

Rheumatoid Arthritis

A. Clinical and Laboratory Manifestations

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- Rheumatoid arthritis affects all ethnic groups, with females 2.5 times more likely than males to develop the disease and an overall prevalence of 1% to 2% of the population.
- Most common mode of onset is insidious fatigue, morning stiffness, and joint pain and swelling involving small distal joints [wrists, metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP)] in symmetrical fashion.
- In most cases, rheumatoid arthritis is a chronic progressive disease that, if left untreated, can cause joint damage and disability. Factors that predict poor outcome include severity of disease, seropositivity, low socioeconomic and educational status, and poor functional status.
- Physical findings are most notable for joint-centered swelling, deformities, and painful or reduced joint motion. Extra-articular disease occurs in seropositive patients and includes rheumatoid nodules, Sjögren's syndrome, interstitial lung disease, and vasculitis.
- Laboratory tests that support a diagnosis of rheumatoid arthritis include elevated erythrocyte sedimentation rate and C-reactive protein, positive rheumatoid factor, positive anti-cyclic citrullinated peptide (CCP) antibody. Further evidence of chronic inflammation includes anemia and hypoalbuminemia. Radiographs may reveal periarticular osteoporosis, joint space narrowing, erosions, and deformities. Magnetic resonance imaging and ultrasound may be more sensitive in early disease.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects all ethnic groups throughout the world. Females are 2.5 times more likely to be affected than males. The onset of disease can occur at any age but peak incidence occurs within the fourth and fifth decades of life. The average annual incidence of RA in the United States is 0.5 per 1000 persons per year (1). The overall prevalence of RA is 1% to 2%, and it steadily increases to 5% in women by the age of 70 (2). However, there are differences in prevalence rates of RA in various ethnic groups, ranging from 0.1% in rural Africans to 5% in Pima or Chippewa Indians (3). Many factors contribute to the risk of developing RA and are reviewed in the following chapter (see Chapter 6B).

PATIENT HISTORY

A detailed history of the articular symptoms is of the utmost importance, with particular focus on the mode of onset (gradual vs. acute), the pattern of joints

involved, and any variance in symptoms according to time of day. It is important to remember that RA is a systemic disease and individuals may therefore present with symptoms such as fever, weight loss, and fatigue; however, joint symptoms are usually the most prominent.

Most commonly, the onset of symptoms of joint pain and swelling is insidious, occurring over weeks to months (4). However, a minority of patients may present with an abrupt explosive onset polyarthritis. Still others may present with transient self-limited episodes of mono- or polyarthritis lasting days to weeks. This presentation is known as *palindromic rheumatism*. Approximately 50% of patients with palindromic rheumatism will go on to develop (i.e., fulfill criteria for) RA, and only 15% remain symptom-free after 5 years. Occasionally RA may present as a monoarthritis; however, infectious and crystalline etiologies should always be ruled out first when inflammation affects a single joint.

Rheumatoid arthritis is the most common form of inflammatory arthritis that affects diarthrodial joints. In

early disease, the wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints of the fingers, interphalangeal joints of the thumbs, and metatarsophalangeal (MTP) joints are most commonly affected. As the disease progresses, larger joints such as the ankles, knees, elbows, and shoulders frequently become affected. In contrast, involvement of the temporomandibular and sternoclavicular joints and cervical spine are relatively uncommon, and the distal interphalangeal (DIP) joints and thoracolumbar spine are nearly always spared.

Joint involvement is classically symmetrical in nature, and morning stiffness lasting more than an hour is a hallmark symptom of RA. Frequently patients with newly diagnosed RA arise from bed 1 to 2 hours earlier than usual to allow time in order to loosen up, and will often describe the need for a warm shower or for soaking their hands in warm water in order to enhance early morning function. Pain with turning door knobs, opening jars, and buttoning shirts is commonly reported due to pain and swelling in the wrists and small joints of the hands. Pain in the ball of the foot (metatarsalgia) upon arising from bed, and widening of the forefoot necessitating an increase in shoe size, are frequently reported and are due to inflammation of the metatarsophalangeal joints. Neck pain and stiffness tend to occur later in disease and may signal tenosynovitis of the transverse ligament of C1, which stabilizes the odontoid process of C2. The symmetry, bilaterality, and predilection for small joints (especially early in disease) are incorpo-

rated into the Revised 1987 American Rheumatism Association (now the American College of Rheumatology) Criteria for the classification of RA (Table 6A-1).

In addition to articular symptoms, patients with early RA frequently have constitutional symptoms such as low grade fevers, fatigue, malaise, myalgias, decreased appetite, and weight loss that are due to systemic inflammation. In some individuals, constitutional symptoms may even overshadow the articular symptoms. Organ involvement other than the joints tends to occur in longstanding disease and includes firm nontender bumps (rheumatoid nodules) that occur most commonly on the elbows, Achilles tendons, and fingers; shortness of breath or chest pain due to pleuropulmonary involvement; orbital redness and pain due to scleritis; and dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) due to secondary Sjögren's syndrome. Extra-articular symptoms are present in approximately 40% of RA patients. Other organ systems involved will be described later in this chapter.

In most cases, RA is a chronic progressive disease that, if left untreated or inadequately treated, can cause extensive joint damage and chronic pain. A number of prognostic variables that predict a poor outcome have been identified and include female sex, strong family history, human leukocyte antigen-DR4 cluster susceptible genes (the so-called shared epitopes; see Chapter 6B), a high number of swollen/tender joints, a high score on a patient-rated instrument for measuring disability (the Health Assessment Questionnaire or HAQ),

TABLE 6A-1. THE 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF RHEUMATOID ARTHRITIS (TRADITIONAL FORMAT).^a

CRITERION	DEFINITION
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in item 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

SOURCE: From *Arthritis and Rheumatism*, 1988;31:315–324, with permission.

^aFor classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probably rheumatoid arthritis is not to be made.

high titer of rheumatoid factor (RF), high titer of anti-cyclic citrullinated peptide (anti-CCP) antibodies, low socioeconomic status, low educational status, psychosocial problems, and the presence of erosions on joint radiographs. Several studies have demonstrated the highest predictor of disability at 5 years after diagnosis to be a high score on the HAQ at 1 year after initial diagnosis. Additional predictors of poor outcomes include elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), persistently high scores on the HAQ, and persistent pain.

PHYSICAL EXAMINATION

Patients with suspected or confirmed RA should undergo a thorough initial physical exam to gauge the extent of articular and extra-articular involvement. Patients should be followed every 2 to 4 months henceforth to monitor disease activity and response to treatment, the frequency depending upon the severity of the disease and the medication regimen.

Joint Examination

Not surprisingly, the articular manifestations of RA are the most common findings on physical exam. Symmetrical swelling and tenderness of the joints is invariably observed. Careful palpation of the joint line is necessary in order to feel joint space fullness (swelling) and synovial boggy in order to differentiate those features from joint enlargement secondary to the bony hypertrophy (osteophytes) of primary or secondary osteoarthritis. Frank synovitis can sometimes be subtle and difficult to confirm early on but, as the disease progresses,



FIGURE 6A-1

Swelling of the proximal interphalangeal joints in a patient with early rheumatoid arthritis. (From the ACR slide collection on the rheumatic diseases, 3rd ed. Slide 17 (#9105020), with permission of the American College of Rheumatology.)



FIGURE 6A-2

Ulnar deviation and subluxation of the metacarpophalangeal joints are present in the hand on the left. Muscle atrophy is also evident in the dorsal musculature of both hands. (From the ACR slide collection on the rheumatic diseases, 3rd ed. Slide 19 (#9105030), with permission of the American College of Rheumatology.)

warmth, mild erythema, and swelling of the joints becomes more apparent. Joint swelling is usually confined within the joint capsule (in contrast to gout, e.g., which can also cause considerable periarticular edema). It is important to record the location, symmetry, and degree of swelling in each joint at the initial evaluation, and to repeat this examination at subsequent visits in order to gauge response to treatment. The examiner should also identify the joints that are painful on active and/or passive motion, the range of motion of each joint, and any deformities of the joints. The presence of joint swelling is indicative of active synovitis, whereas joint deformity, decreased range of motion, malalignment, or frank dislocation is indicative of joint damage.

Fusiform swelling of the proximal interphalangeal joints (PIP) is one of the earliest findings (Figure 6A-1), whereas deformities of the hands occur later in disease and include ulnar deviation of the fingers, dorsal subluxation of the MCP joints, and hyperextension (Swan neck) or hyperflexion (boutonniere deformity) at the proximal interphalangeal joints (Figure 6A-2). Swelling of the wrists and elbows is common and is easily palpable as both joints are superficial. Loss of extension at the elbows and wrists may result from active synovitis or from loss of cartilage; treatment should restore extension in the former, but not the latter instance. Compressive ulnar neuropathy may develop as a complication of synovitis in the elbow, whereas compressive median neuropathy (carpal tunnel syndrome) can result from synovitis in the wrist. Thus, a careful neurologic examination is important if sensory–motor symptoms are elicited during the history taking.

Synovitis in the shoulder is more difficult to assess by physical examination because the joint is deep and the

joint capsule is not very distensible. If there is a complete tear in the rotator cuff, an effusion in the glenohumeral joint may extravasate into the subacromial space and become more visible. Painful synovitis in the shoulder can result rather rapidly in loss of range of motion due to contracture of the joint capsule and should be aggressively and proactively treated. Hip involvement in RA occurs in only 20% of patients. This joint, like the shoulder, is deep and therefore difficult to palpate or visualize on physical exam; thus, it is particularly important to ask about symptoms. Synovitis in the hip typically causes groin, thigh, buttock, low back, or referred ipsilateral knee pain, but early hip involvement may be asymptomatic. Knee involvement is quite common in RA and effusions are easily detected on physical exam. Large knee effusions may herniate posteriorly, creating a popliteal (Baker's) cyst that can dissect or rupture into the calf, causing calf pain, swelling, pitting edema, and bruising around the ankle (the so-called crescent sign). These symptoms may also be suggestive of a deep venous thrombosis but ultrasonography can differentiate the two entities. Synovitis in the ankle may be due to inflammation in the tibiotalar joint (which mediates flexion and extension) or in the joints of the hind foot (which mediate inversion and eversion of the ankle). Range of motion of the tibiotalar joint is usually fairly well preserved early on, while diminished inversion and eversion are more common. Synovial hypertrophy in the ankle can compress the tarsal tunnel, causing a compressive neuropathy. Tenosynovitis and frank rupture of the posterior tibialis tendon (inferomedial to the medial malleolus) is common in patients with RA, resulting in disabling heel valgus and chronic pain. Physical examination of the MTPs in early disease reveals tenderness, a widened and puffy forefoot, and frequently splaying of the toes. In more chronic disease, dorsal subluxation of the MTPs resulting in cock-up toe deformities, and hallux valgus (bunion) are commonly seen.

Early symptoms of cervical spine involvement consist primarily of neck stiffness due to tenosynovitis of the transverse ligament of C1, which stabilizes the odontoid process of C2. With persistent inflammation, erosion of the odontoid process and/or attrition and rupture of the transverse ligament may occur, leading to cervical myelopathy. The amount of neck pain does not correlate with the severity of myelopathy. Therefore, a careful neurologic exam is helpful in uncovering significant myelopathy as abnormalities of cervical spine joints are neither visible nor palpable.

Extra-Articular Examination

Because extra-articular manifestations can be seen in almost 50% of all RA patients at some point during the course of their illness (Table 6A-2) (5), an organ-specific evaluation should be done periodically and in response

TABLE 6A-2. ORGAN SYSTEMS INVOLVED IN RHEUMATOID ARTHRITIS.

Skin	Rheumatoid nodules (25%–50%)
Hematologic	Normocytic normochromic anemia (25%–30%), thrombocytosis, thrombocytopenia, ^a lymphadenopathy ^a
Felty's syndrome	Splenomegaly with neutropenia, large granular lymphocytes, thrombocytopenia ^a
Hepatic	Nonspecific transaminitis
Pulmonary	Pleural thickening, pleural effusions, pulmonary nodules, diffuse interstitial lung disease, BOOP, Caplan's syndrome, cricoarytenoid arthritis (pulmonary arteritis, PAH, shrinking lung ^a)
Cardiac	Pericarditis, accelerated atherosclerotic disease, valvulitis ^a
Ophthalmologic	Keratoconjunctivitis sicca (10%–15%), episcleritis, scleritis, uveitis, ^a ulcerative keratitis ^a
Neurologic	Peripheral entrapment neuropathy, cervical myelopathy due to cervical spine subluxation
Muscular	Muscle atrophy, inflammatory myositis ^a
Renal	Low grade membranous glomerular nephropathy, reactive amyloid
Vascular	Small vessel vasculitis, systemic vasculitis ^a

^aLess than 5%.

Percentage range of rheumatoid arthritis patients reported to have this organ system involvement is presented in parentheses.

to new symptoms. The most common extra-articular manifestation of RA is Sjögren's syndrome, manifested by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), and occurring in approximately 35% of patients. Rheumatoid nodules are also relatively common, with a reported frequency of approximately 25%. Rheumatoid nodules develop over pressure areas of the body such as the elbows, Achilles tendons, fingers, scalp, and ischial tuberosities (Figure 6A-3). The nodules are firm, nontender, and are frequently adherent to the underlying periosteum. Nodules are usually associated with seropositivity for rheumatoid factor. Up to 50% of RA patients will have pleural thickening on autopsy, but this is usually asymptomatic. Pleural effusions and pleurisy can be bilateral in up to 25% of the cases. The pleural fluid typically exhibits a low to modestly elevated white blood cell count, low glucose, high lactate dehydrogenase, and high protein concentration. Up to 30% of RA patients will have parenchymal lung disease including pulmonary nodules (usually asymptomatic)

**FIGURE 6A-3**

A large subcutaneous nodule is located on the extensor surface of the forearm near the elbow. (From the ACR slide collection on the rheumatic diseases, 3rd ed. Slide 37 (#9105190), with permission of the American College of Rheumatology.)

and/or diffuse interstitial lung disease that resembles idiopathic pulmonary fibrosis, obliterative bronchiolitis, bronchiectasis, or bronchiolitis obliterans organizing pneumonia (BOOP). From a cardiac standpoint, pericarditis is the most common manifestation of RA and, as with pleural disease, is generally asymptomatic and found on autopsy. Patients with RA also have a higher incidence of fatal and nonfatal cardiovascular events (myocardial infarction and stroke) than the general population, presumably due to accelerated atherosclerosis from chronic systemic and/or vascular inflammation. Hematologically, most RA patients are anemic. The most common cause is due to inflammation-induced anemia of chronic disease but iron deficiency anemia due to gastrointestinal blood loss from nonsteroidal anti-inflammatory agents also occurs (see Chapter 41). Small vessel vasculitis is relatively uncommon and is generally restricted to the digits and nailfold areas but may also cause peripheral neuropathy and/or mononeuritis multiplex presenting as wrist or foot drop.

LABORATORY FINDINGS

Routine laboratory studies at baseline are important in assessing the degree of systemic inflammation, in ruling out other potential confounding conditions, and in guiding the use of therapies that have known organ-specific toxicities. These should include a comprehensive metabolic panel, a complete blood count with differential, and inflammatory biomarkers such as the ESR and/or C-reactive protein. The serum electrolytes, liver function, and renal function are usually normal in patients with RA. Abnormal liver function tests usually signal the presence of a concomitant disease process

that may limit the use of hepatically cleared medications such as methotrexate or leflunomide. Likewise, renal insufficiency will preclude the use of nonsteroidal anti-inflammatory medications. In some individuals, high levels of systemic inflammation are associated with depressed hepatic synthesis of albumin (hypoalbuminemia) and increased gamma globulin production by B cells (hypergammaglobulinemia), leading to elevated serum levels of nonalbumin protein (so-called protein gap or gamma gap). It is important in these cases to rule out a monoclonal gammopathy. Most often in RA a broad-based polyclonal increase in gamma globulins will be observed on serum protein electrophoresis. Approximately 25% of RA patients will have a normocytic normochromic anemia as a result of chronic inflammation. If iron deficiency anemia is found, further workup is warranted to evaluate for gastrointestinal blood loss, especially if the patient chronically uses nonsteroidal anti-inflammatory medications. Rarely, RA patients may exhibit leucopenia or thrombocytopenia, which can be due to Felty's syndrome (splenomegaly and neutropenia associated with longstanding severe RA) or due to medications.

The most commonly used inflammatory biomarkers in clinical practice are the ESR and CRP. These markers are usually, but not always, elevated in RA patients with active disease and decline with treatment. Thus, the two inflammatory markers can be followed along with the patients' symptoms and joint examination to monitor disease activity over time. High ESR and CRP at the onset of disease are predictive of more aggressive disease and potentially worse prognosis.

In addition to the routine bloodwork discussed above, two autoantibodies should be assessed in patients suspected of having RA. These are the RF and anti-CCP antibodies. RFs are antibodies against the Fc portion of IgG and can be of any immunoglobulin subclass (IgA, IgG, and IgM) but are most commonly IgM. The cutoff value for a positive RF varies depending on the methodology used in the local laboratory, but a common cutoff point is greater than 45 IU/mL by enzyme-linked immunoabsorbent assay (ELISA) or laser nephelometry, or greater than a titer of 1:80 by latex fixation. Similarly, the cutoff point for a positive anti-CCP test varies according to the assay used, but greater than or equal to 80 IU/mL is commonly used.

Rheumatoid factor is detectable during the course of disease in approximately 75% to 85% of patients with RA. Approximately 50% are positive in the first 6 months of illness and 85% become positive over the first 2 years. A low level of RF can also be associated with a number of other chronic inflammatory infectious and noninfectious conditions as well (such as bacterial endocarditis, hepatitis C with cryoglobulinemia, aging, primary biliary cirrhosis), whereas a high level of RF is more likely indicative of RA. In RA patients, high levels

of RF are also predictive of more aggressive erosive articular disease and poorer long-term function, and are associated with more extra-articular disease such as rheumatoid nodules and lung involvement. The sensitivity and specificity of RF for the diagnosis of RA are roughly 66% and 82%, respectively.

Anti-cyclic citrullinated peptide antibodies are also found in the sera of many patients with RA and are directed against the citrullinated residues of proteins. Citrulline is a non-naturally occurring amino acid generated by deimination of arginine residues on proteins by enzymes called *peptidylarginine deiminases*. Deiminated recombinant fillagrin protein in cyclic form is a particularly useful substrate to detect these auto antibodies. The sensitivity of the anti-CCP antibody test for RA is similar (70%), but specificity is superior (95%) to RF. Moreover, 35% of patients with a negative RF at presentation will test positively for anti-CCP antibody (6). Thus, diagnostic yield is enhanced by measuring both RF and anti-CCP in a patient suspected of having RA. Like RF, the higher the level of anti-CCP antibody, the higher the correlation with erosive joint disease, functional disability, and extra-articular disease.

Interestingly, anti-CCP and RF have been demonstrated in sera up to 10 years *before* the onset of articular symptoms in some patients who later develop RA, and anti-CCP antibodies appear somewhat earlier than RF (Figure 6A-4) (7). This important observation has potential implications for screening individuals who are at high risk for developing RA, as well as the potential for instituting preventive therapy in the preclinical stage of disease. These types of innovative approaches are under discussion in academic centers.

A small portion of RA patients will remain seronegative throughout the course of their disease. Antinuclear antibody (ANA) can be present in 20% to 30% of patients with RA. ANA is more common in RA patients

with high titer RF and extra-articular manifestations of the disease. In contrast to systemic lupus erythematosus, in which complement levels are low, complement levels in RA are usually normal or increased because complement is an acute phase reactant.

Synovial fluid analysis can also be useful in the assessment of patients suspected of having RA. Although there is no pathognomonic finding in RA, analysis of the synovial fluid is useful to rule out infectious and crystalline processes. RA patients are at an increased risk of developing septic joints (streptococcal and staphylococcal infection most commonly), which can be diagnosed based on Gram stain and culture of the synovial fluid. A total white blood cell count in the synovial fluid above 2000 cells/mm³ is indicative of an inflammatory process. A total white blood cell count greater than 50,000 cells/mm³ should be worrisome for an infectious process. The differential on the white blood cell count in the rheumatoid joint (whether infected or not) usually demonstrates a neutrophilic predominance. The presence of crystals or bacteria in the synovial fluid speak to an alternate diagnosis. Synovial biopsy is not routinely recommended unless a chronic infectious process such as tuberculosis is suspected.

RADIOLOGICAL FINDINGS

Radiographic abnormalities are very helpful in the diagnosis and treatment of RA. The earliest change on radiographs of the small joints of the hands and feet is periarticular osteopenia; however, this is variable, non-specific, and nondiagnostic. More typical changes of RA are juxta-articular bony erosions and symmetrical joint space narrowing. These changes can be evident in the first 6 to 12 months of disease and accumulate over time if effective control of disease activity is not achieved.

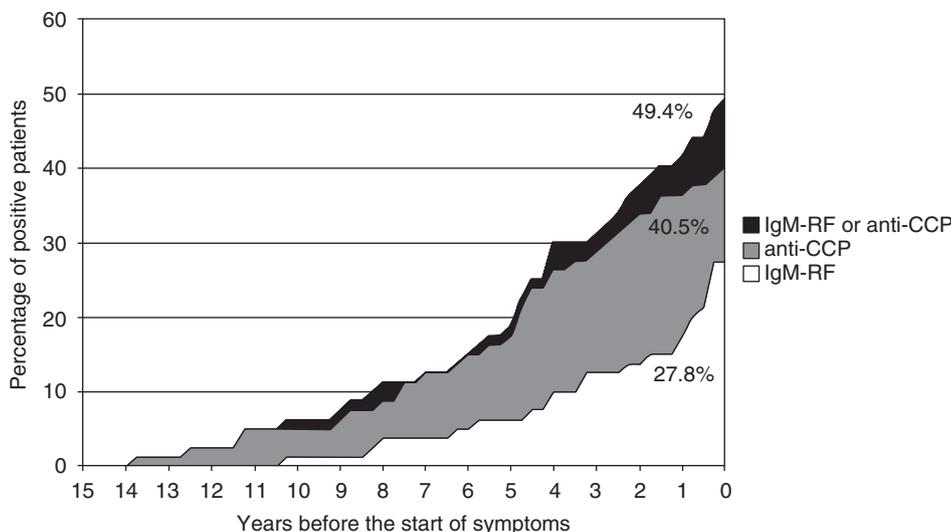


FIGURE 6A-4

Cumulative percentages of patients with one or more positive test results for IgM rheumatoid factor (IgM-RF), anti-cyclic citrullinated peptide (anti-CCP), and IgM-RF and/or anti-CCP before the onset of symptoms of rheumatoid arthritis. (From Nielen M, van Schaardenburg D, Reesink H, et al. *Arthritis Rheum* 2004;50:380–386, by permission of *Arthritis and Rheumatism*.)

Erosions typically appear at the margins of the joints, both medially and laterally, and on both apposing bones. Late radiographic findings include subluxation and loss of joint alignment, due not only to bone and cartilage destruction, but also due to laxity or frank rupture of the ligaments and tendons surrounding the joint. Radiographs in advanced disease may also show degenerative changes such as osteophytes. While not specific for RA, the findings of erosions, symmetric joint space narrowing, and/or subluxation indicate the presence of an inflammatory arthritis that requires urgent assessment and treatment. Radiographs of the hands, wrists, and feet should be obtained at baseline in patients with RA, and can be repeated periodically to ensure that additional damage is not occurring in the face of apparently effective treatment. Radiographs of the hands, feet, and wrists are more informative for following disease progression than radiographs of large joints because of the numerous joints available for assessment; furthermore, because the bone is thinner in these joints, erosions are identified earlier and visualized more easily than in larger joints such as the knees.

Magnetic resonance imaging (MRI) and ultrasound have proven to be more sensitive methods for detecting early joint erosions; in addition, because these methods also image soft tissues, inflammation (tenosynovitis) and integrity (rupture) of the tendons can be evaluated, and cartilage volume can be measured by MRI. In patients suspected of having early RA in whom the articular exam is particularly difficult (e.g., in the obese individual), MRI can also be very helpful in confirming the presence of synovial effusion and hypertrophy. MRI and ultrasound has largely replaced arthrography, particularly for confirmation of ruptured popliteal cysts in the knee.

DIFFERENTIAL DIAGNOSIS

A comprehensive initial evaluation of the patient, including demographic characteristics, characterization of articular and extra-articular complaints, and careful physical examination, will guide the construction of the differential diagnosis and subsequent laboratory and radiological testing. The most common causes of symmetrical inflammatory polyarthritis that may be confused with RA are the other systemic connective tissue disorders, psoriatic arthritis, and viral-induced arthritis (in particular, parvovirus B19- and hepatitis C-associated arthritis).

Other connective tissue disorders that can cause polyarthritis with a rheumatoidlike distribution include systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, and Sjögren's syndrome. In most cases, the presence of extra-articular features such as Raynaud's phenomenon and rash, the absence of

anti-CCP reactivity, and the presence of antinuclear (and other) antibodies will help to differentiate these diseases from RA. It should be noted that RF can be present in most connective tissue diseases and occurs with particularly high frequency in Sjögren's syndrome. Patients with connective tissue diseases who have erosive arthritis should be considered to have an overlap syndrome (e.g., "rupus" as an overlap of RA and systemic lupus).

Hepatitis C-associated polyarthritis with cryoglobulinemia can present a more challenging diagnostic dilemma because cryoglobulins frequently have reactivity in the RF assay. For this reason, it is particularly important to consider hepatitis C risk factors in evaluating patients with rheumatoidlike arthritis and a positive RF. The distribution of joint involvement in patients with parvovirus B19-associated polyarthritis is generally very similar to RA but the intensity of inflammation is considerably less; furthermore, this arthritis resolves spontaneously in weeks to months in most individuals without treatment. The presence of IgM-specific parvo B19 viral antibodies will confirm the diagnosis.

Psoriatic skin involvement most commonly occurs *before* the onset of the arthritis, thus providing a clue to the diagnosis of psoriatic arthritis. Furthermore, unlike RA, psoriatic arthritis typically involves the DIP joints and is less symmetrical. Other causes of inflammatory arthritis that are less symmetrical and typically oligo- or monoarthritic in presentation include the crystalline arthropathies (gout and pseudogout), septic arthritis, and the human leukocyte antigen (HLA)-B27-associated spondyloarthropathies. In patients presenting with an inflammatory *monoarthritis*, the process should be assumed to be septic until proven otherwise. Joint aspiration should be performed and the fluid sent for Gram stain, culture, and crystal examination. Usually patients with bacterial infectious arthritis will appear septic and erosions may be present on radiographs, depending on the duration of infection within the joint. Monoarthritis that is more chronic and accompanied by radiographic damage should evoke the possibility of mycobacterial or fungal infection; in this case, a synovial biopsy for culture may be needed in order to expose the infection. Arthritis caused by disseminated *Neisseria gonorrhoea* should be considered, particularly in younger female patients; skin lesions (pustules, blisters, vasculitic lesions) can provide a clue to the diagnosis along with history of vaginal discharge. If suspected, vaginal and oral cultures should be obtained along with synovial fluid cultures. In patients presenting with oligoarthritis, the spondyloarthropathies should be considered. These include ankylosing spondylitis, psoriatic arthritis (discussed above), reactive arthritis, and arthritis associated with inflammatory bowel disease. Features common to these diseases include involvement of the sacroiliac joints,

asymmetric peripheral joint involvement, uveitis, and Achilles tendonitis. Lyme-associated arthritis is also, in essence, a reactive arthritis, occurring weeks to months after the acute infection. Lyme arthritis tends to occur in the knee and/or ankle as a monoarthritis or oligoarthritis. Patients should be queried about tick bites and Lyme antibody testing should be obtained if suspected. Gout and pseudogout commonly present with an intense inflammation and subcutaneous edema and can be confused with cellulitis. If inadequately treated, gout can evolve to a phase of chronic tophaceous polyarthritis that may be confused with RA.

Non-inflammatory painful conditions, such as fibromyalgia and overuse syndromes, and degenerative arthritis or osteoarthritis, should not be confused with RA as they do not exhibit prolonged morning stiffness, and swelling of the joints is relatively uncommon. In contrast to RA, the DIP joints of the hands are involved in osteoarthritis and bony enlargement (Heberden's and Bouchard's nodes) rather than soft tissue swelling is typical. Fibromyalgia presents with diffuse musculoskeletal pain and the joint examination is usually normal. Another consideration is malignancy, which can occasionally present as polyarthralgias but true synovitis is usually absent. For example, lung cancer can cause hypertrophic osteoarthropathy. In addition, if a large protein gap is present, then one should evaluate for a monoclonal gammopathy by checking a serum protein electrophoresis. Certain metabolic disorders such as hypo- or hyperthyroidism can cause polyarthralgias. Also, hyperparathyroidism and other causes of hypercalcemia predispose to the development of pseudogout.

Making the diagnosis of RA early in the course of disease is imperative so that effective treatment can be initiated in a timely manner. The goals of treatment are reduction of pain and inflammation and prevention of long-term disability and extra-articular morbidity and mortality (see Chapter 6C).

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Rheumatoid Arthritis

B. Epidemiology, Pathology, and Pathogenesis

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- Genetic factors, including the human leukocyte antigen (HLA) shared epitope, hormonal factors, and environmental exposures such as tobacco smoke or infectious agents may predispose to the development of rheumatoid arthritis (RA).
- The primary target organ in RA is the synovial membrane. Changes include increased cellularity, increased vascularity, and infiltration with immune inflammatory cells.
- Autoantibodies in RA include rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies. Importance of humoral immunity is demonstrated by the efficacy of anti-B lymphocyte treatment strategies.
- T cells are involved in RA pathogenesis due to their presence in the synovium, association with HLA, presence of T-cell cytokines, and efficacy of anti-T lymphocyte treatment strategies.
- Cytokines are critical to RA pathogenesis. Proinflammatory cytokines tumor necrosis factor alpha (TNF-alpha), interleukin (IL) 1, and IL-6 have proved to be important as treatments, though many others may also play essential roles.
- Mechanisms that result in destruction of cartilage and bone lead to joint deformities and disability.

Rheumatoid arthritis (RA) is one of the most common inflammatory arthritides. Affected patients suffer from chronic articular pain, disability, and excess mortality. It primarily affects the small diarthrodial joints of the hands and feet, although larger weight-bearing and appendicular joints can also be involved. Extra-articular manifestations and systemic symptoms also occur, but in a minority of patients. RA is a heterogeneous disease of variable severity and unpredictable response to therapy. Genetic and environmental factors are clearly implicated in its etiology and pathogenesis. Translational research efforts have led to novel targeted therapies, although the treatment of RA remains a significant unmet medical need.

EPIDEMIOLOGY AND RISK FACTORS OF RHEUMATOID ARTHRITIS

The prevalence estimates for RA are between 0.5% and 1.0% in European and North American populations. The disease has a worldwide distribution but studies in Asia, including China and Japan, suggest a somewhat lower rate in those regions (0.2%–0.3%). Some Native American populations have a remarkably high prevalence (more than 5%) that is likely related to as yet poorly defined genetic factors.

Genetic Factors

Genetic background contributes disease susceptibility in RA, and the risk of developing the disease in first-degree relatives of a rheumatoid patient is 1.5-fold higher than the general population. The concordance rate is markedly higher for monozygotic twins compared with dizygotic twins (12%–15% vs. 3.5%, respectively), which supports a critical role of genes in addition to shared environmental influences between siblings. The overall heritability of RA has been estimated from twin studies to reach about 50% to 60%.

The Role of HLA-DR and the Shared Epitope Hypothesis

The most potent genetic risk for RA is conveyed by certain major histocompatibility complex alleles (MHC, or HLA for human leukocyte antigen; see Chapter 4). Early studies of MHC associations relied on serologic or cellular HLA typing, which only identified a fraction of the allelic variability. Increased prevalence of RA was reported to be associated with a subset of DR4 alleles in most Western European populations or a subset of DR1 alleles in other populations such as Spanish, Basque, and Israeli cohorts. Current HLA typing can discriminate allelic variants at the nucleotide level and reveals that a conserved amino acid sequence is over-represented in patients with RA. This sequence maps in the third hypervariable region of DR beta chains from amino acids 70 to 74. The shared epitope (SE) (1) is glutamine-leucine-arginine-alanine-alanine (QKRAA), and presence of the SE is associated with increased susceptibility to and severity of RA.

Different models have been proposed to explain the role of the shared epitope in RA. Susceptibility alleles could (1) bind efficiently to arthritogenic peptides, such as those either derived from a self-antigen or a microbial pathogen, (2) lead to the positive or negative selection of autoimmune T cells in the thymus, (3) lead to inadequate numbers of regulatory T cells, (4) become the target of T cells themselves due to molecular mimicry between QKRAA and pathogens implicated in RA, such as *Escherichia coli* DnaJ or Epstein–Barr virus (EBV) peptides.

A recent alternative hypothesis suggests that the association is not necessarily between the SE itself and the development of RA, but instead between the SE and the production of certain autoantibodies, especially anti-cyclic citrullinated peptide (CCP) antibodies. This model implies that anti-CCP antibodies rather than the SE is responsible for the genetic link. One possible explanation is that the SE confers a positive charge to the peptide binding cleft on the class II MHC that prevents the binding of peptides containing arginine. Peptidylarginine deiminases (PADIs) convert arginine to

an uncharged citrulline, thereby permitting the antigen to be loaded onto the MHC and presented to autoreactive T cells. Given this functional role, it is of interest that one of the four isoforms, PADI 4, has been implicated in RA, although the association with RA appears to be mainly in Asian populations rather than Western Europeans.

Other Genetic Risk Factors

Polymorphisms in several other genes may contribute incremental risk for RA that is quantitatively lower than the MHC itself. Many genes have been implicated, although the data vary widely. Some of the putative associations relate to cytokines, chemokines, and their receptors.

The analysis of the genetic predisposition to RA has recently been expanded using genomewide scans (2). An example of a newly described susceptibility gene discovered by this approach is a functional variant (R620W) of the intracellular protein tyrosine phosphatase N22 (PTPN22). The risk of developing RA is about twofold higher in heterozygotes and fourfold higher in homozygotes who carry this polymorphism. The PTPN22 variant is also associated with other autoimmune diseases, including type I diabetes and systemic lupus erythematosus. The product of this gene is an intracellular tyrosine phosphatase that negatively regulates T-cell activity. The R620W allele results in a gain of enzymatic function that alters the threshold for T-cell receptor (TCR) signaling. Theoretically, the defect in TCR signaling caused by R620W could generate autoimmunity by modulating negative selection in the thymus. PTPN22 could also regulate other cell types because it is expressed in myeloid cells and B cells.

Nongenetic Risk Factors

Influence of Sex

Women are two to three times more likely to develop RA than men. Hormonal factors like estrogen and progesterone could potentially explain some of the gender effect. Estrogen might have detrimental effects through its ability to decrease apoptosis of B cells, potentially permitting the selection of autoreactive clones. Hormones also have a complex influence on the balance of T-cell subsets with distinct cytokine profiles. For instance, administration of estrogen in animal models can enhance or suppress T-helper (Th) 1-mediated immunity, depending on the timing and the dose used. In murine collagen-induced arthritis, exogenous administration of estrogen is protective primarily by inhibiting Th1 immunity. However, the precise explanation for the greater prevalence of RA in females and the role of hormones remains uncertain.

The situation during pregnancy exemplifies complex influence that sex has on RA. Seventy-five percent of pregnant women with RA experience spontaneous remission, although the disease typically flares within weeks after delivery. Soluble mediators released by the placenta like transforming growth factor (TGF) beta, IL-10, or alpha-fetoprotein might contribute to this effect. Alternatively, the immune system in pregnant women displays a shift towards a Th2 bias, which could suppress the characteristic Th1 profile of RA (see T-cell subsets p. 127).

The presence of fetal cells in the maternal circulation that contain potentially alloreactive, paternal HLA molecules has been implicated in immune modulation during pregnancy. Generation of alloantibodies to the MHC or competition of fetal peptides with maternal autoantigens for MHC binding could potentially modulate the disease. In one study, most pregnant women experiencing RA remission had maternal–fetal disparity in HLA class II molecules, whereas HLA mismatch was less common in pregnancies that did not show RA improvement. This association was not observed in a second study, so the immunological effects of a maternal–fetal HLA mismatch remains to be clearly established.

Tobacco

Exposure to various environmental factors increase the risk for RA, and cigarette smoke is one of the best characterized. Of interest, smoking also enhances the risk of developing anti-CCP positive RA in patients with the SE (3). The mechanism of anti-CCP antibody generation from inhaled smoke probably relates to inflammation and activation of innate immunity in the airway, which then induces peptide citrullination. In a susceptible host, such as someone carrying the SE and with genetically determined immune hyperreactivity, these repeated insults followed by chronic exposure to citrullinated peptides could lead to the production of anti-CCP antibodies and other antibodies like rheumatoid factors. While the link between autoantibody production and the onset of RA is not always exact, this situation could enhance the synovial inflammatory response when innate immunity in the joint is activated by unrelated stimuli.

Bacteria and Their Products

Infectious agents have long been considered prime candidates as initiating factors for RA, although the search for a specific etiologic agent has been unrewarding. Bacterial DNA is present in synovial tissue by sensitive polymerase chain reaction techniques, but the species are not unique and have also been identified in many other arthropathies. Other microbial components, such

as peptidoglycans, are also present in RA joints in the absence of active infection. Bacterial peptidoglycans, like prokaryotic DNA, can activate Toll-like receptors (TLR) and stimulate synovial innate immune responses. Even nonspecific bacterial products could thus play a role in synovitis by activating cytokine networks or acting enhancing adaptive autoimmune responses. Such phenomena are well described in animal models where arthritis can be induced and/or enhanced by injecting purified bacterial products, in particular lipopolysaccharide (LPS) or extracts of mycobacteria. Importantly, LPS shares a common signaling pathway with IL-1 and can substitute for this cytokine in a mouse model of antibody-mediated arthritis.

Viruses

Several viruses have been implicated as possible etiologic factors in RA. A relationship between RA and EBV was suggested by several observations. For instance, EBV is a polyclonal activator of B lymphocytes and increases the production of rheumatoid factor (RF). Rheumatoid arthritis patients have an increased EBV load, and their synovium can express viral RNA. The viral gp110 protein is also one of the many xenoproteins that contains the QKRAA sequence also found in the SE. Such proteins might trigger autoimmune responses by a process known as *molecular mimicry*, leading to an inappropriate immune response directed against a similar endogenous protein. Parvovirus B19 has also been suggested as an etiologic agent in RA. B19 DNA is more often found in RA joints than in controls, although only about 5% of newly diagnosed RA patients have evidence of recent parvovirus infection. The mechanisms of B19–induced synovitis, when it does occur, could include increased invasive properties of infected fibroblastlike synoviocytes.

Based on current data, the bacterial products or viral nucleic acids detected in RA joints are not likely to be part of an active infectious process. Even so, these products could still participate indirectly to arthritis in genetically susceptible individuals by stimulating their innate immune system, which can amplify adaptive immunity.

SYNOVIAL PATHOLOGY

The synovium is the primary site of inflammation in RA. Morphological and functional studies of this target tissue have led to improved understanding of RA through systematic comparison of rheumatoid samples with other joint diseases and normal tissue. Serial biopsies are also used increasingly in clinical studies, thus providing insight into pathogenic mechanisms at the molecular level.

The Normal Synovium

The normal synovium consists of an intimal lining layer that is usually discontinuous, one to two cell layers thick, and lacks an underlying basal membrane. The sublining below the intima contains blood vessels, lymphatics, nerves, and adipocytes distributed within a less cellular, fibrous matrix. The intimal lining layer comprises roughly equal proportions of two different cell types, macrophagelike synoviocytes or type A synoviocytes, and fibroblastlike synoviocytes (FLS) or type B synoviocytes. The latter are responsible for the synthesis of extracellular matrix proteins including collagen, fibronectin, hyaluronic acid, and other molecules that facilitate the lubrication and function of cartilage surfaces. Type A cells are phagocytic and express numerous markers of the monocyte–macrophage lineage.

The Synovium in Rheumatoid Arthritis

The complex histological architecture of the synovial tissue in RA is the result of a dynamic process involving coordinated molecular signals (chemokines, adhesion molecules, cytokines, and growth factors) and cellular events (apoptosis, proliferation, cell migration, and survival). Increased numbers of both type A and B synoviocytes augment the depth of the lining layer, sometimes to 10 cell layers, and mononuclear cells infiltrate the sublining (Figure 6B-1). The lining is the primary source of inflammatory cytokines and proteases, thus participating in joint destruction in concert with activated chondrocytes and osteoclasts. Villous projections protrude into the joint cavity, invading the

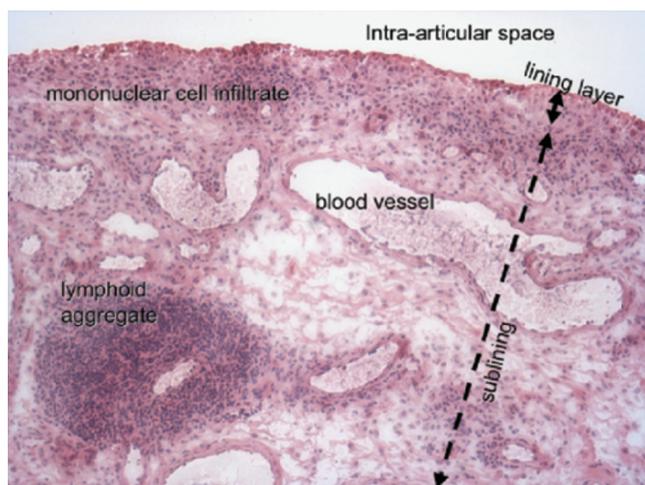


FIGURE 6B-1

Synovium in rheumatoid arthritis. Only modest synovial lining hyperplasia is present in this example, although sublining mononuclear cell infiltration, lymphoid aggregates, and vascular proliferation are prominent.

underlying cartilage and bone where the proliferating tissue is called *pannus*. In the synovial sublining region, edema, blood vessel proliferation, and increased cellularity lead to a marked increase in tissue volume.

T and B lymphocytes, plasma cells, interdigitating and follicular dendritic cells (IDC and FDC), and natural killer cells (NK cells) accumulate in rheumatoid synovium and can be distributed diffusely throughout the sublining or organized into lymphoid aggregates. The dominant cells, CD4+ T cells, are mostly of the memory CD45RO+ and display the chemokine receptors CXCR3 and CCR5 characteristic of Th1 cells. CD4+ T cells are especially enriched in aggregates, whereas CD8+ T cells are present in the periphery of the aggregates or scattered throughout the sublining. In about 15% to 20% of patients, structures typical of secondary lymphoid follicles can be found. T- and B-cell infiltrates are not specific to RA and can be found in many chronic inflammatory arthropathies.

The Synovial Fluid in Rheumatoid Arthritis

Normal joints contain a small amount of synovial fluid to lubricate articular surfaces. The volume of synovial fluid can increase dramatically in RA due to increased leakage from the synovial microvasculature. Neutrophils (polymorphonuclear leukocytes, or PMNs) are the predominant cell type, although lymphocytes, macrophages, NK cells, and fibroblasts are also present. PMNs are drawn into the articular cavity by a gradient of chemokines and other chemotactic factors, such as C5a and leukotriene B4. The dramatic influx of neutrophils into joint effusions might be due, in part, to low expression of adhesion molecules on PMNs that would retain these cells within the synovial tissues compared with mononuclear cells. The former can readily migrate out of the tissue while the latter are retained. PMNs in the synovial fluid are activated by factors such as immune complexes and cellular debris. They degranulate, generate products of oxygen metabolism, metabolize arachidonic acid, and release proteinases and cytokines. The lymphocyte population in synovial effusions differs from the synovium, with a higher number of CD8+ T cells in the fluid compared with CD4+ T-cell predominance in the tissue.

AUTOIMMUNITY AND AUTOANTIBODIES IN RHEUMATOID ARTHRITIS

The role of autoimmunity in RA was first suggested by the discovery of autoantibodies like rheumatoid factor in the sera of patients, which suggests that autoreactive

B cells are generated. Risks conveyed by the SE also serve as an argument for a pathogenic role of adaptive immunity. The advent of B- and T-cell-directed therapies provide compelling evidence that adaptive immune processes are involved in RA (see Chapter 6C).

B-Cell Autoimmunity and Autoantibodies

Antibodies directed against joint-specific and systemic autoantigens are commonly detected in the blood of RA patients. Autoantibodies are also found in immune complex deposits in rheumatoid joints and probably contribute to the local inflammation by activating complement. In mouse models of arthritis, synovitis can be induced by injecting purified antibodies directed against joint-specific proteins like type II collagen or against ubiquitous proteins that localize to joint tissue by non-specific interactions with cartilage. Although antibodies can be arthritogenic, the arthritis generated by injection of antibodies is generally transient, whereas active production of autoantibodies and persistent disease requires T-cell help. The concept that autoantibodies and immune complexes are pathogenic fostered the development of targeted B-cell depletion in RA (see Chapter 6C) (4).

Rheumatoid Factors

Rheumatoid factors (RFs) are autoantibodies directed against the Fc portion of IgG (5). They were first detected in the sera of patients in 1940 and fostered the concept that humoral autoimmunity contributes to the pathogenesis of RA. IgG and IgM RFs are found in up to 90% of RA patients. Testing for IgM RF is about 70% sensitive and 80% specific for RA. However, these autoantibodies can also be produced during chronic infections, malignancy, and in a variety of inflammatory and autoimmune syndromes. RFs are also detectable in 1% to 4% of healthy individuals, and up to 25% of healthy individuals over the age of 60 years. They can be detected in the blood up to 10 years before the onset of RA, with an increasing incidence in the period immediately before clinical symptoms develop (see Chapter 6A). Therefore, the mere presence of RF is not sufficient to cause arthritic symptoms. The presence of RF in RA, however, has prognostic significance. Seropositive patients have more aggressive disease while seronegative patients tend to experience less severe arthritis with fewer bone erosions.

B cells isolated from RA synovium can secrete RF, indicating that the autoantibody is produced locally in the joint. The variable domains of the RF light chain from RA patients contain somatic mutations that encode high affinity antibodies, which are a hallmark of anti-

genic driven B-cell selection. In contrast, RFs produced by healthy individuals have avidity for the Fc portion of IgG several orders of magnitude lower than in RA and contain mostly germline-derived sequences.

Anti-Cyclic Citrullinated Peptide Antibodies

Anti-cyclic citrullinated peptide antibodies are another key autoantibody system in RA. Anti-CCP testing has a sensitivity of up to 80% to 90% and a specificity of 90% for RA, which increases to >95% specificity if combined with the presence of IgM RF (see Chapter 6A). Anti-CCP antibodies are occasionally produced in other inflammatory diseases, such as psoriatic arthritis, autoimmune hepatitis, and pulmonary tuberculosis (TB). Similar to RF, anti-CCP antibodies are a risk factor for more aggressive disease and are produced early in disease.

The process of citrullination involves conversion of arginine to citrulline by PADIs. Of the four isoforms, PADI 2 and PADI 4 are most abundant in the inflamed synovium. In RA, citrullination occurs in the inflamed synovium and the antibodies produced by resident B cells. A variety of citrullinated proteins are present in the rheumatoid joint, including fibrinogen, collagen, and fibronectin. The precise pathogenic role of the autoantibodies in RA is not well defined. However, anti-CP antibodies bind to intra-articular antigens in mice with collagen-induced arthritis and can enhance joint damage.

Other Autoantibodies

Many other autoantibodies can be detected in RA sera, indicating that aberrant immune responses can be directed against a broad range of autoantigens. Anti-type II collagen antibodies are especially interesting because they are pathogenic in a mouse model of arthritis. Synovial B cells in RA produce anticollagen antibodies that fix complement. However, elevated serum titers are found in only a minority of patients.

T-Cell Autoimmunity

T cells have been implicated in RA due to their presence in the synovium and the class II MHC association. Synovial T cells isolated from patients respond to some cartilage-specific proteins as well as ubiquitous antigens like heat-shock peptides. In animal models, T cells contribute at various levels to the development and progression of experimental arthritis. Several models rely on active immunization protocols against joint antigens such as type II collagen, which requires T-cell help. In one mouse model, a mutation in a signal transduction protein linked to TCR signaling causes arthritis through

abnormal thymic selection of arthritogenic T cells. Despite evidence implicating T cells in RA, the results of early targeted therapies were disappointing. More recently, a biologic agent that blocks T cell costimulation (CTLA4-Ig; abatacept) demonstrated efficacy and has renewed the interest in targeting T cells to treat RA (see Chapter 6C) (6).

T-Cell Subsets

Naive CD4⁺ T cells can be differentiated into multiple effector types, including Th1 and Th2 phenotypes. Experimental systems have shown that precursor cells can be polarized towards one of these phenotypes depending on the nature of the antigen, characteristics of the antigen-presenting cells, and the cytokine milieu. Th1 cells are involved in the defense against intracellular pathogens and have been implicated in many autoimmune diseases. Th2 cells participate in host defense against parasitic worms but can also contribute to allergy and asthma. Each subtype is induced by cytokines present in the milieu (mainly IL-12 for Th1 cells, IL-4 for Th2 cells) and secretes characteristic effector cytokines (IFN-gamma and IL-2 by Th1 cells, IL-4 and IL-10 by Th2 cells). IL-4 and IL-10 inhibit Th1 cells, while IFN-gamma suppresses Th2 function.

Additional subsets have also been defined, including Th3 cells that produce TGF-beta and Th17 cells that produce IL-17 after precursor cells are exposed to IL-6 and TGF-beta or IL-23. Another subset, regulatory T cells (Tregs) can suppress arthritis in several experimental models of autoimmunity. Tregs co-express the surface markers CD25 and CD4 and inhibit T-cell responses by poorly defined cell-contact mechanisms. In RA, CD4⁺CD25⁺ regulatory T cells isolated from patients might be functionally compromised, and anti-TNF-alpha therapy appears to this defect.

T-Cell-Derived Cytokines

CD4⁺ T cells infiltrating the synovium primarily display the Th1 phenotype. Nevertheless, levels of Th1 cytokines in the rheumatoid synovium are surprisingly low. IFN-gamma can be detected in most patients, but its concentration is much less than in other Th1-mediated diseases. Another prototypic Th1 cytokine, IL-2, is also quite low in RA. However, cytokines that enhance Th1 differentiation, such as IL-12, can be readily detected in the rheumatoid joint.

Of the T-cell cytokines implicated in RA, IL-17 may be especially important. This cytokine synergizes with IL-1 and TNF-alpha *in vitro* to induce inflammatory cytokine production by fibroblasts and macrophages and enhance osteoclast activation. In animal models of arthritis, IL-17 deficiency or blockade markedly decrease clinical arthritis and destruction of the extracellular

matrix. IL-17 has been detected in the synovium of patients with RA, although its functional role *in vivo* remains to be determined.

Th2 cytokines, such as IL-4 and IL-10, have also been examined in RA, in part because they tend to antagonize Th1 cells and are effective treatments when administered in animal models of arthritis. Levels of Th2 cytokines are generally very low in RA, perhaps reflecting the Th1 bias of the synovium. Of the Th2 factors present, IL-10 has been most consistently detected; however, a clinical trial of IL-10 in RA did not demonstrate significant benefit.

MACROPHAGE AND FIBROBLAST CYTOKINES IN RHEUMATOID ARTHRITIS

Cytokine Networks

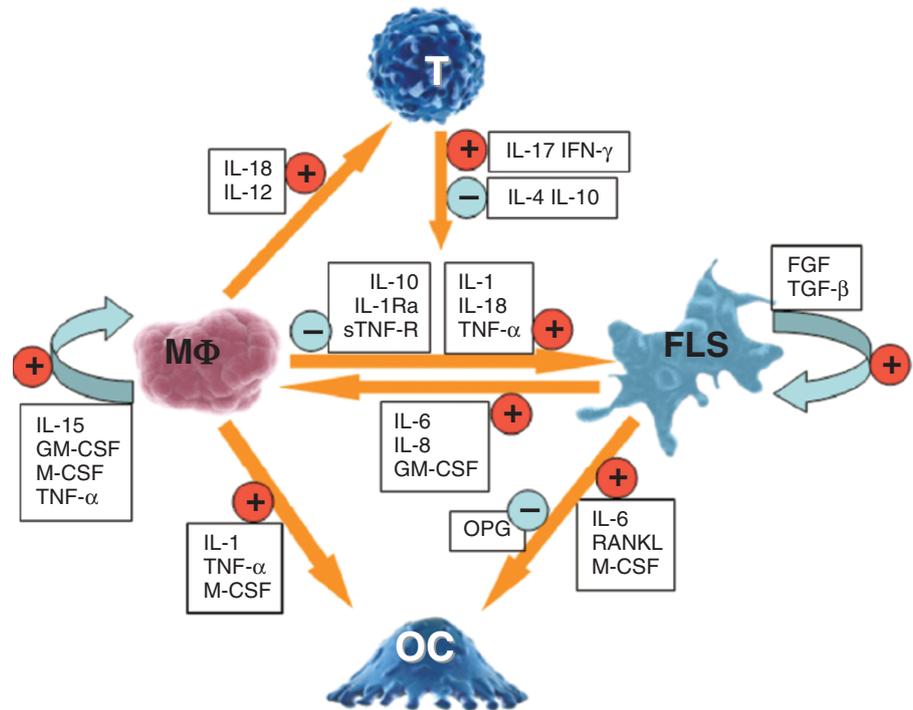
Macrophages and fibroblasts are the primary sources of cytokines in the rheumatoid synovium. Synovial macrophages and fibroblasts produce a plethora of proinflammatory factors in the joint involved in the cytokine network (Figure 6B-2), including IL-1, IL-6, IL-8, IL-12, IL-15, IL-16, IL-18, IL-32, TNF-alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), and multiple chemokines (7). These cytokines can participate in paracrine and autocrine networks that enhance and perpetuate synovial inflammation. For instance, macrophages and fibroblasts in the intimal lining can activate adjacent cells that, in turn, can produce mediators that can stimulate their neighbors. The concept of cytokine networks dominated by synovial lining cells played a major role in the advent of anticytokine therapy in RA.

Although proinflammatory cytokines can be counterbalanced by the suppressive cytokines (IL-10, TGF-beta), soluble receptors (TNF-alpha), binding proteins (IL-18), and naturally occurring receptor antagonists (IL-1Ra), all of which are produced by macrophages and fibroblasts in the synovial intima, the concentrations are below those required to suppress inflammation. Although the cytokine network can be highly redundant, disease control can be achieved in many patients by inhibiting a single cytokine. TNF-alpha antagonists are the most salient example, in which one third to one half of patients have dramatic clinical responses to cytokine blockade (see Chapter 6C).

Some of the key cytokines produced by macrophages and fibroblasts in RA are discussed below. This is by no means a complete list, and the network becomes more complex with each passing year. In some cases, the contribution of more recently described proinflammatory cytokines has not been defined.

FIGURE 6B-2

Cytokine networks. Macrophages ($M\Phi$), fibroblastlike synoviocytes (FLS), and synovial and T cells produce proinflammatory cytokines (denoted with +) that can activate either themselves (autocrine loops, *blue arrows*) or their adjacent cells within the joint (paracrine loops, *orange arrows*). They also secrete inhibitory cytokines (denoted by -) that only partially suppress the inflammation. Cytokines also stimulate osteoclasts, the main cell type responsible for bone destruction. RANKL produced by FLS and T cells (not shown in the figure) activate osteoclasts in the rheumatoid joint.



Tumor Necrosis Factor Superfamily

Tumor necrosis factor alpha is a pro-inflammatory cytokine that is synthesized as a membrane-bound protein and released after proteolytic cleavage by TNF convertase (TACE). It is the eponymous member of a larger group of related cytokines known as the TNF superfamily, many of which are also produced in the rheumatoid joint. Some members of the family regulate the subsynovial microarchitecture (lymphotoxins and LIGHT) while others participate in apoptosis (TRAIL, Fas ligand) or osteoclast activation (RANKL, receptor activator of NF- κ B ligand).

In RA, TNF-alpha is mainly produced by synovial macrophages. The stimulating signals have not been defined but could involve TLRs, a family of receptors that recognize specific molecular patterns and activate the innate immune system, and other cytokines like IL-15. TNF-alpha can then bind to two ubiquitously expressed receptors (TNF-RI and TNF-RII) to induce the release of other cytokines and metalloproteases by fibroblasts, decrease the synthesis of proteoglycans by chondrocytes, and promote the differentiation of monocytes to osteoclasts in the presence of RANKL. TNF-alpha inhibitors improve signs and symptoms of RA and also decrease the progression of bone erosions due to effects on other cytokines and osteoclasts. In addition to its role in RA, TNF-alpha is an important molecule in the host response to certain infectious agents. Opportunistic infections, including reactivation of latent TB,

or defective tumor immune surveillance represent potential adverse effects of anti-TNF-alpha agents.

Interleukin 1 Family

Interleukin 1

Interleukin 1 exhibits many properties that can contribute to inflammation in RA, including increased synthesis of IL-6, chemokines, GM-CSF, prostaglandin and collagenase. It also plays a pivotal role in many animal models of inflammatory arthritis. Of the two forms of IL-1, IL-1 beta is secreted, whereas IL-1 alpha is expressed within cells and associated with cell membranes. The bioactive form of IL-1 beta is cleaved from a precursor protein by the cysteine protease caspase-1, also known as interleukin 1 converting enzyme (ICE). IL-1 acts via the type I IL-1 receptor (IL-1R1), whereas IL-1R2 is a decoy receptor that does not transduce an intracellular signal. Macrophages are the main source of IL-1 in the rheumatoid synovium. A variety of inflammatory factors induce IL-1 production in RA, including TNF-alpha, GM-CSF, immunoglobulin Fc fragments, collagen fragments and, to a lesser extent, immune complexes.

Interleukin 18

Interleukin 18 is another proinflammatory member of the IL-1 family and induces the production of IFN-gamma, IL-8, GM-CSF, and TNF-alpha by synovial

macrophages. IL-18 also biases the immune responses of T cells toward the Th1 phenotype. It is expressed mainly by synovial fibroblasts and macrophages in response to TNF- α and IL-1 stimulation. IL-18 inhibition significantly attenuates collagen-induced arthritis in the mouse. A human IL-18 binding protein blocks IL-18 activity in vitro and is a potential therapeutic agent.

Interleukin 1 Receptor Antagonist Protein

Interleukin 1 receptor antagonist protein is a natural inhibitor of IL-1 present in the RA joint, but at concentrations too low to counteract IL-1 activity. Administration of exogenous IL-1Ra is very effective in IL-1–dependent diseases such as systemic onset juvenile idiopathic arthritis, adult Still’s disease, or familial cold autoinflammatory syndrome. IL-1Ra, along with other IL-1–directed approaches like caspase-1 inhibitors and engineered IL-1 binding proteins, have modest efficacy in RA (see Chapter 6C). Taken together, these data suggest that IL-1 might not be a central cytokine regulating synovial inflammation in this disease.

Interleukin 6 Family

Interleukin 6 has pleiotropic effects and influences systemic inflammation through its actions on hematopoiesis and many cell types of the immune system. IL-6 is perhaps the major factor that induces acute phase proteins like CRP by the liver. Very high levels of IL-6 are present in the synovial fluid of RA patients and type B synoviocytes are the major source. IL-6 is also implicated in the activation of the endothelium and contributes to bone erosion by stimulating the maturation of osteoclasts. In RA, IL-6 levels decrease dramatically after treatment with TNF inhibitors. Clinical trials of IL-6 inhibitors show a degree of efficacy that is similar to TNF- α antagonists (see Chapter 6C).

Other Key Cytokines

The number of additional cytokines and growth factors produced by macrophages and fibroblasts in RA is extensive and a complete description is beyond the scope of this chapter. For instance, many C-C and C-X-C chemokines are produced by the synovium that recruit mononuclear cells and PMNs into the joint. IL-15 is a macrophage-derived cytokine that activates T cells and can increase endogenous TNF- α production. Certain macrophage products, like IL-12, can influence T-cell differentiation and bias cells towards the Th1 phenotype. Colony stimulating factors, such as

M-CSF and GM-CSF, are produced by both macrophages and fibroblasts in the intimal lining and can enhance osteoclast differentiation and macrophage activation, respectively.

MECHANISM OF JOINT DESTRUCTION

Angiogenesis and Cell Migration

The generation of new blood vessels is required to provide nutrients to the expanding synovial membrane and is an early event in the development of synovitis. The expanding tissue can ultimately outstrip angiogenesis in RA; synovial fluid oxygen tension is quite low and is associated with low pH and high lactate levels. Hypoxia is a potent stimulus for angiogenesis in the synovium, and factors that promote blood vessel growth, such as vascular endothelial growth factor (VEGF), IL-8, angiopoietin-1, and many others, are expressed in RA. Several anti-angiogenesis approaches can markedly attenuate arthritis in animal models. For instance, targeting the integrin α -v β -3 expressed by proliferating blood vessels in the synovium or treating with antibodies to the type 1 VEGF receptor (VEGF-R1) suppress clinical and histologic evidence of disease.

Proinflammatory cytokines induce the expression of specialized receptors on capillaries and postcapillary venules that regulate the migration of the inflammatory cells into the synovium. E- and P-selectins, which mediate leukocyte rolling, and vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (I-CAM), which control immobilization and ingress of cells into tissue, are adhesion molecules identified on the inflamed synovial endothelium in RA. Once leukocytes have migrated into the tissue, they adhere to the matrix through surface receptors and their survival and proliferation is stimulated by the cytokine milieu.

The Role of Fibroblastlike Synoviocytes

Activated type-B synoviocytes are a major source of inflammatory mediators and metalloproteinases in RA. Synoviocytes can be grown in vitro to study signal transduction systems that relay information from the environment to the nucleus and activate gene expression. Several intracellular pathways have distinctive but overlapping functions, including NF- κ B, mitogen-activated protein kinases (MAPK), and signal transducers and activators of transcription (STATs). For instance, p38 MAPK regulate production of IL-6 by

synoviocytes, while c-Jun N-terminal kinase (JNK) is a critical MAPK that induces collagenase expression and regulates joint destruction in experimental arthritis. These studies have contributed to the notion that targeting signaling molecules that regulate synoviocyte and macrophage activation might have therapeutic potential in RA.

Fibroblastlike cells derived from the synovium of RA patients exhibit some unique aggressive properties. Unlike synovial fibroblasts from normal or osteoarthritis donors, RA synoviocytes transferred to severe combined immunodeficient (SCID) mice invade and destroy human cartilage explants. Insufficient synoviocyte apoptosis in RA probably contributes to intimal lining hyperplasia of the synovium due to several mechanisms, including low expression of anti-apoptotic genes and abnormal function of tumor suppressor genes like p53. RA synoviocytes also express a variety of oncogenes and display some evidence of de-differentiation, as demonstrated by expression of the *wnt* family of embryonic genes.

Extracellular Matrix Damage

Cartilage Destruction

Aggressive synoviocytes at sites of pannus overgrowth, cytokine-activated chondrocytes, and PMNs are major cell types responsible for destruction of the cartilage in RA. They release destructive enzymes in response to IL-1, TNF- α , IL-17, and immune complexes. Once the cartilage is compromised, mechanical stress works as an accelerating factor to enhance destruction. A variety of enzymes participate in extracellular matrix degradation of the joint, such as matrix metalloproteinases (MMPs; collagenases, gelatinases, and stromelysin), serine proteases (trypsin, chymotrypsin), and cathepsins (see Chapter 11B). Reversible loss of proteoglycans occurs early, most likely due to the catabolic effect of cytokines and the production of stromelysins and aggrecanases. Cleavage of native type II collagen by collagenases is an irreversible step that permanently damages the cartilage.

Protease inhibitors are also present in the RA joint; like endogenous cytokines antagonists, they are overwhelmed by massive production of degradative enzymes. In addition to protecting the matrix, serine protease inhibitors can also prevent the activation of MMPs through limited proteolytic digestion. Tissue inhibitors of metalloproteinases (TIMPs) inhibit the active form of MMPs and are expressed by intimal lining and sublining synovial cells. The relative balance between MMPs and TIMPs is unfavorable in RA compared with osteoarthritis and

is improved in patients treated with chronic low dose methotrexate.

Bone Destruction

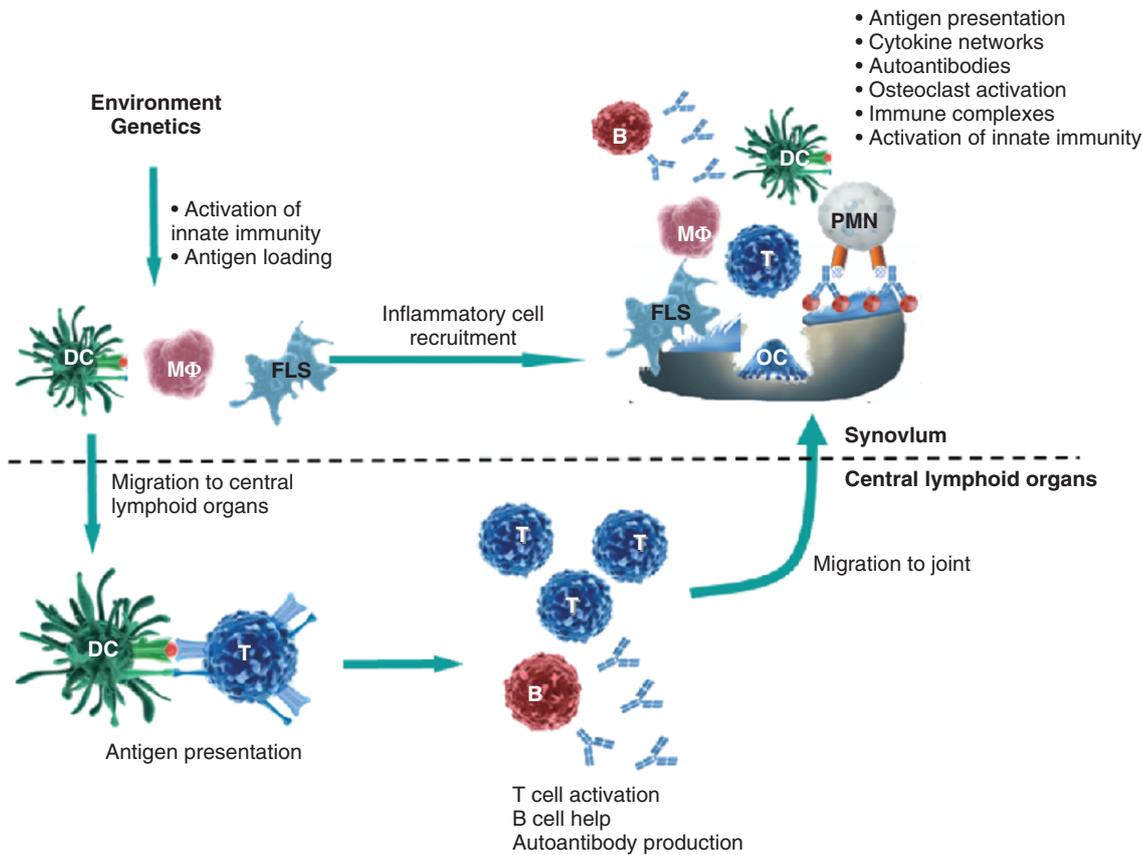
Focal bone erosions are a hallmark of RA that can occur early in the disease and cause significant morbidity due to subchondral and the cortical bone damage. RA is also associated with periarticular bone loss adjacent to inflamed joints and generalized osteopenia, leading to increased risk of fracture in both the appendicular and axial skeleton.

The cellular and molecular mechanisms underlying cartilage destruction and focal bone erosions are distinct. Synoviocytes, chondrocytes, and neutrophils are probably the major effectors of the former. Bone erosions are mainly caused by osteoclasts, which are derived from macrophage precursors (8). They accumulate at the pannus–bone interface and the subchondral marrow space.

Receptor activator of NF- κ B (RANK) and its ligand RANKL form the most important receptor–ligand pair that modulates bone resorption in RA. RANK is expressed by osteoclasts and modulates their maturation and activation. Expression of the RANKL on T cells and fibroblastlike synoviocytes is promoted by cytokines such as TNF- α , IL-1, and IL-17. The RANK–RANKL system is antagonized by a soluble decoy receptor, osteoprotegerin (OPG), that binds to RANKL. Injection of OPG or deletion of the RANKL gene in animal models inhibits bone destruction but does not suppress inflammation. Of interest, anti-TNF- α agents can slow the progression rate of bone erosions in RA, even in patients without clinical improvement. Therefore, the inflammatory and destructive mechanisms in RA can be distinct.

CONCLUSION

The pathogenesis of RA is highly complex and involves interconnected cellular and molecular pathways ultimately causing joint inflammation and damage (9). Interaction between innate and adaptive immunity explain many aspects of RA (Figure 6B-3). Basic research and clinical studies have not clearly established a hierarchy among the different pathogenic pathways because therapies that target cytokines, T cells, or B cells exhibit a similar efficacy. The self-perpetuating mechanisms of RA are resistant to current treatments because established disease usually relapses when therapy is discontinued, even if a full remission had been achieved. A better understanding of these unre-

**FIGURE 6B-3**

Innate and adaptive immunity both contribute to the pathogenesis of RA. Genetic predisposition places individuals at risk for RA, perhaps due to abnormal T-cell selection, elevated cytokine production, or enhanced propensity to protein citrullination. Stochastic events, such as environmental exposures, might enhance immune reactivity and permit a breakdown of tolerance. Nonspecific inflammation due to environmental exposures or endogenous ligands, such as stimulation of the TLR, can also directly induce cytokine production, activate synoviocytes and macrophages that secrete chemokines, and recruit lymphocytes that can respond to local antigens. Self-antigens derived from the inflamed tissues can be processed by tissue dendritic cells, which migrate to central lymphoid organs and activate T cells. B cells and T cells activated in the central tissues can subsequently migrate back to the joint. At later stages, local cytokine networks amplify and maintain a self-sustained inflammatory loop within the joints and perhaps lead to local antigen presentation and the formation of secondary lymphoid aggregates. The activation of enzymes that degrade the matrix and osteoclasts can cause irreversible joint destruction.

solved issues will hopefully lead to improved diagnostic and prognostic tools that are needed to achieve early disease control in RA before irreversible joint damage has occurred.

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Rheumatoid Arthritis

C. Treatment and Assessment

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- Ongoing assessment of rheumatoid arthritis (RA) should include evaluation of tender and swollen joints, acute phase reactants [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], subjective evaluation of pain and overall disease activity, functional limitations, and radiographs.
- The treatment goal in RA is early and effective control of synovitis to prevent joint damage, disability, and secondary consequences of chronic inflammation such as cardiovascular disease.
- Symptomatic relief of pain and swelling can be achieved using nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids.
- Disease-modifying drugs, such as methotrexate, should be initiated within the first 3 to 6 months of disease and, in most cases, effective control of disease activity will require more than one medication.
- If RA cannot be controlled with one or more conventional therapies, biologic treatments such as anti-tumor necrosis factor (TNF) drugs should be used.
- Knowledge of drug toxicities and institution of appropriate monitoring is required to effectively manage RA patients.

ASSESSMENT OF RHEUMATOID ARTHRITIS

The assessment of patients with rheumatoid arthritis (RA) incorporates multiple domains, which include clinical, functional, biochemical, and imaging parameters. The history and physical examination are vital for ongoing evaluation of any patient with a diagnosis of RA. The history should document the location of the affected joints, and presence of joint pain and swelling. Morning stiffness of the joints is an important symptom that should be documented as well. While RA predominantly affects the joints, it also may lead to systemic manifestations, including fatigue, Raynaud's phenomenon, dry eyes and mouth (secondary Sjögren's syndrome), interstitial lung disease, pleuritis, pericarditis, peripheral nervous system involvement, and vasculitis, to name a few. Therefore, the history must be complete to evaluate for possible extra-articular disease. In addition, the medical history is important to assess the patient's extent of disability, including the effect of the disease on daily activities, family life, recreational pursuits, and work.

During the musculoskeletal examination, each joint is carefully palpated for tenderness, inspected for swell-

ing, and tested for impaired range of motion. Inflamed joints are typically tender and swollen, with visible effusions. Synovitis may also be reflected by impaired or painful joint motion. Other findings, such as subcutaneous rheumatoid nodules on extensor surfaces, are associated with positive rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (CCP) and should also be documented.

Several patient-reported measures may be used in clinical practice to evaluate the activity of disease. The duration of morning stiffness often exceeds 1 hour in patients with active synovitis and tends to correlate with the amount of inflammation (e.g., more prolonged stiffness associated with more active disease). Patient self-reported pain and fatigue may be quantified using a visual analog scale. The Health Assessment Questionnaire Disability Index (HAQ-DI) measures a patient's functional ability by asking questions in different categories of functioning and can be useful in monitoring the patient's course and response to therapy.

Laboratory Studies

Once the diagnosis of RA is established and seropositivity has been determined, testing for RF and anti-CCP

to follow disease activity is not useful. Acute phase reactants, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are measures of systemic inflammation. The finding of an elevated ESR or serum CRP level is usually indicative of active disease and, if repeatedly elevated over the disease course, portends a greater risk of disease progression.

Radiographic Studies

Serial radiographs of the hands and feet may be used to monitor disease progression and the effectiveness of treatment. The accumulation of erosions or worsening of joint space narrowing implies an inadequate response to disease-modifying antirheumatic drugs (DMARDs) or biologics and may warrant a change in medical management. In fact, scoring systems (e.g., van der Heijde modification of the Sharp score) to quantify the extent of joint damage have been developed to assess radiographic progression in clinical trials of DMARDs and biologics. Magnetic resonance imaging (MRI) and ultrasonography have been increasingly utilized in patients with early RA because they are imaging modalities that can detect erosions with greater sensitivity than plain radiographs and uniquely visualize the synovium and adjacent soft tissue structures. However, they are mostly used as research tools, and are not yet validated for routine use.

Disease Activity Indices

The assessment of disease activity in RA is drawn from a composite of clinical, laboratory, and radiographic measures. In clinical practice, the number of tender and swollen joints is the dominant variable that drives the overall assessment of disease activity. However, treatment decisions are not strictly dependent on the joint count and may be influenced by other factors. For example, large joints with synovitis may assume more importance in treatment decisions because of their disproportionately greater impact on physical dysfunction. Individual patient factors, such as age and occupation, are also frequently taken into account to ensure an appropriate balance of risk and benefit. A patient's overall rating of pain, degree of functional disability, serum levels of acute phase reactants, and extent of radiographic progression of disease also influence the assessment of disease activity. A formula incorporating selected clinical and laboratory variables has been derived to produce a disease activity score (DAS28), which is calculated from the number of tender and swollen joints (28-joint count), patient self-assessment of disease activity (visual analog scale), and ESR or serum CRP level. This formula has been applied in clinical practice to monitor disease activity and guide treatment decisions and is increasingly being used as an endpoint in clinical trials.

TREATMENT OF RHEUMATOID ARTHRITIS

There has been a growing emphasis on diagnosing and treating RA early and intensively due to the recognition that disability and damage rapidly accrue during the first several years of the disease. This more intensive approach has been made possible in light of the expanding therapeutic armamentarium over the past decade. The classes of drugs used for the treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors, DMARDs, biologics, and corticosteroids. NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful cotherapies because of their anti-inflammatory and analgesic effects (see Chapter 41). DMARDs are a diverse group of therapeutic agents that reduce the signs and symptoms of RA as well as retard radiographic progression of joint damage. This class of drugs is central to the control of RA, and is part of nearly every patient's treatment regimen. The ability of a drug to slow disease progression or produce a disease-modifying effect is that property which defines it as a DMARD. The biologics are structurally engineered versions of natural molecules (e.g., monoclonal antibodies) designed to specifically target pathogenic mediators of joint inflammation and damage. In general, biologics are also considered to be DMARDs when they have been shown in large clinical trials to significantly inhibit the progression of joint damage. Corticosteroids are versatile agents with potent anti-inflammatory effects that represent yet another class of drugs (see Chapter 42). They are prescribed in a variety of clinical situations to control disease activity, but their use is limited by significant long-term toxicity. These different classes of drugs are frequently combined in a multidrug regimen to afford optimal suppression of disease activity for the individual patient.

Several overarching principles guide the treatment of RA. Most importantly, treatment decisions are based on accurate assessment of disease activity. There are no specific standards for optimal care of RA, but the outcome measures described above provide a framework for determining if patients need a change in therapy or have achieved an adequate therapeutic response. Treatment decisions are shaped by experienced clinical judgment and balanced by the possibility of improving disease control with the risks of drug toxicity. The goals of therapy are to reduce or eliminate joint pain and swelling, prevent joint damage, minimize disability, and maintain employability. Presently, treatment decisions are largely made on empiric grounds given the lack of reliable biomarkers that can tailor therapies to the individual patient. Thus, the same drugs are generally employed for the treatment of all patients with RA.

Treatment with Disease-Modifying Antirheumatic Drugs

The initiation of DMARD therapy within the first 3 to 6 months of disease onset is now the standard of care for RA. The most common DMARD of choice in this setting is methotrexate (MTX) because of its proven clinical benefits and well-understood long-term efficacy and toxicity profile. Moreover, MTX may be combined effectively with most other DMARDs, making it a highly adaptable drug. Alternatively, sulfasalazine (SSZ) and hydroxychloroquine (HCQ) may be employed for the treatment of patients with milder forms of RA. In early disease, corticosteroids may be used to provide rapid control of the signs and symptoms of RA and serve as a bridge between the initiation of DMARD therapy and its onset of action, which is often delayed by a few months.

While remission is the ultimate goal of therapy, it is usually not achievable with standard DMARD monotherapy. Thus, many different two- and three-drug combinations

of DMARDs have been tested in patients with RA and found to be more effective than MTX therapy alone. For example, a popular DMARD combination is the triple therapy of MTX combined with HCQ and SSZ (1). MTX is also frequently combined with a tumor necrosis factor alpha (TNF-alpha) blocker, such as etanercept, infliximab, or adalimumab. Many other DMARD combinations with MTX as the anchor drug have proven to be more effective than MTX alone. It is also important to realize that complete remission, while desirable, is often not attainable despite treatment with an optimal, empirically derived regimen given the current available agents.

An empiric approach to the treatment of RA is the so-called step-up method in which DMARDs are added in sequential fashion until the signs and symptoms of RA are adequately controlled to reach the desired outcome (Figure 6C-1). As MTX is often the initial DMARD used for the treatment of RA, it is usually continued as other DMARDs or biologics are added to enhance clinical benefit. In some cases, MTX may be

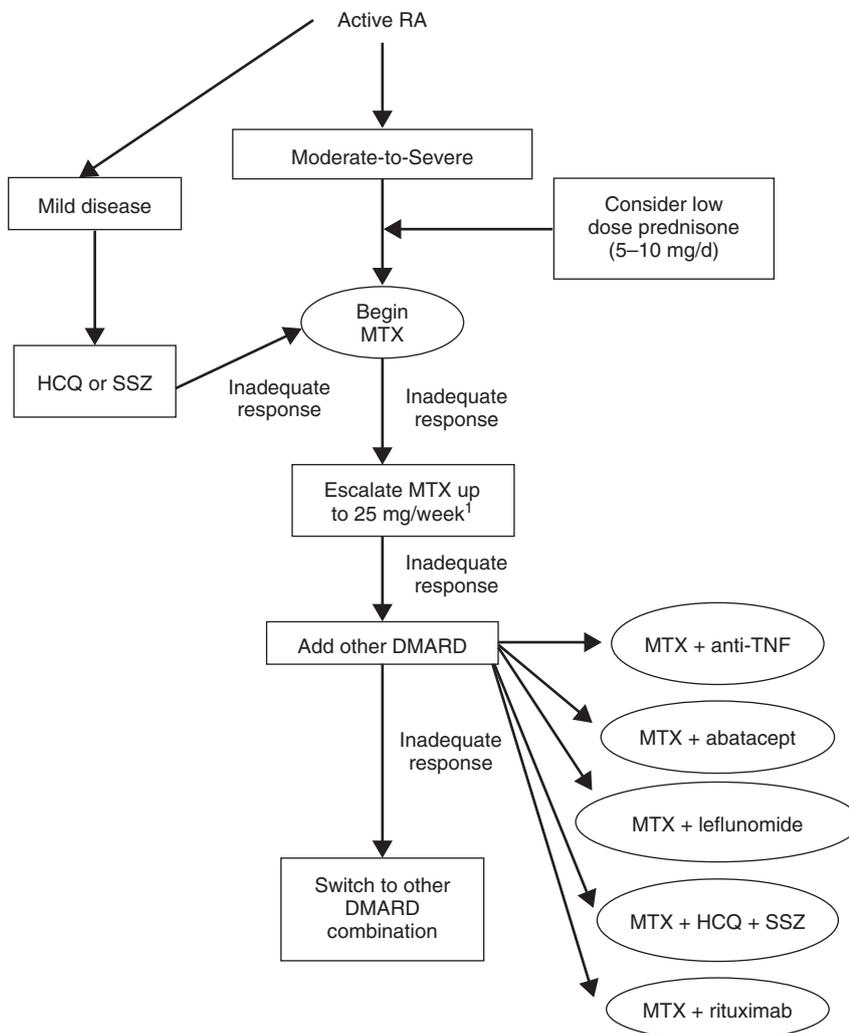


FIGURE 6C-1

Algorithm for treating active RA. In general, patients with moderate-to-severe RA are initially treated with methotrexate (MTX) therapy. Alternatively, patients with milder forms of RA may be treated initially with hydroxychloroquine (HCQ) or sulfasalazine (SSZ), and if necessary, advanced to MTX therapy depending on clinical response and disease progression. The MTX dose may be increased from 10 to 25 mg/week, as tolerated, to afford optimal control of disease activity. DMARD combinations are employed for those patients with an inadequate response to MTX therapy. If patients fail to achieve any clinical benefits from MTX therapy, or are intolerant of this drug, they are usually switched from MTX to another DMARD, such as leflunomide or an anti-TNF blocker (not shown in the figure).
¹If inadequate response to oral weekly MTX therapy, consider switching from oral to subcutaneous route of administration to improve bioavailability.

withdrawn if the patient fails to achieve even a partial clinical response or suffers intolerable side effects. Conversely, a step-down method may be employed in which two to three DMARDs are initiated simultaneously in combination to produce a maximal clinical effect at the outset of disease. The disadvantage of this approach is that some patients with a favorable prognosis may be overtreated and exposed to unnecessary side effects. Following this paradigm, patients achieving a sustained clinical response are then weaned from some of their medications to a less intensive regimen that maintains disease control. This approach is also referred to as *induction therapy* and is based on a theory that early, intensive treatment may alter the natural history of the disease, an appealing feature of this strategy. To this point, a 52-week study investigated the use of SSZ (2 g/day), prednisolone (60 mg/day), and MTX (7.5 mg/week) in patients with early RA. Those receiving this combination regimen had significantly less joint damage at the end of 52 weeks than those receiving SSZ alone (2). Interestingly, the inhibition of disease progression was maintained in those patients receiving the combination regimen for up to 5 years (2,3). The clinical efficacy and

safety of induction regimens continues to be a focus of investigation.

Successful treatment of RA depends on a detailed knowledge of the different drugs, including their pharmacokinetics, interactions with other drugs, side effects, and monitoring (Tables 6C-1 and 6C-2). A full discussion of this information is beyond the scope of this chapter but some of the most important aspects of the individual DMARDs and biologics are described below. In clinical trials of DMARD therapy for RA, treatment responses are usually defined according to the American College of Rheumatology (ACR) criteria for improvement. These criteria are based on a composite set of disease measures, including the number of tender and swollen joints, patient self-reported assessment of pain, patient and physician assessment of overall disease severity, patient self-assessment of functional disability, and serum levels of acute phase reactants (ESR or CRP). For example, an ACR20 response is defined as a 20% improvement in the number of tender and swollen joints plus 20% improvement in at least three of the five other disease measures. The ACR20 response is a minimum amount of improvement that has

TABLE 6C-1. DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs) FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: SIDE EFFECTS, MONITORING, AND OTHER CONSIDERATIONS.

DMARD	CLINICALLY IMPORTANT SIDE EFFECTS	SCREENING/MONITORING	OTHER WARNINGS AND CONSIDERATIONS
Methotrexate	Nausea, diarrhea, stomatitis, fatigue, alopecia, elevated liver enzymes, myelosuppression, pneumonitis, increased risk of infection	CBC, renal function, liver enzymes every 8–12 weeks	Viral hepatitis B and C screening; contraindicated in renal disease (creatinine \geq 2 mg/dL), teratogenic
Leflunomide	Nausea, diarrhea, rash, alopecia, elevated liver enzymes	CBC, renal function, liver enzymes every 8–12 weeks	Screening for viral hepatitis B and C; teratogenic
Hydroxychloroquine	Nausea, rash, skin hyperpigmentation, retinopathy (rare)	Yearly ophthalmologic exam ^a	Adjusted dose in renal insufficiency
Sulfasalazine	Nausea, abdominal bloating, rash, granulocytopenia	CBC, liver enzymes every 8–12 weeks	Screen for G6PD deficiency; reduce dose in renal or hepatic insufficiency
Injectable gold	Stomatitis, proteinuria, myelosuppression	CBC, urinalysis prior to each dose	
Oral auranofin	GI upset, stomatitis, proteinuria, myelosuppression	CBC, urinalysis every 8–12 weeks	
Minocycline	Skin hyperpigmentation, rash, nausea, drug-induced lupus		Avoid sun exposure
Cyclosporine	Nausea, abdominal pain, nephrotoxicity, hypertension, hypertrichosis, paresthesias, tremor, gum hyperplasia, increased risk of infection	CBC, renal function	Cyclosporine levels increase with concomitant use of ketoconazole, calcium antagonists, and H2 blockers; decreased levels with use of anticonvulsants and rifampicin; contraindicated in renal insufficiency

ABBREVIATIONS: CBC, complete blood count; G6PD, glucose 6-phosphate dehydrogenase.

^aAmerican Academy of Ophthalmology recommends annual eye exams for individuals older than 50 years.

TABLE 6C-2. BIOLOGICS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: SIDE EFFECTS, MONITORING AND OTHER CONSIDERATIONS.

BIOLOGIC	CLINICALLY IMPORTANT SIDE EFFECTS	MONITORING	OTHER WARNINGS AND CONSIDERATIONS
TNF antagonists Etanercept Infliximab Adalimumab	Injection site reaction, infusion reaction, reactivation of latent TB, increased risk of serious bacterial and opportunistic infection, possible increased risk of lymphoma, rare occurrence of demyelinating disorders and lupuslike syndromes	Periodic CBC	Question about prior history of TB exposure and screen with tuberculin skin testing; avoid in NYHA class III–IV heart failure
Kineret	Injection site reaction, neutropenia, increased risk of serious bacterial infection		Screen with tuberculin skin testing
Abatacept	Infusion reaction, increased risk of serious bacterial infection		Screen with tuberculin skin testing; use with caution in individuals with COPD because of an increased risk of adverse events and serious infections in this group; avoid live vaccines
Rituximab	Infusion reaction, increased risk of infection	Periodic CBC	Screen for viral hepatitis B infection

ABBREVIATIONS: CBC, complete blood count; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; TB, tuberculosis.

been shown to distinguish between an effective drug and placebo. Compared with an ACR20 response, ACR50 and ACR70 responses correspond to 50% and 70% improvement in these same disease measures, and are viewed as more robust levels of improvement with greater clinical relevance.

METHOTREXATE

As indicated above, the mainstay of DMARD therapy for RA is methotrexate (MTX). MTX inhibits dihydrofolate reductase, an enzyme needed for DNA synthesis. Its therapeutic action was originally thought to be due to suppression of lymphocyte proliferation. However, MTX's mechanism of action is most likely due to its anti-inflammatory effects, although the specific mechanisms remain unclear. Inside cells, MTX is converted to a polyglutamated form that inhibits the enzyme 5-aminoimidazole-4-carboxamidoribonucleotide (AICAR) transformylase. This enzymatic block leads to the intracellular accumulation of AICAR and, in turn, extracellular adenosine release. Adenosine binds to specific receptors on the surface of lymphocytes, monocytes, and neutrophils, and downregulates inflammatory pathways. MTX also has been reported to inhibit neovascularization, neutrophil activity and adherence, interleukin (IL) 1 and IL-8 production by stimulated peripheral blood mononuclear cells, and TNF production by stimulated peripheral T cells.

Methotrexate can be taken orally or by subcutaneous injection. Generally, the oral form of MTX is initiated for convenience, but may be switched to the subcutaneous route to improve gastrointestinal tolerability as well as bioavailability. Initial doses of MTX range from 7.5

to 15 mg weekly and may be escalated to a maximum dose of 25 mg weekly to yield maximal disease control. Weekly MTX therapy has been shown in randomized, controlled trials to reduce the signs and symptoms of RA and slow its rate of radiologic progression (4,5). When used alone, MTX therapy is associated with an ACR20 response rate of nearly 60% (6), which compares favorably with the other most effective DMARDs. MTX also has been shown to reduce the rate of radiological progression of disease. Importantly, women of childbearing age must use appropriate contraceptive measures because of the known teratogenic effects of MTX. Because MTX is partially eliminated through the kidney, this DMARD is generally avoided in patients with a serum creatinine of greater than 2.0 mg/dL. Suppression of bone marrow occurs more commonly if renal insufficiency is present. In addition, MTX may cause an increase in serum transaminases and, rarely, liver fibrosis. Periodic laboratory monitoring of complete blood counts and liver enzymes are recommended in all patients taking MTX (see Appendix II).

LEFLUNOMIDE

Leflunomide was approved in 1997 for the treatment of RA, and represents an alternative oral agent to MTX. It inhibits an enzyme involved in pyrimidine synthesis, orotic acid dehydrogenase. Leflunomide is taken once a day orally, in doses of 10 or 20 mg. Leflunomide's active metabolite has a long half-life of 15 to 18 days, which is a notable feature of its pharmacokinetics. In a double-blind, randomized trial, leflunomide was clinically superior to placebo and showed ACR20 response rates similar to MTX or SSZ (7,8). Leflunomide also has

been proven to reduce structural damage. Its use is limited to some extent by gastrointestinal side effects and potential for teratogenicity. Similar to MTX, leflunomide therapy has been associated with elevated serum transaminases and should be monitored by regular liver enzyme testing.

HYDROXYCHLOROQUINE AND SULFASALAZINE

Hydroxychloroquine and SSZ have been both shown in clinical trials to reduce the signs and symptoms of RA. They are typically used to treat milder forms of RA and in combination with other DMARDs. The mechanism of action of HCQ is not well understood but may, in part, be due to the fact that it concentrates inside cells, principally within acidic cytoplasmic vesicles. In lysosomes, accumulation of HCQ raises the intravesicular pH and may thereby interfere with the processing of autoantigenic peptides (9). The clinical efficacy of HCQ therapy has been shown in a randomized, controlled trial of patients with relatively mild disease of less than 5 years' duration (10). To date, no studies have shown that HCQ alone can decrease the rate of structural damage in RA.

Sulfasalazine was initially designed as a drug that linked an antibiotic, sulfapyridine, with an anti-inflammatory agent, 5-aminosalicylic acid (5-ASA), which was based on a belief many decades ago that RA was an infectious disease. Approximately 30% of SSZ is absorbed from the gastrointestinal (GI) tract. The remainder is degraded in the gut to sulfapyridine and 5-ASA. Whereas the bulk of the sulfapyridine is absorbed from the gut, most 5-ASA is excreted in the feces. SSZ suppresses various lymphocyte and leukocyte functions and, like MTX, inhibits AICAR transformylase, resulting in extracellular adenosine release (11). In a randomized, double-blind, placebo-controlled trial, an ACR20 response was achieved by 56% of patients receiving SSZ after 24 weeks of treatment, compared with a 29% response rate for placebo-treated subjects (8). SSZ also has been shown to reduce the development of joint damage.

OTHER ANTIRHEUMATIC MEDICATIONS

Several well-designed controlled trials attest to the clinical efficacy of minocycline and doxycycline for the treatment of RA, but they appear to be suited primarily for mild disease. Large trials have not been performed using these agents, and they are not approved drugs for the treatment of RA. The mechanisms by which tetra-

cyclines exert their ameliorating effects are unknown, but they have been shown *in vitro* to inhibit collagenase activity and nitric oxide production. In addition, minocycline upregulates the synthesis of IL-10, an anti-inflammatory cytokine. Minocycline and doxycycline have been shown to decrease the signs and symptoms of RA, but their effects on radiographic progression remain unclear (12).

Gold compounds are seldom used now because of their frequent toxicity and the availability of other agents with better tolerability. There are two parenteral gold formulations, gold sodium malate and myochrysin, and an oral compound, auranofin. Treatment with injectable gold and methotrexate produce similar response rates in clinical trials but gold therapy has higher rates of drug discontinuation due to toxicity (13). Auranofin has fewer side effects than gold injections, but has had limited use in clinical practice due to slow onset of action, lack of sustained clinical efficacy, and poor gastrointestinal tolerability.

In clinical trials, cyclosporine has been shown to reduce the signs and symptoms of RA, as well as slow the development of joint erosions. Cyclosporine has been shown to produce incremental clinical benefit in combination with MTX therapy (14,15). The microemulsion-based formulation of cyclosporine (Neoral™) has higher oral bioavailability and more predictable absorption than the standard form. Cyclosporine's effectiveness may be due to its biologic activities of inhibiting IL-2 production and the proliferation of activated T cells. Its renal side effects have been a major limiting factor in long-term use.

TUMOR NECROSIS FACTOR ANTAGONISTS

Etanercept, infliximab, and adalimumab are TNF inhibitors approved for the treatment of RA. These biologic agents have revolutionized the treatment of RA because of their substantial benefits on the signs and symptoms of this disease, as well as their ability to significantly retard the radiographic progression of joint damage. These drugs were engineered to specifically inhibit TNF, which is a critical mediator of joint inflammation. TNF has been shown to be a pivotal proinflammatory cytokine that regulates the production of other proinflammatory cytokines, such as IL-1 and IL-6 (see Chapter 6B). TNF also activates endothelium, upregulates the expression of adhesion molecules, promotes the release of matrix metalloproteinases, and stimulates osteoclastogenesis. All of these pathways are believed to be important in the pathogenesis of RA.

Etanercept is a soluble receptor fusion protein that binds to soluble TNF, neutralizing its biologic activities. Infliximab is a chimeric monoclonal antibody that binds

to both soluble and membrane-bound TNF, whereas adalimumab is a fully human monoclonal antibody with binding properties similar to infliximab. Etanercept and adalimumab are administered as a subcutaneous injection while infliximab is administered as an intravenous infusion. Clinical trials indicate that all of these TNF blockers, when added to MTX, produce incremental ACR20 response rates of approximately 50% to 70%. These agents have also been studied in patients with early RA and when used in combination with MTX, produce ACR50 response rates of 40% to 50%. Although etanercept and adalimumab can be used as monotherapy, the combination of MTX and a TNF blocker appears to be the most effective regimen for preventing radiographic progression of disease.

While TNF blockers have proven to be clinically efficacious in RA, their use has been associated with side effects, some of which may have serious consequences. Etanercept and adalimumab have caused injection site reactions but they are rarely severe enough to limit therapy. Infliximab has been associated with infusion reactions, which can range from rash to urticaria and fever, and rarely to anaphylaxis. Neutralizing antibodies can develop in infliximab-treated individuals that may inhibit the efficacy of the drug and predispose to infusion reactions. There is also an increased risk of serious bacterial and opportunistic infections, especially reactivation of latent tuberculosis. A long-term study of etanercept therapy for RA showed that the rate for serious infection was 4.2 per 100,000 patient years, which remained relatively stable throughout the time period (16). The German Biologics Registrar showed a relative risk of 3.0 for serious infection in patients receiving infliximab (17). Additionally, recent meta-analysis of trial data found a twofold increased risk for serious infections in RA subjects treated with anti-TNF antibodies (18). Data from the FDA in 2001 revealed 8.2 cases of tuberculosis (TB) in the United States for every 100,000 patient years of etanercept or infliximab therapy, although more cases of reactivated TB have been reported with infliximab therapy. There have also been cases of TB reported with the use of adalimumab. Because of the increased risk for reactivation of latent TB, it is now standard practice to screen individuals for prior TB exposure and with skin testing before starting a TNF antagonist. The rate of TB infection while using TNF antagonists appears to be declining due in large part to this routine screening.

Use of anti-TNF agents may also confer an increased risk for lymphoproliferative disorders, namely lymphoma. The strength of this link remains unclear because of the fact that RA itself is associated with an increased risk of lymphoma and that the magnitude of this risk appears to rise with increasing disease severity. Patients with RA have an increased risk of lymphoma, corresponding to a standardized incidence ratio (SIR) of 1.9.

In trials, the SIR increases to 2.6 and 3.8 with the use of infliximab and etanercept, respectively (19). Based on trial data, a meta-analysis has shown that infliximab and adalimumab therapy has a pooled odds ratio of 3.3 for malignancies, including nonmelanoma skin cancers, suggesting a possible relationship between TNF blockers and an increased risk for solid tumors (19).

Other rare side effects of note include demyelinating disorders and drug-induced lupus reactions. The anti-TNF agents should not be used in patients with New York Heart Association (NYHA) class III to V heart failure because these drugs may exacerbate heart failure.

ANAKINRA

Anakinra is a human recombinant anti-IL-1 receptor antagonist that has been approved for the treatment of RA. It is administered as a daily 100mg subcutaneous injection and has been shown to improve the signs and symptoms of RA. However, in a randomized, controlled trial the ACR20 response rates using this drug were only 38% (20). Modest reductions in radiographic progression of joint disease were also seen using this drug compared to controls (21). Overall, the clinical benefits of anakinra are less than those of the TNF blockers. For this reason, the use of anakinra in RA has been limited to selective patients with refractory disease.

ABATACEPT AND RITUXIMAB

Abatacept and rituximab are among the recent additions to the biologics available for the treatment of moderate-to-severe RA. They are currently approved for patients with active RA who have had an inadequate response to other DMARDs or have failed treatment with an anti-TNF agent. Abatacept (CTLA-4Ig) is a recombinant fusion protein consisting of the extracellular domain of human CTLA-4 and the Fc domain of human IgG1. Abatacept binds to CD80/CD86 on the surface of antigen-presenting cells, thus preventing their binding to CD28 on T cells. Blockade of CD28 binding prevents the so-called second signal of T-cell activation. A randomized, double-controlled trial has shown that abatacept therapy produces an ACR20 response of 50% in patients with active RA who had previously failed an anti-TNF drug, compared to placebo rate of 19% (22). Abatacept has also been shown to be effective in patients with an inadequate response to MTX therapy. Moreover, in those taking a combination of both abatacept and methotrexate, radiographic progression was reduced in comparison to controls (22).

Initially approved in 1997 for non-Hodgkin's lymphoma, rituximab is a chimeric anti-CD20 monoclonal antibody now approved for the treatment of moderate-to-severe RA. Rituximab depletes B cells that have CD20 on their surface. Its mechanism of action is incompletely understood but may involve inhibition of T-cell activation through reduction of antigen presentation by B cells or reduction of B-cell cytokines. Despite the depletion of peripheral B cells by more than 97%, immunoglobulin levels usually remain within the normal range. RF may decline; however, clinical improvement often starts before the RF titers decline. Rituximab is infused at a dose of 1000mg and repeated 2 weeks later.

Initial studies of rituximab therapy were performed in patients who had failed MTX therapy. In one study, they were treated for 24 weeks with MTX alone, rituximab alone, MTX and rituximab, and rituximab and cyclophosphamide. An ACR20 was achieved by 38%, 65%, 73%, and 76%, respectively (23). To reduce the likelihood of infusion reactions, intravenous methylprednisolone was given with the infusion followed by tapering doses of oral prednisone. A subsequent study has found that such corticosteroid therapy has no effect on efficacy, but that methylprednisolone given at the time of the infusion does decrease the severity and rate of infusion reactions (24). In rituximab-treated individuals, B cells remain depleted for greater than 3 months. Repopulation of B cells occurs at a mean of 8 months and repopulation occurs preferentially with naive B cells (25). Repeated rituximab dosing appears to be effective in restoring disease control. Remarkably, rituximab therapy has been generally well tolerated except for infusion reactions of mild-to-moderate severity, although little is known about the long-term risks of repeated rituximab dosing.

COMORBIDITIES

Osteoporosis is a major comorbidity in RA and can result from both the disease itself and the use of corticosteroids. Most patients are routinely advised to take calcium and vitamin D to prevent osteoporosis. Bone densitometry should be performed in patients with risk factors for osteoporosis to address the need for a bisphosphonate or a selective estrogen receptor blocker.

Cardiovascular (CV) disease is the number one cause of death in RA patients. Indeed, RA itself is a CV risk factor. It is unclear if intensive treatment of RA influences this risk, though available data suggest that MTX and anti-TNF treatment reduces the rate of CV events. Low dose aspirin should be considered in patients over the age of 50 years as primary prevention for CV disease. Cholesterol levels should be regularly monitored and

cholesterol-lowering medications prescribed as needed. Other CV risk factors, such as hypertension, diabetes, and obesity, should be treated according to usual recommendations.

SUMMARY

The assessment of RA demands a careful history and examination, with a detailed joint count to determine disease activity. The level of clinical disease activity largely determines the need for therapy. DMARDs are central to the control of disease activity and resulting joint damage. The availability of an expanding array of DMARDs and biologics has created new opportunities to effectively intervene in this condition. The standard of care for RA continues to evolve with increasing evidence that persistent joint inflammation leads to irreversible damage and disability. As a result, combination DMARD regimens are being employed to afford optimal disease control in order to avert permanent joint injury.

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