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Rheumatoid Arthritis: Diagnosis and Management

Vikas Majithia, MD,[a,b] Stephen A. Geraci, MD[a,b]

[a]Department of Medicine, University of Mississippi School of Medicine, Jackson, [b]Medical Service, G.V. (Sonny) Montgomery Veterans Affairs Medical Center, Jackson, Miss.

ABSTRACT

Accurate diagnosis of rheumatoid arthritis may be difficult early in its course and demands high clinical suspicion, astute examination, and appropriate investigations. Early use of disease-modifying antirheumatic drugs and biologics has improved outcomes but requires close monitoring of disease course and adverse events.

KEYWORDS: Diagnosis; Review; Rheumatoid arthritis; Therapy

Rheumatoid arthritis is a chronic, systemic, inflammatory autoimmune disorder causing symmetrical polyarthritis of large and small joints, typically presenting between the ages of 30 and 50 years.[1] The most common inflammatory arthritis, it afflicts an estimated 25 men and 54 woman per 100,000 population and is responsible for 250,000 hospitalizations and 9 million physician visits in the US each year.[1-3]

The etiology of rheumatoid arthritis is not fully understood but involves a complex interplay of environmental and genetic factors. Genetics also play a role in disease severity. A triggering event, possibly autoimmune or infectious, initiates joint inflammation.[2] Complex interactions among multiple immune cell types and their cytokines, proteinases, and growth factors mediate joint destruction and systemic complications.[2]

DIAGNOSIS

The diagnosis of rheumatoid arthritis is primarily clinical. The typical presentation is polyarticular, with pain, stiffness, and swelling of multiple joints in a bilateral, symmetric pattern. A minority of patients present with oligoarticular asymmetric involvement.[1] The onset is usually insidious, with joint symptoms emerging over weeks-months and often accompanied by anorexia, weakness, or fatigue. Patients usually note morning stiffness lasting more than an hour. Commonly involved joints are the wrists, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints, with distal interphalangeal joints and spinal joints usually spared.[1] Typical examination findings include swelling, bogginess, tenderness and warmth of, with atrophy of muscles near, the involved joints. Weakness is out of proportion to tenderness.

Rarely, patients may present with single joint involvement or with severe systemic symptoms of fever, weight loss, lymphadenopathy, and multiple organ involvement such as lung or heart.[1]

Infection-related reactive arthropathies, seronegative spondyloarthropathies, and other connective tissue diseases may have symptoms in common with rheumatoid arthritis, as may an array of endocrine and other disorders. These must be excluded in the initial diagnostic evaluation.[1] Table 1 lists some common diseases that should be considered in the differential diagnosis.

There is no single test that confirms rheumatoid arthritis. Initial laboratory tests should include a complete blood cell count with differential, rheumatoid factor, and erythrocyte sedimentation rate or C-reactive protein. Rarely, joint aspiration also may be required, especially with monoarticular presentations, to rule out infectious or crystal-induced arthritis. Baseline renal and hepatic function tests are recommended to guide medication choices.[3] Anticyclic citrullinated peptide antibody carries high specificity and positive predictive value but is present in fewer than 60% of rheu-

Requests for reprints should be addressed to Vikas Majithia, MD, Division of Rheumatology and Molecular Immunology, Department of Medicine, University of Mississippi School of Medicine, 2500 N. State Street, Jackson, MS 39216.

E-mail address: vikasmajithia@medicine.umsmed.edu

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Table 1 Diseases that Can Mimic Rheumatoid Arthritis

Category	Common Examples
Other connective tissue syndromes	Systemic lupus erythematosus, Systemic vasculitides, Scleroderma
Systemic diseases	Sarcoidosis, Still's disease, Infective endocarditis, Rheumatic fever
Spondyloarthropathies	Psoriatic arthritis, Reactive arthritis
Infectious arthritis	Viral arthritides (esp. Parvo virus), Bacterial arthritis, Gonococcal arthritis
Crystal-induced arthritis	Polyarticular gout
Endocrinopathies	Thyroid disorders
Soft-tissue syndromes and Degenerative disorders	Fibromyalgia, Polyarticular osteoarthritis
Deposition disorders	Hemochromatosis
Malignancy (paraneoplastic syndromes)	Lung cancer, Multiple myeloma

matoid arthritis patients.[4] Tests to rule out other disorders in the differential diagnosis (Table 1) should be performed as clinically indicated.

The American College of Rheumatology criteria (Table 2) are helpful in formally diagnosing and following rheumatoid arthritis patients in research trials.[5] In the clinical setting, a definitive diagnosis using these criteria is not possible in all the cases; they should be used only in combination with all other available information in an individual case.

KEY POINTS: DIAGNOSIS AND INITIAL MANAGEMENT DECISIONS

There are 2 questions for the primary care physician when evaluating a patient with arthritis: Is the diagnosis of rheumatoid arthritis likely? Does the patient need early treatment or referral to a rheumatologist, or both? Findings making rheumatoid arthritis the likely diagnosis and prompting initiation of treatment are:

- Joint swelling (and pain) of 3 or more joints
- Metacarpal or metatarsal joint involvement (a positive squeeze test, ie, significant pain when squeezed across these joints)
- Morning stiffness lasting more than 30 minutes
- Elevated erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor

Referral to a rheumatologist is indicated if the diagnosis is unclear, more than 5 joints or large joints are involved with accompanying significant subjective symptoms, or laboratory abnormalities are present.

TREATMENT

A comprehensive approach to managing rheumatoid arthritis consists of patient education, physical/occupational therapy, and drug treatment. Patients should be educated about the disease and referred to these ancillary specialists to maintain joint function and delay disability. Drug treatment generally involves a 3-pronged approach: nonsteroidal anti-inflammatory drugs and low-dose oral or intra-articular glucocorticoids; disease-modifying antirheumatic drugs; and consideration of biologic response modifiers/biologics. Nonsteroidal anti-inflammatory drugs reduce joint pain and swelling, but do not alter the disease course and should not be used alone.[3] Steroids (prednisone 10 mg daily or equivalent) relieve symptoms and may slow joint damage;[3] they should be prescribed at a low dose for short duration, primarily as "bridge" therapy, and with daily calcium (1500 mg) and vitamin D (400-800 IU) oral supplements to limit bone demineralization.[3]

All patients with rheumatoid arthritis should be evaluated for disease-modifying antirheumatic drugs treatment.[3] Early use slows disease progression and improves overall long-term prognosis.[3] Although there is consensus among rheumatologists that rheumatoid arthritis should be treated early and aggressively, a number of issues (choice of initial therapy, timing and patient criteria for initiation of combination therapy, or use of biologics) remain under evaluation.

The following is an approach consistent with the available evidence. Patients with mild disease (typically <5 joints involved and mild subjective symptoms) and normal radiographic findings can receive hydroxychloroquine, sulfasalazine, minocycline, or possibly methotrexate. Methotrexate remains the initial treatment of choice in moderate-severe disease (typically >5 joints or large joint involvement with significant subjective symptoms) or radiographic changes of bone loss/erosion. The target dose (15 mg/week) should be reached within 6-8 weeks if tolerated. When response is inadequate, leflunomide, azathioprine, or combination therapy (methotrexate plus another agent) may be considered. Combinations of disease-modi-

Table 2 Classification Criteria for Rheumatoid Arthritis*

Morning stiffness (lasting >1 hour)†
Arthritis of 3 or more joint areas (areas are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints)†
Arthritis of hand joints (proximal interphalangeal or metacarpophalangeal joints)†
Symmetric arthritis, by area†
Subcutaneous rheumatoid nodules
Positive rheumatoid factor
Radiographic changes (hand and wrist, showing erosion of joints or unequivocal demineralization around joints)

*At least 4 are needed for diagnosis. Adapted from Arnett et al:[5] *Arthritis Rheum*. 1988;31:315-324. Copyright John Wiley & Sons, Inc., 1988, reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

†Present for ≥ 6 weeks.

Table 3 Rheumatoid Arthritis Treatment: Disease-Modifying Antirheumatic Drugs and Biologic Agents

Drug	Dosage	Onset of Effect	Adverse Events	Monitoring
Abatacept	500-1000 mg (weight based) at 0, 2 and 4 weeks then every 4 weeks	2-12 weeks	ISR, infections, hypersensitivity, COPD exacerbation	Monitor for TB, other infections; CBC, chemistry and LFTs at baseline and with each infusion
Adalimumab	40 mg sc biweekly	2-12 weeks	ISR, infections, TBr; demyelinating disorders (rare)	TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months
Anakinra	100 mg sc daily	4-12 weeks	ISR, leucopenia, infections, hypersensitivity	CBC at baseline and every 3 months
Azathioprine	50-150 mg po daily	2-3 months	GI intolerance, cytopenia, hepatitis, infections	CBC, LFTs every 2-4 weeks initially, then every 2-3 months
Cyclosporine	2.5-5 mg po daily	2-3 months	GI intolerance, cytopenia, infections, hypertension, renal disease	Cr every 2 weeks at initiation, then monthly; consider CBC, LFTs, and K^+
Etanercept	25 mg sc twice/ week or 50 mg sc weekly	2-12 weeks	ISR, infections, TBr; demyelinating disorders (rare)	TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months
Hydroxychloroquine	200-400 mg po daily	2-6 months	GI intolerance, Retinal toxicity	Fundoscopy every 12 months
Infliximab	3 mg/kg at weeks 0, 2 and 4, then every 8 weeks	2-12 weeks	ISR, infection, TBr; demyelinating disorders (rare)	TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months
Leflunomide	20 mg daily	4-12 weeks	GI intolerance, skin rash, hepatitis, cytopenia; highly teratogenic	Hepatitis B and C serology in high-risk patients; CBC, Cr and LFTs monthly x6, then every 1-2 months; reduce dose or stop if LFTs elevate
Methotrexate	15-25 mg orally, sc or IM weekly	1-2 months	GI intolerance, oral ulcers, alopecia, hepatitis, pneumonitis, cytopenia, rash; teratogenic	CBC, Cr and LFTs monthly x6, then every 1-2 months; adjust dose or stop if LFTs elevate
Minocycline	100 mg twice daily	1-3 months	Dizziness, skin pigmentation	none
Rituximab	1000 mg at 0 and 15 days	2-12 weeks	ISR, infection risk, new and reactivation viral infections, respiratory difficulty, cytopenia	Monitor for TB, other infections; CBC, chemistry and LFTs at baseline and 2 weeks, every 2-3 months thereafter
Sulfasalazine	2-3 gm daily	1-3 months	GI intolerance, oral ulcers, cytopenia, rash	CBC every 2-3 months

Sc = subcutaneous; po = orally; im = intramuscularly; ISR = injection site reaction; CBC = complete blood count; LFTs = liver function tests; UA = urinalysis with microscopic examination; Cr = serum creatinine; TBr = tuberculosis reactivation.

fying antirheumatic drugs may be more effective than single-drug regimens.[3] Women of childbearing age should use adequate contraception when taking certain (teratogenic) disease-modifying antirheumatic drugs (Table 3).

Biologics, the latest generation of antirheumatic drugs, have novel molecular mechanisms that target cytokines, signaling molecules and cells involved in inflammation and joint destruction. These include the tumor necrosis factor antagonists: adalimumab, etanercept, and infliximab (first line agents); the Interleukin-1 antagonist, anakinra; the anti-B cell antibody, rituximab; and the down-regulator of T-cell co-stimulation, abatacept. All biologics are associated with an increased risk of infection (bacterial, viral, and fungal) and tuberculosis reactivation. Table 3 lists disease-modifying antirheumatic drugs and biologic dosing regimens, times to onset of benefit, adverse effects, and safety monitoring.[3]

It is important to note that there is disagreement among rheumatologists about the choice of initial therapy. There is evidence that combination of methotrexate and a biologic agent is the most effective current therapy but the short- and long-term risks, as well as the cost-effectiveness of biologic agents, are not well defined.[3] Due to these unanswered questions, common rheumatology practice is to begin methotrexate alone as initial therapy.

Chronic treatment of rheumatoid arthritis is a continuous process, and periodic patient re-assessment is paramount. Patients should be evaluated every 2-3 months for control of

disease activity, extra-articular manifestations, medication side effects, and functional capacity. Annual hand and feet radiographs (for joint surface erosions and demineralization) also are recommended.[3]

KEY POINTS: MANAGEMENT

In managing chronic rheumatoid arthritis, the primary care physician should assess course (improvement or progression), net disability, and medication side effects (including osteoporosis with chronic steroid use). Ongoing surveillance for infection, tuberculosis, and malignancy (age-appropriate screening), osteoporosis and immunizations (influenza vaccine and pneumovax) are essential components of care. Cardiovascular risk factor reduction is warranted due to a higher risk for development of coronary artery disease related to the underlying disease or medications.

SUMMARY

Prompt and accurate diagnosis, early aggressive treatment, including disease-modifying antirheumatic drugs or biologics, symptom control, and close monitoring of disease state and medication toxicity are the keys to effective management of the patient with rheumatoid arthritis. Subspecialty referral should be considered in all patients with moderate-severe disease or demonstrating incomplete response.

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