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Rheumatoid arthritis has often been a diagnostic and therapeutic challenge for primary care physicians. The manifestations are often varied in presentation, and an accurate and confident diagnosis can be missed or delayed. Recent advances that provide effective treatment of newly diagnosed disease have markedly improved the morbidity of what used to be a devastating disease leading to deformity and disability. This article highlights the important role of the primary care physician in determining a proper diagnosis, knowing when to refer to a rheumatologist or orthopedic surgeon, and effectively employing the increasingly wide therapeutic armamentaria.

—The Editor

Rheumatoid Arthritis: Diagnosis and Management

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Introduction and History

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by swelling, pain, stiffness, and destruction of joints.[1] RA is the most common form of inflammatory arthritis, estimated to affect 0.5-2% of the population in the United States.

While RA is truly a systemic disease with potentially multi-organ involvement and systemic consequences, the musculoskeletal manifestations are responsible for the majority of morbidity and disability in affected individuals.

Currently, treatment in the field of rheumatology is moving at a quick pace with multiple molecular targets individually singled out for disease modification. In many cases of RA, with these newer therapies disease remission is essentially achieved. Treatment strategies include early diagnosis, recognition of complications of RA, aggressive treatment of the disease with chemotherapeutic agents (disease modifying anti-rheumatic drugs, or DMARDs) and the newer biologic agents which need to be used in close cooperation with an arthritis specialist. Palliation of symptoms is no longer acceptable in the treatment of RA.

Statement of Financial Disclosure

To reveal any potential bias in this publication, we disclose that Dr. Colburn (author) serves on the speaker's bureau for Abbot. Dr. Hawkins (peer reviewer) serves on the speaker's bureau and owns stock in Pfizer. Dr. Lee (author) and Dr. Wise (Editor-in-Chief) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Epidemiology

Years of research show that there are particular genetic links to the development of RA. Studies of twins show high concordance rates for acquiring RA. Moreover, there are several populations of Native Americans that have higher prevalence rates of RA than are present in the general population. The Yakima and Pima tribes, in particular, have a relative risk of 3.3 for developing RA if they have the allele HLA DRB1*1402.[2] Among Asians the gene susceptibility for RA is HLA DRB1*0405, and for Caucasian North Americans they are HLA DRB1*0101,*0401, and*0404.[3]

RA classically affects women in childbearing years. Population studies demonstrate that RA is also a disease of aging, hence the bimodal age curve for acquiring RA. Like so many other conditions including cancer and atherosclerosis, RA may exhibit a senescence of the immune system, in particular the T lymphocytes, as a part of its pathogenesis. This partially may explain why RA frequently affects the elderly.[4]

Another risk factor for the development of RA is smoking. According to recent studies, tobacco use increases the incidence and severity of RA and of autoantibody production.[5]

Pathophysiology

There are many complex molecular pathways in the pathogenesis of RA, and thus multiple potential targets for therapy. Many cells of the immune system are important in the inflammatory cascade and have mechanistic importance for the tissue damage seen in patients with RA.

The key cell involved in the inflammatory response mounted by the body against the rheumatoid synovium is the T lymphocyte.[6] T cells found in aggregates in diseased synovial tissues are activated in an antigen-dependent fashion. Other immune cells like synovial fibroblasts, macrophages, and B-lymphocytes are subsequently activated, with expression of pro-inflammatory cytokines and proteases, like matrix metalloproteinases.[7]

In the last decade, pro-inflammatory cytokines have become the therapeutic targets most exploited in treating RA. Tumor necrosis factor alpha (TNF-alpha) is central in the process of inflammation. TNF-alpha expression leads to downstream expression of other powerful inflammatory cytokines, including interleukin-6 and interleukin-1. These three cytokines and many others are presently targets for therapy with the new biologic agents that will be discussed later in this paper.

Clinical Manifestations

Almost any synovial joint in the body can be affected by RA. However, the small joints of the hands and feet are the most commonly inflamed. Typically the initial symptoms of active RA include pain with swelling, warmth, erythema, and stiffness in the small joints of the hands and feet, later spreading to many other synovial joints.

As the synovium becomes chronically inflamed, surrounding structures such as ligaments and tendons become damaged, often leading to the ulnar and fibular deviation, which is readily recognizable in patients with years of uncontrolled disease. In severe cases, subluxation of the metacarpophalangeal (MCP) and proximal interphalangeal joints (PIP) from ligament damage as well as frank rupture of tendons can be seen. Marked decreases in the range of motion from joint contractures are commonly seen in the wrists and elbows. Interestingly, the distal interphalangeal joints (DIP) are rarely affected with RA, although osteoarthritis can occur concomitantly. Disease involvement in the DIPs suggests another type of arthritis, such as osteoarthritis, psoriatic arthritis, reactive arthritis, or crystal-induced arthritis.

Constitutional symptoms including fever, weight loss, malaise, and fatigue are commonly seen in the active stages of RA. The stiffness is worse in the mornings, typically lasting over one hour, which often improves with a hot shower or bath. Stiffness also accompanies periods of inactivity.

The onset of RA may be profoundly abrupt. However, it may also have a more insidious beginning, sometimes with a monoarticular presentation followed by the progression to involve other joints over time.

Chronic synovial inflammation at the C1-C2 junction can lead to atlanto-axial instability with potentially severe consequences that are described later in this article. Of particular interest to the primary care practitioner making a decision about a patient's suitability for surgery requiring anesthesia, is the fact that cervical spine instability in patients with RA may make intubation a very complicated and dangerous procedure.

Extra-articular Clinical Manifestations. RA affects more than joints. Many organs of the body may be severely affected

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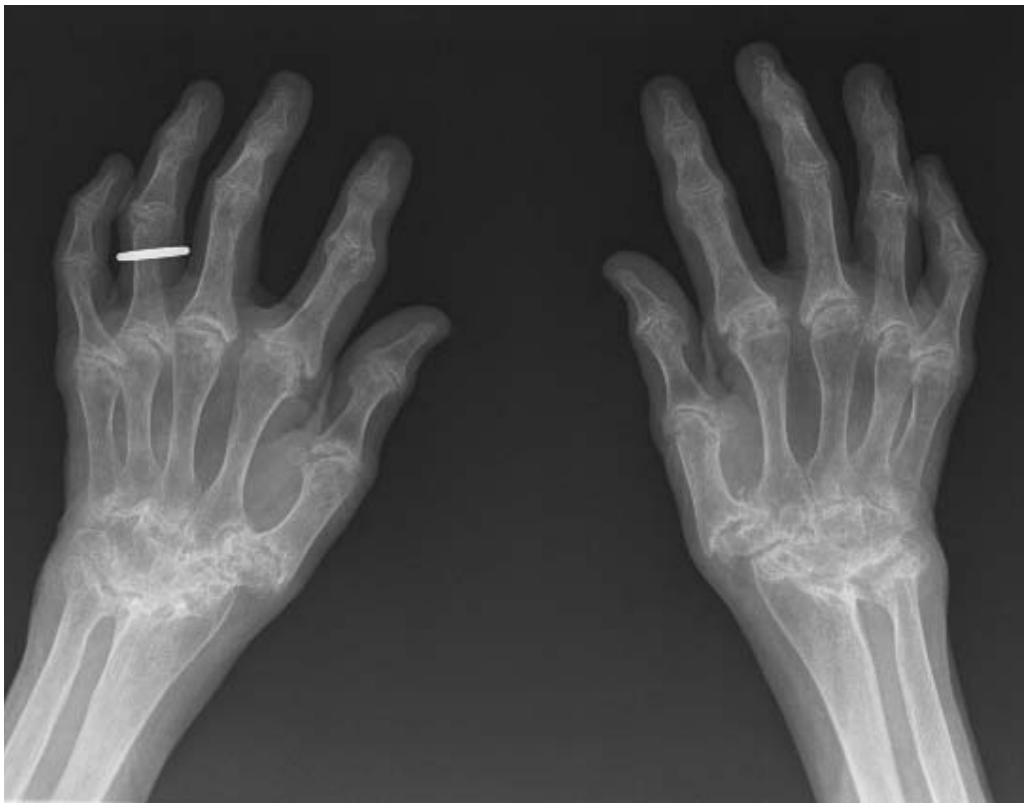
Figure 1. Marked Changes at the MCPs and Narrowing of the Intercarpal Joints



There is also secondary osteoarthritis at the DIPs.

by this disease. Rheumatoid vasculitis is a rare but potentially serious, life-threatening complication of RA. Without appropriate treatment, the average life expectancy of these patients is about two years. Symptoms of rheumatoid vasculitis in some ways resemble polyarteritis nodosa except for the skin manifestation. Small digital infarctions, especially around the nails, may be the first clue of vasculitis in the patients with RA. Early skin findings may also appear as small, raised purpuric lesions that can advance, if untreated, to significant tissue ischemia. Ulcerations of the legs are another skin manifestation of this condition. Rheumatoid vasculitis occurs mainly in the seropositive RA patients with severe, longstanding disease. Patients with Felty's syndrome are more likely to develop rheumatoid vasculitis, although they may not have active synovitis at its onset. Sensorimotor neuropathy and mononeuritis multiplex, especially with wrist or foot, drop can occur. Other manifestations of rheumatoid vasculitis include major organ failure including mesenteric, coronary and cerebral artery infarction. Laboratory tests that can be helpful in recognizing rheumatoid vasculitis include an increased sedimentation rate, a high rheumatoid factor level, pANCA, low complement levels, serum cryoglobulins, and circulating immune complexes. It is thought that widely fluctuating doses of corticosteroids may be associated with the onset of this condition. Corticosteroids and immunosuppressive agents, especially cyclophosphamide, are required to manage the potentially life-threatening complications of RA vasculitis that can occur. This condition is seen less commonly today given the newer advances in therapy.

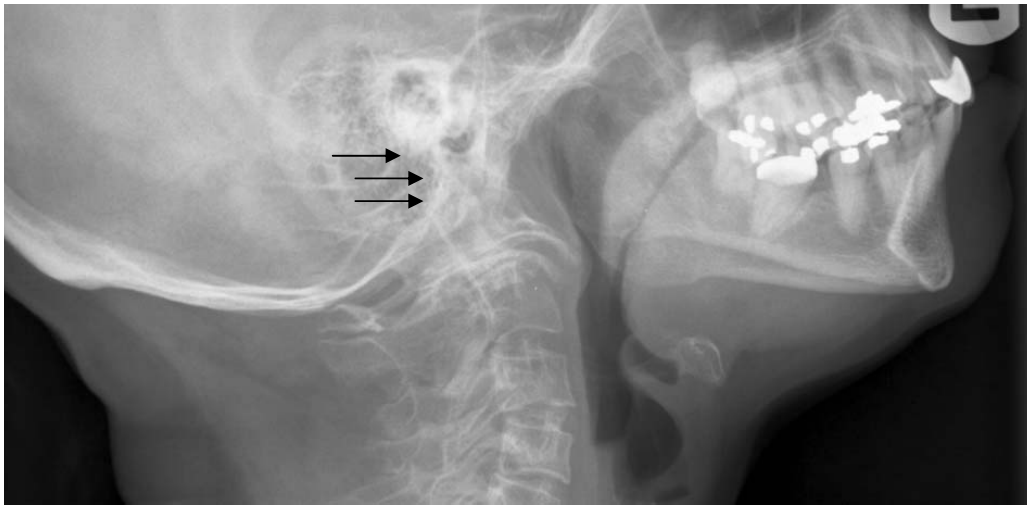
Felty's syndrome is another uncommon manifestation of longstanding, severe RA. It is characterized by granulocytopenia, splenomegaly, and frequent infections and skin ulcers. The focus of treatment should be directed at the underlying RA. Patients with Felty's typically respond to methotrexate, but higher doses of prednisone are sometimes required to raise the granulocyte count. Typically 30-50 mg of prednisone daily is required for several days and IV methylprednisolone may be required. Additionally, granulocyte stimulating factors like GM-CSF (Neupogen) are sometimes required to raise the white blood cell count.

Subcutaneous rheumatoid nodules, resulting from a form of vasculitis in rheumatoid patients, are another skin manifestation. They are most commonly found in the seropositive RA population. The nodules are firm and rubbery in consistency and usually form on extensor surfaces like the elbow, but can be found in multiple other sites, including the lung and heart valves. They occasionally worsen with the concomitant use of methotrexate.[8]

RA-associated eye disorders are also rare, but can lead to blindness. Milder, frequently self-limiting episcleritis features injection of the small vessels on the surface of the eye and a pressure like pain and discomfort. Scleromalacia is recognized by the graying or blackening of the sclera as the result of scleral thinning due to chronic ocular inflammation. Paradoxically, the scleromalacia perforans, which is the rupture of the sclera with loss of the vitreous, is not as painful as scleritis, simple scleromalacia, or episcleritis. Globe rupture is rare. It is believed that the inciting lesion in fact may be a rheumatoid nodule on the sclera.[9]

Secondary amyloidosis is the deposition of protein that can be a consequence of many inflammatory conditions, including RA. The kidney is the most commonly affected organ with amyloidosis in patients with RA. For unknown reasons, renal amyloidosis in patients with RA rarely occurs in the United States, but occurs more frequently in Europe. Renal involvement is first manifested as proteinuria, and is mainly seen in longstanding, aggressive seropositive patients with RA.[10]

Figure 2. Cervical Subluxation into the Base of the Cranium with the Dens of the Axis Penetrating the Foramen Magnum



Laboratory Findings

The serum rheumatoid factor (RF) determination was one of the early tests that supported the diagnosis of RA and suggested an aberrant immunoregulatory basis of the disease. RFs, as measured in most clinical laboratories, are IgM immunoglobulins autoreactive against IgG. RFs are present in 75-80% of all patients with RA. Those patients who are seropositive for RFs tend to have more aggressive disease with joint erosions and extra-articular involvement.[11]

Recently, the measurement of antibodies to cyclic citrullinated peptides (anti-CCP) has emerged as a more highly specific diagnostic tool differentiating RA from other inflammatory arthritides.[12,13] The anti-CCP test combined with a positive RF has specificity for the diagnosis of RA of 96%.[14] Studies indicate that anti-CCP are present in the sera of individuals years before they develop the clinical findings of RA.[15] Circulating anti-CCP autoantibodies may also predict a more aggressive subtype of RA that is more refractory to treatment.[16]

Other biomarkers that are useful in the diagnosis and monitoring of disease activity are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The ESR and CRP are not specific for RA. Other factors including red blood cell disorders and anemia as well as paraproteins can alter the accuracy of the ESR. The CRP is a more accurate indicator of acute inflammation. Together, the ESR and the CRP can predict more aggressive tissue damage and joint erosions in patients with RA.[17]

Nonspecific indicators of inflammation such as anemia, thrombocytosis, and an elevated ferritin may be found in laboratory tests of patients with RA, as is seen in other chronic inflammatory disorders.

Proteinuria in a longstanding patient with RA may indicate the need to screen for amyloidosis.

Radiographic Findings

One of the earliest radiographic findings of patients with RA is the soft-tissue swelling of synovial inflammation, which transitions later to marginal joint erosions with periarticular osteopenia and joint space narrowing (as a result of cartilage loss). Radiographic findings tend to be symmetrical. Joint space narrowing typically occurs in joints like the metacarpophalangeal, the proximal interphalangeal, radiocarpal, and intercarpal joints. (*See Figure 1.*) The earliest signs of erosive disease often occur in the MTP joints of the feet. As opposed to the superior joint space narrowing of osteoarthritis, there may be axial or medial narrowing of the hip joints in RA. A hallmark of the synovial inflammatory changes of RA is joint space narrowing with the absence of osteophytes, which are typically present in osteoarthritis.

Later x-ray findings include mal-alignment of joints, including the classical ulnar deviation of the hands and fibular deviation of the toes, as well as the destruction and fusion of the carpal bones. The damage to the supporting ligaments of the fingers can lead to the classic swan-neck and boutonniere deformities that characterize advanced RA.

Advanced synovial inflammation of the atlanto-axial joint mandates an examination of the x-rays of the cervical spine in flexion and extension by an experienced radiologist. Instability of the upper cervical joints may pose a potentially lethal complication for an RA patient if he/she suffers even minor whiplash or other neck trauma since the spinal cord is not protected as in someone with a normal C-spine. There are pre- and peri-operative complications possible in these patients if advanced changes of cervical spine subluxation or cranial settling are present. (*See Figure 2.*) This is especially true during intubation or while moving the patient around during anesthesia.

Emerging imaging modalities have helped in identifying some of the more challenging cases of RA. Techniques such as musculoskeletal ultrasound can clarify if nonspecific thickened tissue around a joint is clearly synovitis with hyperemia, and if early erosions of cartilage not apparent on plain radiographs are indeed present.

Magnetic resonance imaging (MRI) is another of the new joint imaging techniques with more sensitivity to the early changes of RA than seen in plain x-rays. In particular, several studies have demonstrated, in the first 6 months of disease, the superiority of MRI over plain x-rays for detection of subtle erosions.[18] As costs of these modalities become more affordable and practitioners acquire the knowledge to utilize them, earlier detection should be possible.

Diagnosis

It is casually noted by some rheumatologists that a good his-

Table 1. 1987 Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis

CRITERIA	DEFINITION
1. Morning stiffness	Morning stiffness of affected joints lasting at least 1 hour
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft-tissue swelling or fluid. Included are the PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Involvement of the same joints bilaterally
5. Rheumatoid nodules	Subcutaneous nodules over extensor surfaces
6. Serum rheumatoid factor	Abnormal titers of serum rheumatoid factor
7. Radiographic changes	Radiographic changes of periarticular osteopenia, joint space narrowing, or erosions

Adapted with permission 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.

tory from the patient makes up 85% of the information necessary for a diagnosis in, and differentiation of, rheumatologic diseases. The physical exam is worth about 15% of the diagnosis, and the laboratory and x-rays make up the last 5% of the information necessary to diagnose a rheumatologic condition. This is certainly true for RA if one accepts the above premise. Early recognition and the careful consideration of the many mimickers of RA are important because the early treatment and reduction of symptoms will affect long term prognosis of the disease. The American College of Rheumatology (ACR) established the ACR classification criteria for RA in 1987.[19] (*See Table 1.*)

Classification criteria were originally used for epidemiologic and research purposes and should not be a substitute for good clinical judgment. If a patient meets 4 of these 7 criteria with symptoms for at least 6 weeks, these criteria can be a useful tool to assist the clinician in making a diagnosis of RA versus other forms of arthritis.

Classification criteria, however, are not perfect, and many patients with RA may not strictly meet the ACR criteria, especially early in the disease. The criteria on occasion may not be met even later in the disease progression.[20]

Differential Diagnosis

The importance of differentiating RA from other mimickers is important given the implications of some of the treatment used for RA. (*See Table 2.*) Acute hepatitis B infection can have a polyarthritis as one of its presenting symptoms,[21] but treating a hepatitis B patient with immunosuppression might be disastrous.

Osteoarthritis is differentiated from RA by a careful history and physical examination and the appearance of the joint x-rays. In OA, the joint symptoms tend to worsen with activity and weight-bearing joints are more frequently affected, whereas in RA activity usually results in improvement of the pain and stiffness. Unlike in RA, patients with OA may have involvement of their DIP joints of the fingers. Fibromyalgia can be mistaken for an inflammatory arthritis, as many of these patients complain of morning stiffness, but the physical exam will be devoid of synovitis and there will be no abnormality in their laboratory tests (most importantly, in the acute phase reactants).

Some of the more challenging diagnoses that may resemble RA are systemic lupus erythematosus (SLE), psoriatic arthritis, acute parvovirus B19, hemochromatosis, atypical spondyloarthritis (like ankylosing spondylitis or psoriatic spondylitis) and even crystal deposition arthritides, like gout and pseudogout (or pseudo-rheumatoid arthritis as it sometimes has been called).

Treatments: Conventional

Many of the specific treatments for RA have evolved and indeed so have treatment paradigms. Prior to 1990, the "step-up" approach to RA, starting with bed rest, physical therapy, aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) gradually increasing doses and later adding gold injections to the regimen were the mainstays of therapy for RA. In the mid 1980s methotrexate started to replace gold as the preferred drug therapy for RA. Today, the emphasis in treatment of RA is on early, aggressive treatment with disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate and leflunomide (Arava), and the rapid introduction of one of the new biologic agents to induce control or remission of this disease and to markedly reduce long-term complications of RA. These drugs will be discussed in more detail below.

RA is a heterogeneous disease with variable severity and manifestations in multiple organ systems and does not yet have a cure. Very early in treatment physicians attempt to modify the

Table 2. Rheumatoid Arthritis: Differential Diagnosis

NONINFLAMMATORY
- Osteoarthritis
- Fibromyalgia

METABOLIC
- Hemochromatosis
- Wilson's disease
- Primary biliary cirrhosis

CRYSTAL-INDUCED
- Gout
- Pseudogout/CPPD
- Hydroxyapatite arthropathy

SPONDYLARTHRITIDES
- Ankylosing spondylitis
- Reactive arthritis
- Psoriatic arthritis
- Enteropathic arthritis

INFECTIOUS
- Parvovirus B19
- Hepatitis B
- Bacterial endocarditis
- Rheumatic fever
- Lyme disease
- Infectious arthritis (gonococcal)

VASCULITIDES
- Wegener's granulomatosis
- Behçet's disease
- Polymyalgia rheumatica

CONNECTIVE TISSUE DISEASE/MISCELLANEOUS
- Systemic lupus erythematosus
- Polymyositis
- Multicentric reticulohistiocytosis
- Sarcoidosis
- Still's disease
- Periodic fever syndromes

disease using DMARDs. Even before starting DMARDs, it is important to palliate the symptoms of patients with RA. NSAIDs and/or low dose corticosteroids are often instituted early in the course of RA, based on their anti-inflammatory and analgesic properties. However, the long term use of NSAIDs is of less importance in treating patients with RA because their effect is minimal compared to DMARDs and the biologic agents. Furthermore, there is no evidence that NSAIDs modify the progression of disease. Medications like ibuprofen, naproxen, diclofenac, and indomethacin, if used, are frequently combined with proton pump inhibitors for gastric protection, especially in elderly patients. This combination is probably as effective for prevention of GI symptoms as using the COX-2 NSAIDs.

Corticosteroids are very potent anti-inflammatory drugs that can be instituted early in the treatment of RA, but their chronic use should be limited to less than 10 mg of prednisone equivalent, preferably below 7.5 mg, given their extensive side effect profile when used long term. One initial intramuscular methylprednisolone injection for acute inflammatory polyarticular arthritis at 1-2 mg/kg is very helpful in rapidly reducing the pain and swelling of joints in RA while waiting for the DMARD to take effect. Giving the corticosteroid IM may reduce the temptation a patient may have to self-medicate with prednisone at higher than prescribed doses on their own. However, short courses of low dose oral corticosteroids are preferred by some physicians and may also be used to reduce the signs and symptoms of RA while DMARD therapy is being initiated. If there are only a few affected joints, or if one or two joints are especially inflamed more than others, an intra-articular corticosteroid injection may be the best way to decrease pain and inflammation while minimizing adverse effects.

Methotrexate is the most commonly used first-line treatment for RA by rheumatologists, and is the standard to which most of the newer DMARDs and biologic agents are compared. It can be given orally, or by IM injection for those with GI intolerance to the drug. Methotrexate is commonly used as monotherapy or combined with other DMARDs and as adjunct with the biologic agents. It has been shown to slow radiographic progression of RA.[22] Methotrexate is given once weekly from 7.5 mg to 25 mg. It is usually well tolerated and effective in decreasing the pain, swelling, and joint damage caused by RA. We know that methotrexate inhibits dihydrofolate reductase (among other enzymes), but its actual mechanism of action against RA has not been fully clarified. Prior to initiating therapy with methotrexate, routine laboratory testing should be performed. At a minimum, a metabolic panel, including transaminases, albumin, creatinine, blood glucose, a complete blood count, and a screen for chronic hepatitis B and C should be performed initially to monitor for diabetes, liver or kidney dysfunction, and cytopenias. A chemistry panel (which includes a creatinine and transaminases), an ESR, and a CBC need to be monitored routinely every 4-12 weeks thereafter for signs of disease activity and for potential side effects of methotrexate. These tests need to be monitored more frequently when doses of methotrexate are increased or if other conditions that affect the liver or kidneys are present.

Liver biopsies generally are not recommended by rheumatologists for routine patients on uncomplicated regimens of methotrexate unless there is highly significant or unresolved laboratory evidence of liver dysfunction (transaminitis, hypoalbuminemia) that is not otherwise explained. Common potential side effects of methotrexate include nausea, alopecia, hepatotoxicity, infections, stomatitis, and bone marrow suppression.

These symptoms occur less often by having the patient take 1-2 mg of folic acid daily. Folinic acid (Leucovorin) at doses of 5-20 mg, 12-24 hours post methotrexate dose, may be necessary for patients on methotrexate if side effects are not controlled by folic acid. Methotrexate lung, a hypersensitivity reaction, can be an early and serious consequence of treatment with this drug manifesting as diffuse interstitial pulmonary infiltrates with acute dyspnea. This condition requires at least temporary discontinuation of methotrexate and treatment with corticosteroids. Methotrexate's significant potential as an abortifacient precludes its safe use in pregnancy. It is also contraindicated in breastfeeding. Both female and male patients who want to conceive a child need to stop methotrexate at least 3 months before stopping contraception.

Leflunomide is a somewhat newer and effective disease modifying agent for RA that inhibits pyrimidine synthesis, which interferes with the proliferation of B and T lymphocytes. Its effectiveness in amelioration of RA symptoms rivals that of methotrexate.[23] The side effect profile is also similar to that of methotrexate. It has a particularly long half-life of approximately 2 weeks. While generally well tolerated, should a patient have severe adverse side effects, or if a patient chooses to become pregnant, a regimen of daily cholestyramine for 11 days may be employed to bind circulating leflunomide and allow for recovery of the liver or allow for a safe pregnancy.

Other DMARDs are considered somewhat less effective than methotrexate in their ability to reduce the activity of RA, but still have places in the treatment regimens for many patients. In situations of intolerance and/or co-morbidities associated with the commonly used drugs discussed above, these other DMARDs may be efficacious individually or in combination with each other. Some of these medications include sulfasalazine, hydroxychloroquine, cyclosporine, and azathioprine.

A frequently used and well-studied regimen, the so-called "triple therapy," combines methotrexate with sulfasalazine and hydroxychloroquine. It was shown to be more efficacious than methotrexate alone or with only one of the other DMARDs.[24]

Previous studies demonstrated that the inexpensive antibiotic doxycycline can improve the signs and symptoms of RA when combined with methotrexate or with triple therapy.[25]

In addition to pharmacological agents, a treatment program for RA patients should include other members of the health care team. Physical therapists, occupational therapists, and podiatrists are important in reducing complications of chronic joint damage. Braces, prosthetics, splints, and a home program of exercises and home safety screening can benefit patients with RA. Given the severity of permanent changes that some patients suffer, psychologists and psychiatrists may occasionally need to intervene.

Orthopedic surgery plays an essential role in the treatment of patients with RA. One of the most important advances in treatment of RA in the last half century is the development and perfection of joint replacement. Replacement of hips and knees are especially gratifying since many thousands of arthritis patients who would otherwise have to use canes, crutches, or walkers, or stay in bed or require wheel chairs can walk normally with little or no disability or pain. Replacement of other joints including elbows, shoulders, ankles, and finger joints are improving at a rapid rate and have an important place in treatment of RA. Orthopedic surgeons' contributions are very important in other conditions brought on by RA including repair of ruptured tendons, arthroscopic joint repairs, and procedures that improve function and cosmetic appearance of hands and feet. It is occasionally necessary to stabilize the neck at C1-C2 location because of the erosion and laxity of ligaments normally holding the spine in alignment caused by RA. Either a neurosurgeon or an orthopedist specializing in the spine may have to fuse these joints and the skull to protect the patient from life-threatening spinal injury.

Treatments: The Biologics

A huge paradigm switch of RA treatment occurred in 1998, when the first of the biologic agents became available. Past strategies of gradual increases in medication dosage and the slow addition of more potent medications was replaced with an emphasis on early aggressive treatment of RA. The first agent in the anti-cytokine biologic group was infliximab (Remicade). It is a monoclonal antibody to TNF-alpha, developed initially to treat inflammatory bowel disease and recognized in the mid 1990s to be effective for RA. Etanercept (Enbrel) was developed for treatment of RA followed shortly thereafter. It is a soluble fusion protein that blocks the receptors for tumor necrosis factor-alpha (TNF-alpha) and TNF-beta. The third of the TNF inhibitors is adalimumab (Humira), a fully human monoclonal antibody. Multiple large studies demonstrate the effectiveness of these agents in controlling disease activity in patients with RA like no other medication before. There is evidence of amazing clinical improvement, including data that show all three TNF inhibitors demonstrate a marked decrease or even an arrest of radiographic progression of erosions, joint space narrowing, and peri-articular osteopenia.[26-28]

One can switch to another TNF inhibitor successfully when the first loses efficacy.[29] Of great significance is that with two newer biologic agents available in the therapeutic armamentarium, some experts in the field advocate switching to one of them instead.

Rituximab (Rituxan) is a monoclonal antibody to the CD20 surface marker found on B-lymphocytes. When B cells are activated, they differentiate into antibody secreting plasma cells. In RA, B cells produce autoantibodies that are possibly implicated in disease pathogenesis. By targeting pro B cells, early B cells but not plasma cells, rituximab also decreases inflammatory cytokine production. Rituximab has been used since 1997 for the treatment of B cell lymphomas and has recently been approved for the treatment of TNF inhibitor refractory RA.

Abatacept (Orencia) is the newest biologic agent on the market for TNF-refractory RA, or it may be used as a first-line biologic. It features an entirely new mechanism of action. In order for cytokine secreting T lymphocytes to become active, they

require two distinct signals from an antigen-presenting cell (APC). The first step is antigen presentation via the major histocompatibility complex (MHC) and the T cell receptor (TCR). The second step is the interaction of CD28 with CD80/86. Abatacept competitively binds this second or costimulation step, thus inhibiting activation of T cells.

Both newer biologics are IV infusions. DMARDs are recommended as adjunct therapy for all of the biologics for them to work most effectively. However, there are safety issues that make it unadvisable to combine biologic agents. This practice significantly increases the number of infections studied in controlled trials.

Infections remain the most important adverse event in treatment with the biologics. Because of the activation of latent tuberculosis (TB) in the investigation of these drugs, it is essential that before patients start taking one of the biologics, they have a recent negative PPD skin test. If the PPD is positive, even presumably from BCG vaccination, the patient must be treated with isoniazid or other TB drug such as rifampin, ideally for a month before starting a biologic agent. If a patient taking a biologic agent develops pneumonia or another significant infection, the drug must be stopped and the infection treated completely to resolution before starting back on the biologic agent.

Because of their effect on healing and increased danger of infection, biologic agents need to be stopped 2-4 weeks before elective surgery and resumed when the surgical wound is healed. Surgeons typically prefer that DMARDs be stopped also, although it is not clear that it is necessary to do so.

Anakinra (Kineret) is an anti-Il-1 monoclonal antibody developed to treat RA. It is moderately effective, but has not enjoyed quite the success of the anti-TNF drugs, although it is occasionally used effectively in a small number of RA cases.

Complications

Osteoporosis is one of the overlooked complications of RA. The first signs of bone mineral density loss are the early changes of periarticular osteopenia. Readily visible on plain radiographs in active RA patients, it represents increased osteoclastogenesis, mediated by the molecule RANKL.[30] RA patients, therefore, need to be screened for osteoporosis earlier than those patients with other traditional risk factors for loss of bone mineral and architecture. Thus RA patients should be considered for more aggressive anti-resorptive therapies. And while chronic corticosteroid use is, of course, a risk factor for osteoporosis, the peri-articular bone loss associated with RA disease activity is independent of corticosteroid use. In addition to anti-resorptive therapies like alendronate, risedronate, ibandronate, or zoledronic acid, calcium and vitamin D should be considered as recommended treatment for most RA patients.

It has been recognized for many years that pregnancy can actually reduce the arthritic symptoms of up to 75% of patients with RA.[31] Many theories have been postulated, but a recent study suggests that fetal DNA may induce a regulatory T cell population that exerts an inhibitory effect of the pro-inflammatory processes at play.[32] As mentioned previously, several of the medications, including most of the DMARDs (with the exception of hydroxychloroquine and to some extent, azathioprine), used to treat RA are generally not safe in pregnancy and during breastfeeding and must not be used during this period. Prednisone however, is considered fairly safe during pregnancy. As far as the biologic agents, small data sets have shown that adverse events are not seen in cases of pregnant patients who continued to take anti-cytokine therapy during pregnancy.[33] Still, given the lack of definitive testing of the biologics in pregnancy, they should be stopped when a patient does become pregnant. Evidence shows that patients considering pregnancy can safely use azathioprine to control RA symptoms and then stop the drug after becoming pregnant. However, azathioprine may be used up to the third trimester if needed to control unremitting symptoms of RA.

Another area in RA research that is receiving more scrutiny is the risk of malignancy in patients with RA. Fueled largely by a suspected increased number of lymphomas in trials of the TNF inhibitors, it is now widely accepted that the chronic inflammatory state of RA is itself the a priori risk factor that has resulted in the increased incidence of lymphoma. Many investigators now feel it is not the biologic agents themselves that are responsible for the malignancy, although this opinion is still controversial and is not universally accepted.[34]

Perhaps the most common, yet most overlooked complication of RA is that of atherosclerotic heart disease. Still the major source of mortality in the western world, those with RA have a relative risk for early atherosclerosis of 3.0 when compared to the general population.[35] Chronic inflammatory states and lipid dysregulation are likely the main contributors. Solid evidence that more aggressive treatment of RA leads to less atherosclerosis is lacking at present, but research is ongoing in the field.

Treatment: Future Therapies

There are a number of new treatments not yet available to arthritis practitioners that appear to be on their way to the market and deserve to be mentioned in this review.

Certolizumab pegol is a pegylated antibody against tumor necrosis factor alpha that is both soluble and membrane bound. Tocilizumab is humanized monoclonal antibody against the pro-inflammatory cytokine IL-6. Ofatumumab is another anti-CD20, similar in action to rituximab, which is fully humanized. Ocrelizumab is yet another anti-CD20 monoclonal antibody that is humanized. Golimumab is also a humanized monoclonal antibody against soluble and membrane bound TNF-alpha.[36] Denosumab, for treatment of osteoporosis, is a monoclonal antibody that blocks RANKL, inhibiting osteoclastogenesis, one of the steps in formation of the erosions of RA.[30]

Conclusion

While the musculoskeletal system deserves most of the attention in patients with RA, it is truly a multi-system disease with

variable expression and courses. Since it is a well established fact that patients with uncontrolled or inadequately treated RA do indeed have a shorter lifespan than the general population (up to 15 years shorter if not treated early and aggressively), the primary care practitioner needs to be aware of the seriousness of this disease. It is essential that physicians recognize the early diagnostic signs of RA and closely coordinate care of these patients with a rheumatologist or other practitioner highly skilled and knowledgeable in the diagnosis and treatment of RA, once the diagnosis is suspected. State-of-the-art care demands that physicians ensure that these patients have every opportunity for an early, complete remission of their disease, maintain long term mobility, reduce coronary risk factors, and are regularly surveyed for complications of rheumatoid arthritis and its treatments. Close coordination with an arthritis specialist, and exploitation of the explosion of therapeutic developments made in recent years (and those soon to arrive), make it possible to limit or stop completely the suffering of patients with RA. The huge burden this disease imposes on patients and the health care system can be reduced. It is an exciting, new day in the treatment of RA.

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Physician CME Questions

26. Which of the following is *not* considered a risk factor for the development of RA?
    A. Senescence of T lymphocytes
    B. Women of childbearing age
    C. 20 pack-years of tobacco
    D. Diet high in red meat
    E. HLA DRB1*0401

27. The first commercially available biologic agent developed in the treatment of RA and the most recent biologic agent commercially available for RA target which of the following two molecules, respectively?
    A. TNF-alpha and IL-6
    B. TNF-alpha and IL-1
    C. B cells and TNF-alpha
    D. TNF-alpha and T cells
    E. T cells and IL-1

28. Commonly affected joints in RA include all of the following *except*:
    A. PIP and DIP
    B. C-spine, MCP
    C. MCP, PIP, intercarpal

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

D. MTP, hips
E. Radiocarpal, MTP

29. Which treatment regimens are considered generally safe and acceptable in the treatment of RA?
A. Sulfasalazine, hydroxychloroquine, leflunomide
B. Etanercept, methotrexate, hydroxycholoroquine
C. Adalimumab, methotrexate, etanercept
D. All of the above
E. A and B

30. Which of the folllowing are currently considered unadvisable for use in pregnancy?
A. Leflunomide, methotrexate
B. Hydroxychloroquine, prednisone
C. Infliximab, methotrexate
D. Hydroxychlorquine, etanercept
E. A and C
F. A, C, and D

CME Answer Key

26. D; 27. D; 28. A; 29. E; 30. F

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

In Future Issues:

Coronary Artery Disease Assessment