic and environmental risk factors as well as the presence of autoantibodies creates a phenotype of a person who may be at higher risk for development of RA, or “preclinical RA.” Several trials have enrolled patients meeting a definition of preclinical RA in an attempt to prevent development of disease with disease-modifying therapies approved for the treatment of RA. While some of these disease-modifying therapies may delay the development of RA compared to a placebo, no strategy has yet been successful in preventing disease. Several developments during the past two decades have changed the therapeutic landscape in RA. They include (1) the emergence of methotrexate as the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of early RA; (2) the development of novel highly efficacious biologics that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone. The medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional DMARDs; and biologic DMARDs (Table 370-2). Although disease for some patients with RA is managed adequately with a single DMARD, such as methotrexate, it calls in most cases for the use of a combination DMARD regimen that may vary in its components over the treatment course depending on fluctuations in disease activity, loss of treatment efficacy, and emergence of drug-related toxicities and comorbidities.

NSAIDS

NSAIDs were formerly viewed as the core of RA therapy, but

they are now considered to be adjunctive agents for management of symptoms uncontrolled by other measures. NSAIDs exhibit both analgesic and anti-inflammatory properties. The anti-inflammatory effects of NSAIDs derive from their ability to nonselectively inhibit cyclooxygenase (COX)-1 and COX-2. Although the results of clinical trials suggest that NSAIDs are roughly equivalent in their efficacy, experience suggests that some individuals may preferentially respond to a particular NSAID. Chronic use should be minimized due to the possibility of side effects, particularly gastritis and peptic ulcer disease and kidney injury. **GLUCOCORTICOIDS** Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1- to 2-week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5–10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy. As much as possible, chronic glucocorticoid therapy should be avoided in favor of finding an effective DMARD regimen that adequately controls the disease. Best practices minimize chronic use of low-dose prednisone therapy owing to the risk of osteoporosis and other long-term complications; however, the use of chronic prednisone therapy is unavoidable in some cases. High-dose glucocorticoids may be necessary for the treatment of severe extraarticular manifestations

of RA, such as ILD. Finally, if a patient exhibits one or a few actively inflamed joints, the clinician may consider intraarticular injection of an intermediate-acting glucocorticoid such as triamcinolone acetate. This approach may allow for rapid control of inflammation in a limited number of affected joints. Caution must be exercised to appropriately exclude joint infection as it often mimics a monoarticular RA flare.

CHAPTER 370 Osteoporosis ranks as an important long-term complication of chronic prednisone use. Based on a patient's risk factors, including total prednisone dosage, length of treatment, gender, race, and bone density, treatment with an oral (e.g., alendronate, risedronate) or parenteral (e.g., zoledronic acid) bisphosphonate may be appropriate for primary prevention of glucocorticoid-induced osteoporosis. Other agents, including denosumab and teriparatide, have also been approved for the treatment of steroid-induced osteoporosis and may be indicated in certain cases. Although prednisone use is known to increase the risk of peptic ulcer disease, especially with concomitant NSAIDs, no evidence-based guidelines recommend routine co-administration of proton pump inhibitors for gastrointestinal ulcer prophylaxis. **DMARDs** DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of ~6–12 weeks or longer. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. It was approved for the treatment of RA in 1988 and remains a benchmark for comparison with the newer disease-modifying therapies. At the dosages used for the treatment of RA, methotrexate has been shown to stimulate adenosine release from cells, producing an anti-inflammatory effect. Methotrexate is administered weekly by the oral or subcutaneous route. Folic acid is taken as co-therapy to mitigate some of methotrexate's side effects. The clinical efficacy of leflunomide, an inhibitor of pyrimidine synthesis, appears similar to that of methotrexate; it has been shown in well-designed trials to be effective for the treatment of RA as monotherapy or in combination with

methotrexate and other DMARDs. Rheumatoid Arthritis Although similar to the other DMARDs in its slow onset of action, hydroxychloroquine has not been shown to delay radiographic progression of disease and thus is not considered to be a true DMARD. In clinical practice, hydroxychloroquine is generally used for treatment of early, mild disease or as adjunctive therapy in combination with other DMARDs. It is prescribed at a dosage of 5 mg/kg of body weight or less to decrease the risk of retinal toxicity. Sulfasalazine has been shown in randomized, controlled trials to reduce joint inflammation and radiographic progression of disease. A regimen termed oral triple therapy, which is comprised of hydroxychloroquine, sulfasalazine, and methotrexate, is an effective combination regimen often used in patients with an inadequate response to treatment with methotrexate alone.

BIOLOGICALS Biologic DMARDs have revolutionized the treatment of RA over the past two decades (Table 370-2). They are protein therapeutics designed to target cytokines and cell-surface molecules. The TNF inhibitors were the first biologicals approved for the treatment of RA, but several others have come to market since their introduction in 1999. Additionally, biosimilars are agents that have been designed with the same active properties as the licensed biopharmaceutical product. Several of these biosimilars have been studied for the treatment of RA and demonstrate a similar efficacy and side-effect profile to the reference biological.

Anti-TNF Agents The development of TNF inhibitors was originally spurred by the experimental finding that TNF- α is a critical upstream mediator of joint inflammation. Five original “innovator” TNF inhibitors with various molecular designs have been approved for the treatment of RA. Three of these products are anti-TNF

TABLE 370-2 DMARDs Used for the Treatment of Rheumatoid Arthritis

DRUG	DOSAGE	SERIOUS TOXICITIES
Hydroxychloroquine	200–400 mg/d orally (≤ 5 mg/kg)	Irreversible retinal damage
Cardiotoxicity	Blood dyscrasia	PART 11
Immune-Mediated, Inflammatory, and Rheumatologic Disorders	Sulfasalazine Initial: 500 mg orally twice daily Maintenance: 1000–1500 mg twice daily	Granulocytopenia Hemolytic anemia (with G6PD deficiency)
Methotrexate	10–25 mg/week orally or SQ	Folic acid 1 mg/d to reduce toxicities Hepatotoxicity Myelosuppression Infection Interstitial pneumonitis Pregnancy category X
Leflunomide	10–20 mg/d	Hepatotoxicity Myelosuppression Infection Pregnancy category X
TNF- α inhibitors	Infliximab: 3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks. May increase dose up to 10 mg/kg every 4 weeks	↑ Risk bacterial, fungal infections Reactivation of latent tuberculosis ↑ Lymphoma risk (controversial) Drug-induced lupus Neurologic deficits
Etanercept	50 mg SQ weekly, or 25 mg SQ biweekly	As above Injection site reaction Tuberculosis screening
Adalimumab	40 mg SQ every other week	As above Injection site reaction Tuberculosis screening
Golimumab	50 mg SQ monthly	As above Injection site reaction Tuberculosis screening
Certolizumab	400 mg SQ weeks 0, 2, 4, then 200 mg every other week	As above Injection site reaction Tuberculosis screening
Abatacept	Weight based: <60 kg: 500 mg 60–100 kg: 750 mg	

100 kg: 1000 mg IV dose at weeks 0, 2, and 4, and then every 4 weeks OR 125 mg SQ weekly ↑ Risk bacterial, viral infections Anakinra 100 mg SQ daily ↑ Risk bacterial, viral infections Reactivation of latent tuberculosis Neutropenia Rituximab 1000 mg IV $\times$ 2, days 0 and 14 May repeat course every 24 weeks or more Premedicate with methylprednisolone 100 mg to decrease infusion reaction ↑ Risk bacterial, viral infections Infusion reaction Cytopenia Hepatitis B

reactivation Interleukin-6 inhibitors Tocilizumab: 4–8 mg/kg IV monthly OR 162 mg SQ every other week (<100 kg weight) 162 mg SQ every week (≥100 kg weight) Sarilumab: 200 mg SQ every other week Risk of infection Infusion reaction LFT elevation Dyslipidemia Cytopenias

OTHER COMMON SIDE EFFECTS INITIAL EVALUATION MONITORING Nausea Diarrhea Headache Rash Eye examination if >40 years old or prior ocular disease Optical coherence tomography and visual field testing every 12 months Nausea Diarrhea Headache CBC, LFTs G6PD level CBC every 2–4 weeks for first 3 months, then every 3 months Nausea Diarrhea Stomatitis/mouth ulcers Alopecia Fatigue CBC, LFTs Viral hepatitis panel CBC, creatinine, LFTs every 2–3 months Chest x-ray Alopecia Diarrhea CBC, LFTs Viral hepatitis panel CBC, creatinine, LFTs every 2–3 months Infusion reaction ↑ LFTs Tuberculosis screeningb LFTs periodically Monitor for injection site reactions Monitor for injection site reactions Monitor for injection site reactions Monitor for injection site reactions Headache Nausea Tuberculosis screening Monitor for infusion reactions Injection site reaction Headache Tuberculosis screening CBC with differential CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions Rash Fever CBC Viral hepatitis panel CBC at regular intervals Tuberculosis screening CBC and LFTs at regular intervals (Continued)

TABLE 370-2 DMARDs Used for the Treatment of Rheumatoid Arthritis DRUG DOSAGE SERIOUS TOXICITIES JAK inhibitors Tofacitinib: 5 mg orally twice daily OR 11 mg orally daily Upadacitinib: 15 mg orally daily Baricitinib: 2 mg orally daily Risk of infection LFT elevation Dyslipidemia Neutropenia Thrombosis aViral hepatitis panel: hepatitis B surface antigen, hepatitis C viral antibody. bTuberculosis screening can be performed using a Mantoux tuberculin skin test or blood interferon-gamma release assay. Abbreviations: CBC, complete blood count; DMARDs, disease-modifying antirheumatic drugs; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; LFTs, liver function tests; JAK, Janus kinase; SQ, subcutaneous. monoclonal antibodies: infliximab, a chimeric (part mouse and human) monoclonal antibody; and adalimumab and golimumab, humanized monoclonal antibodies. Certolizumab pegol, a fourth product, is a pegylated Fab' fragment of a humanized monoclonal antibody, while the other, etanercept, is a soluble fusion protein consisting of the TNF receptor 2 in covalent linkage with the Fc portion of IgG1. All of these TNF inhibitors have been shown in randomized controlled clinical trials to reduce the signs and symptoms of RA, slow radiographic progression of joint damage, and improve physical function and quality of life. Anti-TNF drugs may be used alone or in combination with background methotrexate therapy. Patients with RA who have an inadequate response to methotrexate therapy are often treated with a TNF inhibitor, usually in combination with methotrexate. Anti-TNF agents should be avoided in patients with active infection or a history of hypersensitivity to these agents and are contraindicated in patients with chronic hepatitis B infection or class III/IV congestive heart failure. A major concern is the increased risk for infection, including serious bacterial infections, opportunistic fungal infection, and reactivation of latent tuberculosis infection (LTBI). For this reason, all patients are screened for LTBI according to national guidelines with either an intradermal injection of purified protein derivative (PPD) or an IFN-γ release assay prior to starting anti-TNF therapy (Chap. 183). If positive, treatment for LTBI is given for at least 1 month prior to starting anti-TNF therapy. Anakinra Anakinra is the recombinant form of the naturally occurring IL-1

receptor antagonist. Anakinra has seen limited use for the treatment of RA because other biologic DMARDs have seen greater efficacy in practice. Abatacept Abatacept is a soluble fusion protein consisting of the extracellular domain of human CTLA-4 linked to the modified portion of human IgG. It inhibits the co-stimulation of T cells by blocking CD28-CD80/86 interactions and may also inhibit the function of antigen-presenting cells by reverse signaling through CD80 and CD86. Abatacept has been shown in clinical trials to reduce disease activity, slow radiographic progression of damage, and improve functional disability. Most patients receive abatacept in combination with a conventional DMARD. Abatacept therapy has been associated with an increased risk of infection and can inhibit a vaccine response. Rituximab Rituximab is a chimeric monoclonal antibody directed against CD20, a cell-surface molecule expressed by most mature B lymphocytes. It works by depleting B cells, which, in turn, leads to a reduction in the inflammatory response by unknown mechanisms. These mechanisms may include a reduction in autoantibodies, inhibition of T-cell activation, and alteration of cytokine production. Rituximab has been approved for the treatment of refractory RA (failure of treatment with a TNF- α inhibitor) in combination with methotrexate and has been shown to be more effective for patients with seropositive than seronegative disease. Its administration has

(Continued) OTHER COMMON SIDE EFFECTS INITIAL EVALUATION MONITORING Upper respiratory tract infections Diarrhea Headache Nasopharyngitis Tuberculosis screening CBC, LFTs, and lipids at regular intervals CHAPTER 370 Rheumatoid Arthritis been associated with mild to moderate infusion reactions, as well as an increased risk of infection. Notably, there have been rare isolated reports of a potentially lethal brain disorder, progressive multifocal leukoencephalopathy (PML), in association with rituximab therapy, although the absolute risk of this complication appears to be very low in patients with RA (~1:25,000). Most of these cases have occurred on a background of previous or current exposure to other potent immunosuppressive drugs. Studies in recent years have also demonstrated that rituximab significantly inhibits a vaccine response (e.g., response to SARS-CoV-2 vaccination). Anti-IL-6 Receptor Agents IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA, with effects on both joint inflammation and damage. IL-6 binding to its receptor activates intracellular signaling pathways that affect the acute-phase response, cytokine production, and osteoclast activation. Tocilizumab and sarilumab are both monoclonal antibodies directed against the membrane and soluble forms of the IL-6 receptor. Clinical trials attest to the clinical efficacy of these therapies for RA, both as monotherapy and in combination with methotrexate and other conventional DMARDs. Anti-IL-6 receptor agents have been associated with an increased risk of infection, neutropenia, and thrombocytopenia; the hematologic abnormalities appear to be reversible upon stopping the drug. In addition, this agent has been shown to increase LDL cholesterol. However, it is not known if this effect on lipid levels increases the risk for atherosclerotic disease. Anti-IL-6 receptor agents have also been associated with an increased rate of gastrointestinal perforation and should be avoided if possible in patients with a history of diverticulitis and a recent gastric or duodenal ulcer. TARGETED SYNTHETIC DMARDs Because treatment with conventional DMARDs and/or biologic therapies may not result in optimal disease control, other therapeutic strategies have been investigated to fill this gap. The so-called targeted synthetic DMARDs have been designed to target intracellular signaling pathways, which transduce the positive signals from cell-surface receptors activated by cytokines and other inflammatory mediators. They have an advantage over biologics in their oral formulation. JAK Inhibitors Although several different kinases have been evaluated as potential treatment targets, only inhibitors of the JAKs have demonstrated safety and efficacy for the treatment of RA. The JAK

family comprises four members (JAK1, JAK2, JAK3, and tyrosine kinase 2 [Tyk2]) and link a host of extracellular cytokine receptors with their intracellular signaling domains. They form homodimeric and heterodimeric duplexes that mediate signaling of the receptors for the common γ -chain-related cytokines IL-2, -4, -7, -9, -15, and -21, as well as IFN- γ , IL-6, IL-12, IL-23, IL-10, the type I IFNs, and the hemopoietic cytokines and growth factors. Many of these cytokines play critical roles in promoting T- and B-cell activation as well as chronic inflammation in RA.

Tofacitinib is a potent JAK1 and JAK3 inhibitor with minor inhibitory effects on JAK2 and Tyk2; baricitinib is a JAK1 and JAK2 inhibitor with moderate inhibition of Tyk2 and minimal inhibition of JAK3; and upadacitinib is a predominately selective inhibitor of JAK1. Each of the JAK inhibitors can be used as monotherapy or in combination with methotrexate. However, they are associated with an increased risk of infections, including bacterial infections and herpes zoster. Other possible side effects of these agents include elevated liver transaminases, neutropenia, increased cholesterol levels, hypertension, and elevations in serum creatinine. Recent studies have also found an increased risk of thrombosis, major adverse cardiovascular events, and malignancies in patients taking tofacitinib compared with TNF inhibitors, with the highest of these risks in the elderly.

TREATMENT OF EXTRAARTICULAR MANIFESTATIONS In general, treatment of the underlying RA favorably modifies its extraarticular manifestations, and observational studies suggest aggressive management of early disease can potentially prevent their occurrence in established disease. The treatment of patients with RA-ILD, however, can be particularly challenging because some of the DMARDs used for the treatment of RA are also associated with pulmonary toxicity, such as methotrexate and leflunomide. RA-ILD is often treated with high doses of corticosteroids and adjunctive immunosuppressive agents, such as azathioprine, mycophenolate mofetil, or rituximab.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders

APPROACH TO THE PATIENT Rheumatoid Arthritis The treatment of RA adheres to the following principles and goals: (1) early, aggressive therapy to prevent joint damage and disability; (2) frequent modification of DMARD therapy to achieve treatment goals with utilization of combination therapy where appropriate; (3) individualization of DMARD therapy in an attempt to maximize response and minimize side effects; (4) minimal use of long-term glucocorticoid therapy; and (5) achieving, whenever possible, low disease activity or clinical remission. A considerable amount of evidence supports this intensive treatment approach and has been termed “treat to target,” with a target of achieving low disease activity or remission. As mentioned earlier, methotrexate is the DMARD of first choice for initial treatment of moderate to severe RA. Failure to achieve adequate improvement with methotrexate therapy calls for a change in DMARD therapy, usually a transition to an effective combination regimen. Effective combinations include methotrexate, sulfasalazine, and hydroxychloroquine (oral triple therapy); methotrexate and leflunomide; and methotrexate plus a biological. The combination of methotrexate and an anti-TNF agent, for example, has been shown in randomized controlled trials to be superior to methotrexate alone, not only for reducing signs and symptoms of disease but also for retarding the progression of structural joint damage. Predicting which patients are at higher risk for developing radiologic joint damage is imprecise at best, although some factors such as an elevated serum level of acute-phase reactants, high burden of joint inflammation, and the presence of erosive disease are associated with increased likelihood of developing structural injury. In 2021, the ACR updated their guidelines for the treatment of RA. These recommendations do not make a distinction between the treatment of patients with early (<6 months of disease duration) or established disease and highlight the use of a treat-to-target

approach and the need to switch or add therapies for worsening or persistent moderate/high disease activity. For example, in patients with early RA who have persistent moderate/high disease activity despite DMARD monotherapy, providers should consider escalation to combination DMARD therapy or switching to an anti-TNF +/- methotrexate or a non-TNF biologic +/- methotrexate. Since a more intensive initial approach (e.g., combination DMARD

therapy) has been shown to produce superior long-term outcomes compared with starting methotrexate alone, the usual approach is to begin with methotrexate and, in the absence of an adequate therapeutic response, rapidly step up (e.g., after 3–6 months) to a combination of conventional DMARDs or add an anti-TNF or non-TNF biological agent. Some patients may not respond to an anti-TNF drug or may be intolerant of its side effects. Initial responders to an anti-TNF agent who later experience worsening of their condition may benefit from switching to another anti-TNF agent or an alternative biological with a different mechanism of action. Indeed, some studies suggest that switching to an alternative biological such as abatacept is more effective than switching to another anti-TNF drug. Unacceptable toxicity from an anti-TNF agent may also call for switching to another biological or targeted synthetic DMARD with a different mechanism of action or a conventional DMARD regimen. Studies have also shown that oral triple therapy (hydroxychloroquine, methotrexate, and sulfasalazine) may be used effectively for the treatment of early RA. Treatment may be initiated with methotrexate alone and, lacking an adequate treatment response, followed within 6 months by a step-up to oral triple therapy. A clinical state defined as low disease activity or remission is the optimal goal of therapy, although most patients never achieve complete remission despite every effort to achieve it. Composite indices, such as the Disease Activity Score-28 (DAS-28), are useful for classifying states of low disease activity and remission; however, they are imperfect tools due to the limitations of the clinical joint examination in which low-grade synovitis may escape detection. Complete remission has been stringently defined as the total absence of all articular and extraarticular inflammation and immunologic activity related to RA. However, evidence for this state can be difficult to demonstrate in clinical practice. In an effort to standardize and simplify the definition of remission for clinical trials, the ACR and EULAR developed two provisional operational definitions of remission in RA (Table 370-3). A patient may be considered in remission if the patient (1) meets all the clinical and laboratory criteria listed in Table 370-3 or (2) has a composite SDAI score of <3.3. The SDAI is calculated by taking the sum of a tender joint and swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and CRP (in mg/dL). This definition of remission does not consider the possibility of subclinical synovitis or that damage alone may produce a tender or swollen joint. Ignoring the semantics of these definitions, the aforementioned remission criteria are nonetheless useful for setting a level of disease control that will likely result in minimal or no progression of structural damage and disability. With an early, aggressive approach to treatment, a significant number of patients who reach remission may have a reduction in treatment without an increased risk of flare or loss of remission. However, complete withdrawal of DMARD therapy during established disease almost invariably leads to a relapse.

TABLE 370-3
ACR/EULAR Provisional Definition of Remission in Rheumatoid Arthritis

At any time point, patient must satisfy all of the following:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- C-reactive protein ≤ 1 mg/dL
- Patient global assessment ≤ 1 (on a 0–10 scale) OR

At any time point, patient must have a Simplified Disease Activity Index score of ≤ 3.3

Abbreviations: ACR, American College of Rheumatology; EULAR, European League Against Rheumatism. Source: Reproduced with permission from DT Felson et al; American College of Rheumatology/European League Against

Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 63:573, 2011.

PHYSICAL ACTIVITY AND ASSISTIVE DEVICES In principle, all patients with RA should receive a prescription for exercise and physical activity. The ACR has developed guidelines for integrative interventions to accompany disease-modifying therapy and includes evidence-based recommendations for diet and exercise. Dynamic strength training, community-based comprehensive physical therapy, and physical-activity coaching (emphasizing achieving 150 min of moderate-to-vigorous physical activity per week) have all been shown to improve muscle strength and perceived health status, as well as improve DAS-28 scores and inflammatory markers. Foot orthotics for painful valgus deformity decrease foot pain and may reduce disability and functional limitations. Judicious use of wrist splints can also decrease pain; however, their benefits may be offset by decreased dexterity and variably curb grip strength.

SURGERY Surgical procedures may improve pain and disability in RA with varying degrees of reported long-term success—most notably for the hands, wrists, and feet. For large joints, such as the knee, hip, shoulder, or elbow, the preferred option for advanced joint disease may be total joint arthroplasty. A few surgical options exist for dealing with the smaller hand joints. Silicone implants are the most common prosthetic for MCP arthroplasty and are generally implanted in patients with severe decreased arc of motion, marked flexion contractures, MCP joint pain with radiographic abnormalities, and severe ulnar drift. Arthrodesis and total wrist arthroplasty are reserved for patients with severe disease who have substantial pain and functional impairment. Numerous surgical options exist for correction of hallux valgus in the forefoot, including arthrodesis and arthroplasty, as well as primarily arthrodesis for refractory hindfoot pain.

OTHER MANAGEMENT CONSIDERATIONS

Pregnancy Up to 75% of female RA patients will note overall improvement in symptoms during pregnancy but they will often flare shortly after delivery. Flares during pregnancy are generally treated with low doses of prednisone. Hydroxychloroquine and sulfasalazine are probably the safest DMARDs to use during pregnancy, although anti-TNF agents are generally accepted to be safe in this setting. However, current guidelines call for anti-TNF drugs to be discontinued during the third trimester of pregnancy. Methotrexate and leflunomide therapy are contraindicated during pregnancy due to their teratogenicity in animals and humans. The experience with other biologic agents, such as abatacept, anti-IL-6 receptor antibodies, rituximab, and JAK inhibitors has been insufficient to make specific recommendations for their use during pregnancy and are discontinued at conception. Active inflammatory disease is associated with worse pregnancy outcomes, and thus, controlling disease activity remains a priority.

Elderly Patients RA presents in up to one-third of patients after the age of 60; however, older individuals may receive less aggressive treatment due to concerns about increased risks of drug toxicity. Studies suggest that conventional DMARDs and biological agents are equally effective and safe in younger and older patients (with the possible exception of JAK inhibitors). Due to comorbidities, many elderly patients have an increased risk of infection. Aging also leads to a gradual decline in renal function that may raise the risk for side effects from NSAIDs and some DMARDs, such as methotrexate. Renal function must be taken into consideration before prescribing methotrexate, which is mostly cleared by the kidneys. To reduce the risks of side effects, methotrexate doses may need to be adjusted downward for the drop in renal function that usually comes with the seventh and eighth decades of life.

GLOBAL CHALLENGES Developing countries are finding an increase in the incidence of noncommunicable, chronic diseases such as diabetes, cardiovascular disease, and RA in the face of ongoing poverty, rampant infectious disease, and poor access to modern health care facilities. In

these areas, patients

tend to have a greater delay in diagnosis and limited access to specialists and, thus, greater disease activity and disability at presentation. In addition, infection risk remains a significant issue for the treatment of RA in developing countries because of the immunosuppression associated with the use of glucocorticoids and most DMARDs. For example, in some developing countries, patients undergoing treatment for RA have a substantial increase in the incidence of tuberculosis, which demands the implementation of far more comprehensive screening practices and liberal use of isoniazid prophylaxis than in developed countries. The increased prevalence of hepatitis B and C, as well as human immunodeficiency virus (HIV), in these developing countries also poses challenges. Reactivation of viral hepatitis has been observed in association with some of the DMARDs, such as rituximab. Also, reduced access to antiretroviral therapy may limit the control of HIV infection and therefore the choice of DMARD therapies.

CHAPTER 370 Rheumatoid Arthritis Despite these challenges, one should attempt to initiate early treatment of RA in the developing countries with the resources at hand. Hydroxychloroquine, sulfasalazine, and methotrexate are all reasonably accessible throughout the world where they can be used as both monotherapy and in combination with other drugs. The availability of biological agents is increasing in the developed countries as well as in other areas around the world, although their use is limited by high cost; national protocols restrict their use, and concerns remain about the risk for opportunistic infections. SUMMARY Improved understanding of the pathogenesis of RA and its treatment has dramatically revolutionized the management of this disease. The outcomes of patients with RA are vastly superior to those of the prebiologic modifier era; more patients than in years past are able to avoid significant disability and continue working, albeit with some job modifications. The need for early and aggressive treatment of RA as well as frequent follow-up visits for monitoring of drug therapy has implications for our health care system. Primary care physicians and rheumatologists must be prepared to work together as a team to implement a treat-to-target approach with the goal of reaching remission or low disease activity. In many settings, rheumatologists have reengineered their practice in a way that places high priority on consultations for any new patient with early inflammatory arthritis. The therapeutic regimens for RA are becoming increasingly complex with the rapidly expanding armamentarium. Patients receiving these therapies must be carefully monitored by both the primary care physician and the rheumatologist to minimize the risk of side effects and identify quickly any complications of chronic immunosuppression. Also, prevention and treatment of RA-associated conditions such as ischemic heart disease and osteoporosis will likely benefit from a team approach owing to the value of multidisciplinary care. Research will continue to search for new therapies with superior efficacy and safety profiles and investigate treatment strategies that can bring the disease under control more rapidly and nearer to remission. However, prevention and cure of RA will likely require new breakthroughs in our understanding of disease pathogenesis. Several prevention trials in RA are currently underway and focus on a variety of prevention strategies in individuals who have serologic and/or clinical features at higher risk than the general population for developing RA. Equally important is the identification of predictive biomarkers in RA that will enable a personalized approach to DMARD therapy, a foreseeable goal in the future that will take advantage of the advances in technology and scientific understanding of the disease. ■ ■ FURTHER READING Aletaha D, Smolen JS: Diagnosis and management of rheumatoid arthritis: A review. JAMA 320:1360, 2018. Catrina AI et al: Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. Nat Rev Rheumatol 13:79, 2017. Erickson AR et al: Clinical features

of rheumatoid arthritis, in Kelley and Firestein's Textbook of Rheumatology, 10th ed. Firestein GS et al (eds). Philadelphia, Elsevier, 2017, pp 1167–1186.

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