Rheumatoid arthritis and primary care: The case for early diagnosis and treatment

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Rheumatoid arthritis is a chronic inflammatory disease that can cause severe pain and disability. Disease management historically was based on a "therapeutic pyramid" in which treatment escalated as symptoms worsened. However, the demonstration of early joint damage in patients with rheumatoid arthritis has emphasized the importance of early identification and treatment. Key features in establishing a diagnosis include joint examinations, assessments of extra-articular manifestations, laboratory tests, and radiologic examinations. Care must be taken to rule out other disorders with symptoms that overlap those of rheumatoid arthritis. Treatment of rheumatoid arthritis typically involves disease-modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, and low-dose corticosteroids—often used in combination. A new class of therapeutic agents designed to neutralize inflammatory cytokines has added a new dimension to the therapeutic armamentarium against rheumatoid arthritis. Etanercept, a bioengineered soluble receptor fusion protein that blocks tumor necrosis factor activity, is the first compound in this class to be approved for treatment of patients with refractory rheumatoid arthritis. Therapeutic trials indicate that etanercept can reduce disease activity with relatively few drug-related adverse effects, thus helping persons with rheumatoid arthritis return to more normal, healthy lives.

(Key words: Rheumatoid arthritis, diagnosis, disease-modifying antirheumatic drugs, biologic response modifier, nonsteroidal anti-inflammatory drugs, etanercept, tumor necrosis factor)

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that affects multiple joints and sometimes involves more than one body system. Rheumatoid arthritis affects people of all ethnic groups and ages—from children to the elderly. Rheumatoid arthritis affects up to 1% of the adult population and accounts for more than 9 million physician visits and more than 250,000 hospitalizations each year.[1] From 1983 to 1995, the cost of providing medical care for a patient with RA averaged close to $4800 per year.[2]

Rheumatoid arthritis is often accompanied by disability and pain. In a prospective, 18-year study of 823 patients with RA, work disability (that is, joint deformities so severe that the patients were unable to work) was estimated to occur in 25% of patients after 6.4 years of disease and in 50% of patients after 20.9 years of disease. Self-reported pain scores (Visual Analog Scale) were strongly associated with work disability.[3] Even within the first year of diagnosis, both physical disabilities (decreased mobility, decreased dexterity, and difficulties with activities of daily living and household activities) and psychologic disabilities (anxiety and depression) are common.[4] Functional disabilities often progress more quickly during the first few years than later in the course of the disease.[5] An estimated $6.5 billion in patient earnings are lost each year as a result of RA-related disability.[6]

In addition, RA has been shown to decrease life expectancy by 4 to 10 years.[7] As one might expect, patients with more severe RA are at the greatest risk for increased mortality.[8] This increase in death rate is probably attributable to infections, complications of RA treatment (such as gastrointestinal hemorrhage and perforation induced by nonsteroidal anti-inflammatory drugs [NSAIDs]), and complications of RA itself (vasculitis, rheumatoid lung disease, amyloidosis, and atloido-occipital subluxation).[7,9]

Historical approach to treatment

The traditional approach to the treatment of RA was the NSAID-based "therapeutic pyramid." Underlying this approach was the concept that RA was a benign disease that did not merit aggressive treatment until it became very severe. Treatment began with NSAIDs and became more aggressive if these drugs failed. The second-line drugs were the hydroxychloroquine derivatives, gold therapy, penicillamine, and sulfasalazine. If these medications also failed to provide relief, then immunosuppressive or cytotoxic agents (corticosteroids, azathioprine, and methotrexate) were considered.[10] Often, 5 to 8 years passed while a patient progressed in the pyramid to more aggressive therapy.

In the past decade, studies have indicated that joint destruction begins within the first 2 years of RA.[11,12] This evidence has led to the therapeutic pyramid

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scheme being largely replaced by an approach in which early, aggressive treatment with disease-modifying antirheumatic drugs (DMARDs) is used in an attempt to prevent or delay joint destruction. Because of the importance of early treatment with active agents, early identification of patients with RA is a critical first step in the control of the pathogenesis of RA.[13] Primary care physicians have an increasing role and responsibility in this process.

Early diagnosis of rheumatoid arthritis

Two major factors influence how promptly RA is diagnosed after the onset of symptoms: the time that it takes a symptomatic person to see a physician and the time it takes the physician to make the diagnosis after the patient's initial visit. In a retrospective study of patients in whom RA was diagnosed between 1987 and 1990, Chan and colleagues[14] found that the greatest delay from symptom onset until the diagnosis of RA was the time it took the physician to make the diagnosis after the patient presented with possible RA symptoms. The median time from the symptomatic patient's first medical visit to the establishment of a diagnosis was 18 weeks, whereas the median time from the onset of symptoms to the first medical encounter was 4 weeks.[14] Even when patients had symptoms that were classically associated with RA (symmetric arthritis and positive rheumatoid factor), 40% did not have RA diagnosed until more than 6 months after their initial medical visit.[14]

Guidelines to diagnosis

Because delaying the treatment of RA can be detrimental to patients, osteopathic primary care physicians, who see a disproportionate number of patients with musculoskeletal symptoms, are faced with the urgent need to distinguish patients with RA from those with arthralgias stemming from other sources. Performing this task can be a challenge to even the most skilled diagnosticians. The American College of Rheumatology has created guidelines to aid the physician in the diagnostic process (*Figure 1*).[15] In general, RA should be suspected in any patient with the signs and symptoms of inflammatory arthritis. These signs and symptoms include the presence of prominent morning stiffness lasting for more than 30 to 60 minutes in the involved joints, the presence of redness or tenderness over any involved joints, and the detection of palpable synovitis (see "Joint Examination" later in the discussion). The diagnostic likelihood of RA is particularly enhanced when the arthritis involves more than five joints, occurs in a symmetric pattern, and appears in an at-risk individual.

At-risk populations

Rheumatoid arthritis affects people of all ages, although onset is most common in the fourth and fifth decades of life. The disease is approximately two to three times more prevalent in women than in men.[16] Genetics seems to play a role, as most people who have RA have the class II alleles HLA-DR4, HLA-DRB1, or both.[17] In addition, the concordance rate in monozygotic twins is 34%, compared with 3% in dizygotic twins.[5,18]

Joint examination

A thorough examination of the musculoskeletal system is critical to diagnosis. Whereas advanced RA may result in gross deformities, swellings, effusion, redness, warmth, and tenderness, the early findings can be subtle. Swelling of an individual joint is generally due to one of three conditions: bony enlargement, effusion, or synovitis. Synovitis can be distinguished from bony enlargement because it is soft and has a spongy or resilient texture, as opposed to the hard swelling seen in osteoarthritis. Synovitis can at times be difficult to differentiate from simple effusion in small joints, but in larger joints, effusions are ballotable, whereas synovitis is not. The detection of mild synovitis can be an important clinical clue to inflammatory arthritis, particularly RA.

In early RA, swelling in the hands is often noted in the wrists, the second and third metacarpophalangeal (MCP) joints, and the second and third proximal interphalangeal (PIP) joints. The distal interphalangeal (DIP) joints are typically spared. Later, joint erosions and joint space narrowing occur; these changes can be detected by radiographic examinations.[19] Joint and tendon destruction can produce hand deformities, including ulnar deviation of the fingers at the MCP joints, swan neck deformity of the fingers (hyperextension of the PIP joints and flexion of the DIP joints), boutonnière deformity of the fingers (flexion of the PIP joints and hyperextension of the DIP joints), and Z-deformity of the thumb (flexion of the PIP joints and hyperextension of the DIP joints).[5,19]

About one third of patients with RA have involvement of the elbow.[19] The earliest sign of elbow involvement is usually a loss of extension. Effusions and swelling of the elbow can be profound and easily observable. Effusions of the shoulder may be palpated from the anterior, but more often the only notable sign or symptom is a loss in the shoulder's range of motion.[5] Limitations in shoulder motion are observed in approximately 45% of persons with RA.[20]

The temporomandibular joint (TMJ) is commonly affected. Persons with arthritis of the TMJ have difficulty opening the mouth and experience pain while speaking or masticating.[21]

Cervical symptoms affect almost 75% of patients with RA.[19] Subluxation of the spine of patients with RA can occur at any level, but atlantoaxial subluxation is the most common (25% of patients).[19] Symptoms of cervical involvement include neck pain, stiffness, paresthesias, sensory loss, abnormal gait, and urinary retention or incontinence.[5] Although conventional radiography can detect some cervical spine abnormalities, magnetic resonance imaging is usually superior to other modalities in evaluating patients who may have serious cervical cord involvement.[22]

Signs and symptoms of hip inflammation are often difficult to distinguish in early RA. A clue that the hip may be involved is pain in the groin or thigh, particularly when the person tries to put on shoes. Pain may also be felt in the buttock or referred to the knee.[5]

Effusions of the knee are common and can be easily palpated and identified. The way a patient walks into the office can

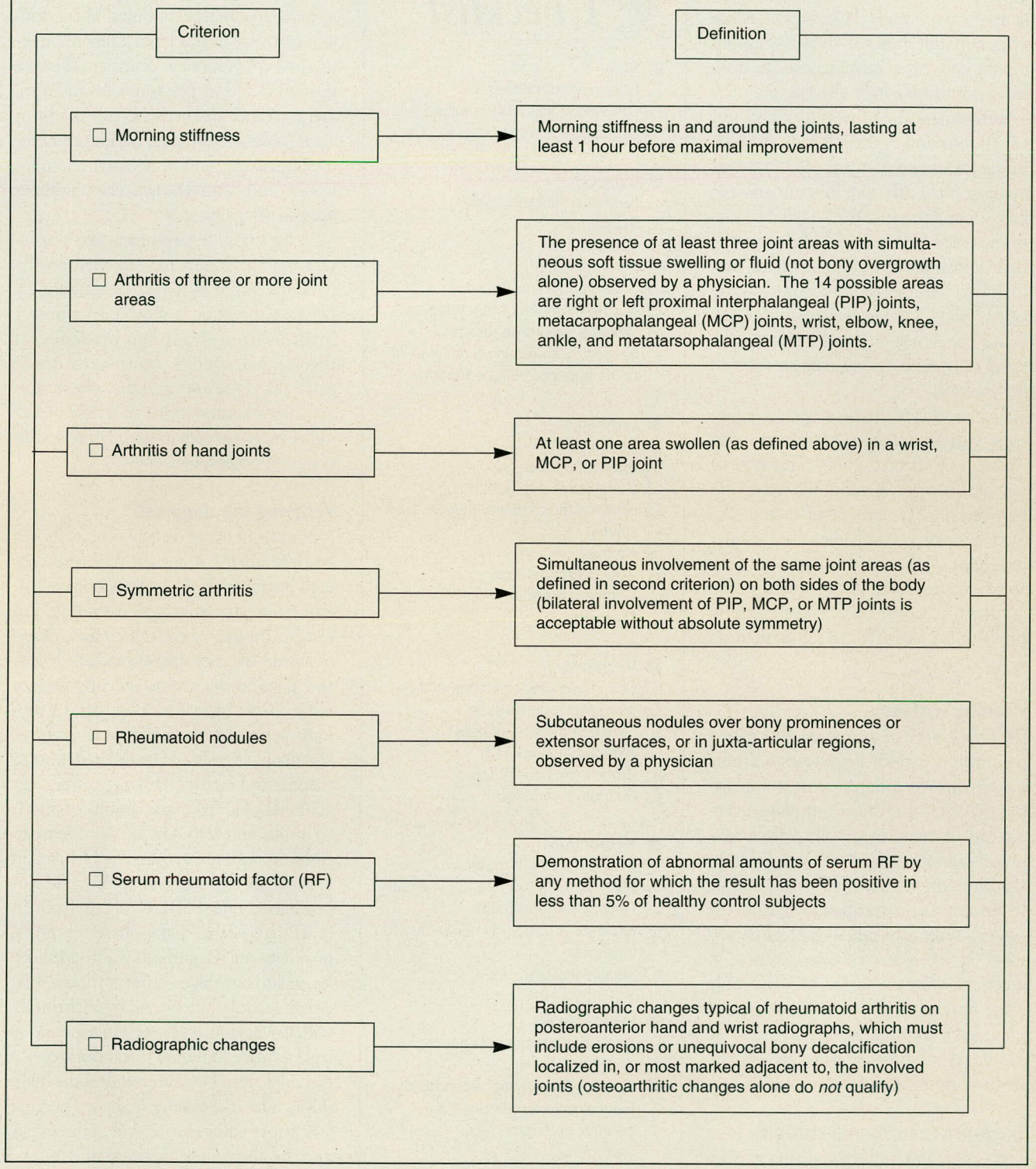

Figure 1. *American College of Rheumatology Criteria for the Classification of Rheumatoid Arthritis. For classification purposes, patients shall be said to have rheumatoid arthritis if they have satisfied at least four of these seven criteria. First four listed must have been present for at least 6 weeks. Patients with two clinical diagnoses are* not *excluded. Designation as classic, definite, or probable rheumatoid arthritis is* not *to be made. (Adapted from Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.* Arthritis Rheum. *1988;31:315-324.)*

suggest involvement of this joint. Effusion of the knee can lead to posterior herniation of the capsule (Baker's cyst). More serious manifestations, such as rupture into the calf (often misdiagnosed as deep vein thrombosis), may also occur.[5]

Inflammation of the ankles and feet is very common in early RA. In the feet, the metatarsophalangeal (MTP) joints are most often affected. Inflammation of these joints can cause the "daylight" sign (the toes spread apart). Arthritis of the MTP joints can cause dorsolateral subluxation, hammertoe deformities, and hallux valgus.[5,19] These changes, however, are late. Early on, tenderness may be noted only with lateral compression of the forefoot.

The archetypal patient with RA presents with an absolutely symmetric distribution of affected joints. This type of patient, however, is more the exception than the rule. A number of factors can affect symmetry. Large joints and less frequently used joints tend to show less deterioration, resulting in asymmetry. For unknown reasons, men tend to exhibit less symmetry of affected joints than do women.[19,23]

Morning stiffness

The importance of the presence of morning stiffness cannot be overstated. Like other forms of inflammatory joint disease, RA characteristically displays a generalized decrease in mobility after prolonged immobility such as a night's sleep. Morning stiffness invariably lasts at least 30 minutes and frequently 1 hour or longer. This prolonged "gel phenomenon" is in contrast to osteoarthritis, in which the relative joint stiffness lasts only a few minutes. Patients will not always relate such morning stiffness to disease and therefore must be asked specifically about symptoms.

Extra-articular manifestations

Extra-articular manifestations can be either very specific to RA or frustratingly vague. Generalized malaise, fatigue, and weight loss are common presenting complaints of patients with RA. Patients often attribute malaise and/or diffuse symmetric joint pain to aging rather than to a disease process. Another characteristic manifestation is the appearance of one or more rheumatoid nodules. These nodules can vary in size from a few millimeters to 2 cm or more in diameter. They are usually found at pressure sites (elbows, sacrum, head, and heels), in subcutaneous areas (extensor surfaces, fingers, and buttocks), or on tendon sheaths (Achilles tendon and hand flexors). These nodules are usually painless.[24]

A variety of less common extra-articular manifestations may be seen on the patient's initial presentation (*Figure 2*). Because the patient may not volunteer information about the presence of rheumatoid nodules, morning stiffness, generalized malaise, and the other extra-articular manifestations of RA, a meticulous interview with a thorough review of systems is necessary.

Checklist

- ■ **Skin**
  - ☐ Rheumatoid nodules
  - ☐ Cutaneous vasculitis (nailfold infarcts)
- ■ **Eyes**
  - ☐ Keratoconjunctivitis sicca
  - ☐ Episcleritis
  - ☐ Scleritis
  - ☐ Scleromalacia
  - ☐ Scleromalacia perforans
  - ☐ "Corneal melt" (corneal thinning)
  - ☐ Brown's syndrome (diplopia caused by stenosing tenosynovitis of the superior oblique tendon)
- ■ **Cardiac**
  - ☐ Pericarditis
  - ☐ Pericardial effusions
  - ☐ Constrictive pericarditis
  - ☐ Nodules (epicardium, myocardium, valves)
  - ☐ Aortitis
  - ☐ Conduction defects
  - ☐ Coronary arteritis
  - ☐ Myocarditis
- ■ **Respiratory**
  - ☐ Cricoarytenoid joint inflammation
  - ☐ Interstitial lung disease
  - ☐ Single or multiple nodules
  - ☐ Pleural effusions
  - ☐ Bronchiolitis obliterans
  - ☐ Pulmonary arteritis
- ■ **Neurologic**
  - ☐ Entrapment neuropathies
  - ☐ Myelopathies (C1 to C2, subaxial)
  - ☐ Peripheral neuropathy
  - ☐ Ischemic neuropathy secondary to vasculitis
  - ☐ Muscle atrophy
- ■ **Hematologic**
  - ☐ Anemia of chronic disease
  - ☐ Thrombocytosis
  - ☐ Splenomegaly/lymphadenopathy
  - ☐ Felty syndrome (rheumatoid arthritis, splenomegaly, leukopenia)

Figure 2. *Extra-articular features of rheumatoid arthritis. (Source: Ahern MJ, Smith MD: Rheumatoid arthritis.* Med J Aust. *1997;166:156-161.)*

Verifying the diagnosis

A number of initial diagnostic tests should be ordered for a person who presents with putative RA. These tests include general chemistry analyses, liver function tests, complete blood cell counts, determination of acute-phase reactant levels, and tests to determine the presence of other disease processes. If signs and symptoms persist for more than a few weeks, additional tests should be ordered: tests of rheumatoid factor (RF) and antinuclear antibodies (ANAs), radiography of affected joints, and tests specific for other diseases. Abnormalities that may be noted in RA include elevations in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and other acute-phase reactants; positivity for RF and other autoantibodies, including ANAs; normocytic anemia, either normochromic or hypochromic; widely varying levels of leukopenia or leukocytosis; and mild thrombocytosis.[25] No single test, however, secures the diagnosis. The *Table*[5,18,26-29] shows normal laboratory values for several of these tests and the alterations expected in RA.

■ *Rheumatoid factor*—Although RF is present in about three quarters of patients with RA, its presence is neither necessary nor sufficient to make the diagnosis of RA. In fact, the patient with the earliest presentation is likely to be RF negative.

Table
Laboratory Tests and Typical Alterations in Rheumatoid Arthritis

Laboratory test	Normal value	Alteration in rheumatoid arthritis	Sensitivity, %
☐ Rheumatoid factor	Negative*	Positive (>1:20 titer)[26]	75
☐ Erythrocyte sedimentation rate, mm/h		Elevated	60 to 80†
— Males	0 mm/h to 15 mm/h		
— Females	0 mm/h to 20 mm/h‡[26]		
☐ Antinuclear antibody (titer)§	Negative (<1:20)[26]	Positive (titers 1:20 or 1:40; titers of ⩾1:320 more clinically meaningful)[27]	30 to 40
☐ C-reactive protein, μg/dL (μg/L)	6.8 to 820 (68 to 8200)[26]	Elevated (>820 μg/dL)	60 to 80
☐ Hematocrit		May be decreased because of drug-induced gastrointestinal bleeding or because of chronic disease[5]	...
— Males	0.39 to 0.49 (39% to 49%)		
— Females	0.33 to 0.43 (33% to 43%)[26]		
☐ White blood cell count, No./mm^3	3200 to 9800[26]	Often elevated in early disease[28]	...
☐ Platelet count, No./mm^3	130,000 to 400,000[26]	Often elevated in early disease[28]	...

* Rheumatoid factor may be elevated in healthy persons.[18]
† Level varies with disease activity.
‡ Normal erythrocyte sedimentation rate may increase with a patient's age.[29]
§ Antinuclear antibody is nonspecific and present in a small percentage of healthy individuals, as well as frequently in the presence of other connective tissue diseases.

Because RF becomes progressively more reactive over time, the same patient may be RF positive 3 to 6 months later.

Alternatively, RF positivity does not secure the diagnosis of RA. Rheumatoid factor is seen in a wide variety of other inflammatory and autoimmune diseases, including systemic lupus, scleroderma, vasculitis, myositis, sarcoidosis, and other conditions, as well as in a wide variety of infections, including subacute bacterial endocarditis and hepatitis C infection. Thus, in considering RF positivity in the diagnosis of RA, it is important to note that it is a test of only moderately high sensitivity and relatively poor specificity. It is most valuable when interpreted in light of a clinical picture suggestive of RA.

Once patients become RF positive, they tend to remain RF positive. Accordingly, repeated testing for RF positivity is not necessary once RA has been definitively diagnosed.

■ *Erythrocyte sedimentation rate and C-reactive protein*—Both the ESR and CRP are acute-phase reactants and nonspecific indicators of inflammation. Elevations of the acute-phase reactant levels are typical of the rheumatoid process, but not diagnostic of it. The sensitivity of elevated acute-phase reactant levels varies in the presence of RA: early and mild disease may be associated with normal or only minimally elevated acute-phase reactants. The specificity of these tests is also extremely low, because their results may be abnormal in virtually any inflammatory disease, including autoimmune disorders, infections, and malignancies. From a practical perspective, the presence of elevated acute-phase reactants is most useful when a patient demonstrates polyarticular joint pains with only equivocal evidence that an inflammatory process is the cause. Marked elevations of the acute-phase reactants would encourage the physician to more actively pursue a diagnosis of an underlying inflammatory condition. Normal levels of acute-phase reactants should reassure the clinician that the musculoskeletal pains are probably of noninflammatory etiology. Common conditions such as osteoarthritis and fibromyalgia syndrome are by definition associated with normal acute-phase reactants.

■ **Radiologic tests**—The presence of bony erosions can add a high degree of

diagnostic specificity for RA, but they are not typically present early in the disease. Radiographic signs of RA often take 1 to 2 years to emerge. Bony erosions can often be seen in the feet before the hands; thus, in patients with long-standing joint symptoms, a screening posteroanterior radiograph of both hands and feet not only serves as a baseline but also may provide useful diagnostic information.

Differential diagnosis

Most patients with RA present with vague stiffness, swelling in a few joints, and perhaps pain or warmth in varying degrees—all symptoms that could be associated with other diseases. Therefore, a thorough history and physical examination are crucial for differential diagnosis. Several conditions that mirror RA are described in the following sections.

■ *Chronic polyarthritis*—Chronic polyarthritis can be caused by a number of diseases with immunologic bases. A detailed discussion of these diseases is beyond the scope of this article. The most common diseases that can resemble RA are systemic lupus erythematosus, vasculitis, polymyositis, scleroderma, and the spondyloarthropathies (ankylosing spondylitis, Reiter syndrome, and enteropathic arthritis). Symptoms of these diseases often overlap and can be diagnostically challenging.[30] The presence of an erythematous facial rash or a history of photosensitivity or serositis may suggest lupus, particularly in a young woman. The presence of marked fever, constitutional symptoms, peripheral neuropathies, or a suggestive rash may suggest the presence of some form of systemic necrotizing vasculitis. The skin should be scrutinized for the changes of scleroderma. The spondyloarthropathies may occasionally present as polyarthritis, although usually the joint manifestations are limited to one joint or fewer than five joints. Prominent involvement of the spine, as well as suggestive genitourinary or gastrointestinal symptoms, should warrant further investigation for one of these disorders.

Chronic polyarthritis can also be caused by diseases such as amyloidosis, hemochromatosis, and sarcoidosis. Even polyarticular gout can be confused with advanced RA, and noninflammatory osteoarthritis occasionally resembles early-onset RA. This confusion can be complicated by the coexistence of osteoarthritis and RA in some older patients.

■ *Viral infections*—Patients with viral illnesses (for example, those caused by hepatitis B virus, parvovirus B19, Epstein-Barr virus, cytomegalovirus, and rubella infections) can present with acute rheumatoid-like features such as malaise, weakness, weight loss, and polyarthritic swelling and pain. A careful interview may elicit a history of recent sick contacts, fevers, or more specific symptoms of viral infection. If a viral infection appears likely, appropriate management should be instituted. However, most virally associated articular syndromes will clear in 4 to 8 weeks or less.

Considerable patience should be exercised in making a diagnosis of RA. Rarely is it necessary to make a diagnosis of RA at the first or second office visit. Symptomatic therapy for arthritis can commence before a secure diagnosis is made. The diagnosis of RA carries a variety of stigmata that affect the psychosocial fabric of the patient and the patient's family. Symptoms should persist for at least 6 months before a definite diagnosis of RA is made, although treatment can and should commence on a systematic basis much earlier. Because so many disease processes can resemble RA, a rheumatologist should be consulted when a patient has symptoms suggestive of RA.

Treatment

The most important aspect of the treatment of RA is counseling the patient and the patient's family. The impact of arthritis on family interactions and on the patient's ability to participate in workplace activities needs to be taken into account. Support from the local chapter of the Arthritis Foundation can be of great help, particularly in providing educational materials.

The role of physical therapy and exercise cannot be overemphasized. Patients need to be instructed in the principles of joint protection and joint motion, that is, putting each major joint through a full range of motions several times each day. Moderate aerobic exercise can also be of benefit in the treatment of RA, as long as excessive impact loading is avoided and the exercise does not cause a significant flare-up of the underlying condition. Counseling on diet and nutrition is also important. The role of the osteopathic primary care physician in instituting these measures is of vital importance.

Drug therapy

Treatment of RA often involves combination modes of therapy, which have proved more effective than single-drug modalities in many studies.[31,32] Often, more than one DMARD is combined with an NSAID and low-dose corticosteroids to provide both aggressive treatment of the disease process and alleviation of patient discomfort.

■ *Nonsteroidal anti-inflammatory drugs*—NSAIDs, formerly the standard treatment for early RA, are now thought to be only palliative. NSAIDs do not appear to change the pathophysiology or progression of RA.[33] These medications affect inflammation at the last steps in the inflammatory cascade. Although they are still a mainstay of treatment, they are used only to improve patient comfort. The new specific cyclooxygenase-2 (COX-2) inhibitors likewise will not halt disease progression, although they reduce gastrointestinal erosions and may prove to be safer than traditional nonselective inhibitors.

■ *Disease-modifying antirheumatic drugs, immunosuppressive drugs*—By definition, DMARDs induce a decrease in general inflammatory activity.[34] Because of their anti-inflammatory effects, DMARDs can "modify" disease activity and positively influence the course of RA.[10] As will be discussed later, the most favorable results are achieved when DMARD therapy is instituted early in the course of RA (within at least 2 years of diagnosis).[31,35] Even a mean delay of 8 months in initiating treatment has been shown to result in significantly greater progression of joint destruction visible on radiographs compared with initiation of DMARD treatment immediately after diagnosis.

The different DMARDs have diverse

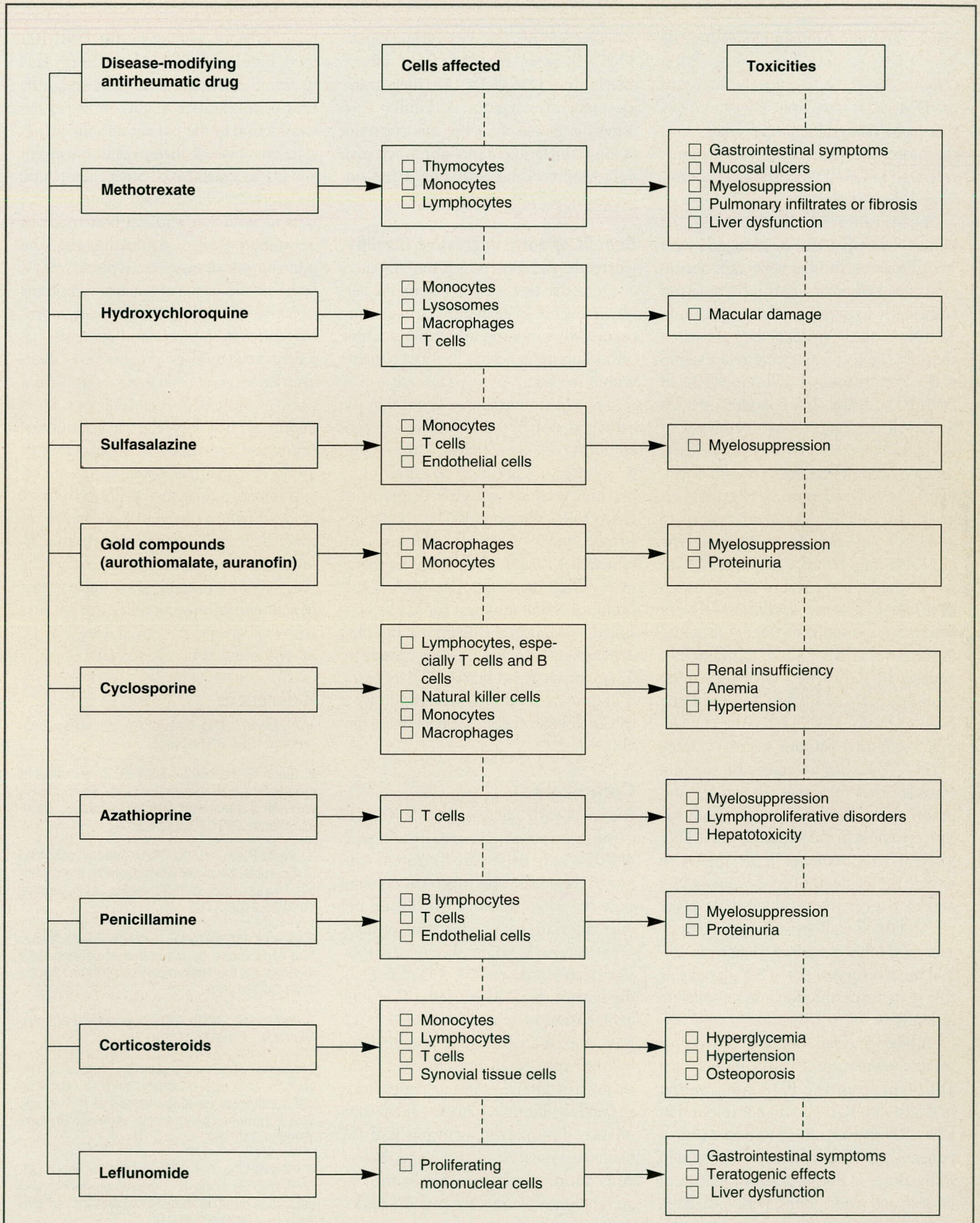

Figure 3. *Characteristics of commonly used disease-modifying antirheumatic drugs. (Sources: References 36 and 37.)*

effects early in the inflammatory cascade that appear to slow disease progression (*Figure 3*[36,37]). Unfortunately, many of the DMARDs have toxic adverse effects that make them difficult to manage. Furthermore, the vast majority of patients receiving DMARD therapy have continuing disease symptoms.

Although a small percentage of patients with RA can be managed with NSAIDs alone, most patients cannot control their symptoms and inflammation sufficiently to avoid disease progression. At this point, the primary care physician should establish a working relationship with a rheumatologist skilled in the use of DMARD therapy. This consultation helps to develop an aggressive program of DMARD therapy that will provide the optimal ratio of benefits to risks. The primary care physician needs to remain an active part of the treatment care team and to be poised to deal with the general health maintenance of patients with RA throughout the rest of their lives.

■ *Biologic response modifiers*—Recent research has sought to target particular cytokines that have a role in the pathogenesis of RA. One major approach recently approved by the Food and Drug Administration (FDA) is the use of a soluble receptor to tumor necrosis factor (TNF).[38] Tumor necrosis factor is a cytokine that regulates cell activity and modulates the production of inflammatory cytokines in the joints. Elevated TNF levels in the rheumatic joint appear to induce the proliferation of synoviocytes and to trigger the production of prostaglandins, metalloproteinases, collagenase, and other cytokines. Data from animal models suggest that TNF plays a key role in tissue destruction and remodeling in RA.[39-41]

A bioengineered soluble TNF-receptor protein (etanercept) has recently received approval from the FDA for treating patients with RA who do not respond to DMARD therapy. In clinical trials, most patients receiving etanercept improved in all measures of disease activity (number of swollen and tender joints, ESR, CRP level, patient and physician assessments, pain, functional disability as assessed by the Health Assessment Questionnaire, and morning stiffness).[42] Etanercept blocks TNF activity and may have fewer adverse effects than DMARDs. Another strategy under investigation to inhibit TNF activity is the use of human chimeric monoclonal antibodies; this approach also appears promising, although it has not yet received FDA approval.[43]

Benefit of early aggressive therapy

Currently, the consensus is that the earlier aggressive treatment is begun, the better. Irreversible cartilage damage may occur within months, and damage visible on radiographs occurs in most patients within the first 2 years of disease.[11]

There is thus ample evidence that the early initiation of therapy is likely to benefit most patients with RA. Unfortunately, months of clinical observation often preclude a confirmed early diagnosis of RA.[14] Once the diagnosis has been confirmed, most nonrheumatologists are reluctant to begin antirheumatic therapy.[44] When the diagnosis of RA is suspected, a rheumatologist should be consulted to confirm the diagnosis and plan a treatment strategy. A recent study of 233 patients found that in 70% of cases, a diagnosis of RA can be made by a rheumatologist within 2 weeks of the first visit.[45]

Comments

Although early identification of RA is of utmost importance, treatment with NSAIDs may be initiated before a confirmed diagnosis. This treatment does not slow the progression of the disease but does alleviate some pain and swelling. When diagnosis becomes certain, aggressive treatment should be initiated. First, the patient should be given a thorough explanation of what is expected if RA progresses and what can be accomplished by therapy. Such education by the rheumatologist can alleviate patient anxiety and significantly increase patient compliance. Any patient who has had RA diagnosed must be carefully and responsibly monitored, and this cannot be accomplished without the patient's understanding and compliance.

Once treatment has begun, improvement should be apparent within weeks to months, depending on the DMARD used. If traditional DMARD therapy fails to significantly decrease pain and stiffness or to improve quality of life to the satisfaction of the patient and the physician, then biologic therapy with etanercept should be considered. Such therapeutic decisions are critical in the treatment of a patient with RA and are best made in consultation with a rheumatologist. The ultimate goal of treatment is disease remission (defined as the absence of symptoms of active inflammatory joint pain, morning stiffness, fatigue, and synovitis on joint examination; no progression of damage visible on sequential radiographs; and normalization of ESR or CRP levels).[13,46] People with RA rarely reach complete remission, but optimal treatment can allow them to feel better (often better enough to return to the lifestyles they enjoyed before they had RA). In the future, the tolerability of new cytokine inhibitors such as etanercept may change the risk-benefit equation, allowing patients to start earlier on second-line therapy and reap the benefits of reduced disease activity without cumulative toxicity.

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