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SPECIAL ARTICLE

Guidelines for the Management of Rheumatoid Arthritis

2002 Update

American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and, in some cases, extraarticular involvement (1). Most patients experience a chronic fluctuating course of disease that, despite therapy, may result in progressive joint destruction, deformity, disability, and even premature death (2). RA results in more than 9 million physician visits and more than 250,000 hospitalizations per year (3,4). Disability from RA causes major economic loss and can have a profound impact on families.

RA affects 1% of the adult population (2). This low prevalence means that the average physician often develops little experience with its diagnosis or management. The following guidelines for the management of RA assume that a correct diagnosis has been made, and this may be difficult in the early stages of the disease (5,6). The complexity of the process needed to establish the diagnosis of RA is beyond the scope of these guidelines.

Guidelines for the management of RA and monitoring of drug therapy were first developed in 1996 (7,8). Since then, there have been major advances in the treatment of RA. There is now evidence of the benefit of treatment early in the disease course and evidence of the impact of treatment on outcomes. New classes of therapeutic agents have also been introduced. Wherever possible, these revised guidelines are evidence-based. However, because significant gaps in our knowledge still exist, some recommendations are based on best practices and a consensus of the committee. These guidelines have been reviewed by rheumatologists, primary care providers who practice rheumatology, and other arthritis health professionals, including occupational therapists, physical therapists, social workers, and patient educators.

Goals of RA management

The ultimate goals in managing RA are to prevent or control joint damage, prevent loss of function, and decrease pain. Figure 1 summarizes the approach to the management of RA. The initial steps in the management of RA are to establish the diagnosis, perform a baseline evaluation (Table 1), and estimate the prognosis. An evaluation by a rheumatologist is strongly rec-

Members of the American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines are as follows. C. Kent Kwoh, MD, Chair: University of Pittsburgh, Pittsburgh, Pennsylvania; Larry G. Anderson, MD: Rheumatology Associates, Portland, Maine; Jerry M. Greene, MD: VA Medical Center, West Roxbury, Massachusetts; Dorothy A. Johnson, DNSc, FNP: Los Angeles County + University of Southern California Medical Center, Los Angeles; James R. O'Dell, MD: University of Nebraska Medical Center, Omaha; Mark L. Robbins, MD, MPH: Harvard Vanguard Medical Associates, Boston, Massachusetts; W. Neal Roberts, Jr., MD: Medical College of Virginia, Richmond; Robert W. Simms, MD: Boston University Arthritis Center, Boston, Massachusetts; Robert A. Yood, MD: The Fallon Clinic, Worcester, Massachusetts.

Dr. Kwoh has been a consultant to Wyeth-Ayerst Laboratories and Immunex (both in 1998) and has served as a member of the advisory boards for Aventis Pharmaceuticals (in 1999) and Pfizer (2001). Dr. Anderson has served as a member of the medical advisory board for Merck & Company. Dr. Greene is a shareholder (not major equity) in Johnson & Johnson and Merck & Company. Dr. O'Dell has served on the speaker's bureaus of Aventis Pharmaceuticals, Pharmacia & Upjohn, and Merck & Company, and has served as a consultant to Amgen, Centocor, Immunex, and Bristol-Myers Squibb. Dr. Roberts has received funding for educational activities and clinical trials from Sanofi, Pfizer, and G. D. Searle & Company (during the 1990s; total funding less than $100,000), but currently receives no industry funding. Dr. Simms has served on the speaker's bureau of Merck & Company and has received grant support from Aventis Pharmaceuticals. Dr. Yood is an investigator of an ongoing research trial of anti–tumor necrosis factor α and interleukin-1 receptor antagonist sponsored by Amgen.

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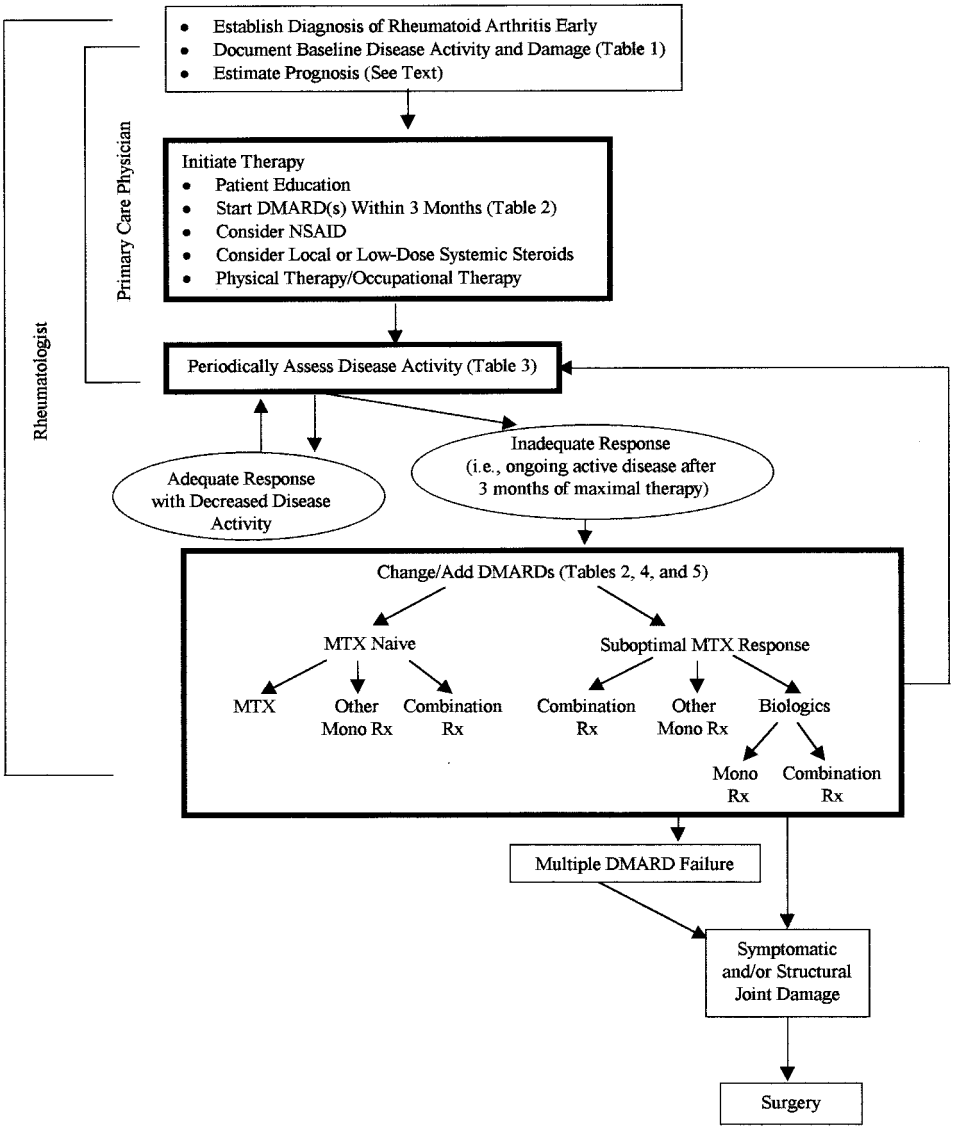

Figure 1. Outline of the management of rheumatoid arthritis. Each step is detailed in the text. Boxes with heavy borders represent major decision points in management. A suboptimum response to methotrexate (MTX) is defined as intolerance, lack of satisfactory efficacy with a dosage of up to 25 mg/week, or a contraindication to the drug. DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug; mono Rx = monotherapy; combination Rx = combination therapy.

ommended if the primary care provider is uncertain about any of these initial steps.

Treatment begins with educating the patient about the disease and the risks of joint damage and loss of function, as well as reviewing the risks and benefits of existing treatment modalities. Patients will benefit from consultation with physical therapists, occupational therapists, social workers, and/or patient educators. Nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoid joint injection, and/or low-dose prednisone may be considered for control of symptoms. The majority of patients with newly diagnosed RA should be started on disease-modifying antirheumatic drug (DMARD) therapy within 3 months of diagnosis. The DMARDs commonly used in RA are shown in Table 2.

Since DMARDs control rather than cure RA, the management of RA is an iterative process, and patients should be periodically reassessed for evidence of disease

Table 1. Baseline evaluation of disease activity and damage in patients with rheumatoid arthritis

Subjective
Degree of joint pain
Duration of morning stiffness
Duration of fatigue
Limitation of function
Physical examination
Actively inflamed joints (tender and swollen joint counts)
Mechanical joint problems: loss of motion, crepitus, instability, malalignment, and/or deformity
Extraarticular manifestations
Laboratory
Erythrocyte sedimentation rate/C-reactive protein level
Rheumatoid factor*
Complete blood cell count†
Electrolyte levels†
Creatinine level†
Hepatic enzyme levels (AST, ALT, and albumin)†
Urinalysis†
Synovial fluid analysis‡
Stool guaiac†
Other
Functional status or quality of life assessments using standardized questionnaires
Physician's global assessment of disease activity
Patient's global assessment of disease activity
Radiography
Radiographs of selected involved joints§

* Performed only at baseline to establish the diagnosis. If initially negative, may be repeated 6–12 months after disease onset.
† Performed at baseline, before starting medications, to assess organ dysfunction due to comorbid diseases. AST = aspartate aminotransferase; ALT = alanine aminotransferase.
‡ Performed at baseline, if necessary, to rule out other diseases. May be repeated during disease flares to rule out septic arthritis.
§ Helps to establish a baseline for monitoring disease progression and response to treatment.

activity or progression and for any toxic effects of the treatment regimen. Repetitive flares, unacceptable disease activity (i.e., ongoing disease activity after 3 months of maximum therapy), or progressive joint damage require consideration of significant changes in the DMARD regimen. If disease activity is confined to one or a few joints, then local glucocorticoid injection may help. For patients with severe symptoms, systemic glucocorticoids may need to be initiated, or the dosage may need to be increased, for a short period of time.

Active joint disease may impair physical function and may also be aggravated by physical activity. Therefore, consultation with a physical therapist, occupational therapist, and/or vocational counselor should be considered early in the disease course. Periods of rest, job modification, time off from work, changes in occupation, or termination of work may be necessary. Reconstructive surgery should be considered for patients with end-stage joint damage that is causing unacceptable pain or limitation of function with significant alteration of joint anatomy. Reconstructive surgery can be done at any point in the course of RA.

Some patients have resistant disease and experience a progressive course despite exhaustive trials of DMARDs, whether used alone or in combinations. While the ultimate goal of treating RA is to induce a complete remission, this occurs infrequently. Complete remission is defined as the absence of the following: 1) symptoms of active inflammatory joint pain (in contrast to mechanical joint pain), 2) morning stiffness, 3) fatigue, 4) synovitis on joint examination, 5) progression of radiographic damage on sequential radiographs, and 6) elevation of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels (9).

If complete remission is not achieved, the management goals are to control disease activity, alleviate pain, maintain function for activities of daily living and work, and maximize quality of life. Achieving these goals challenges the management skills of the rheumatologist to determine the most efficacious combination of pharmacologic therapy, which may include NSAID, DMARD(s), low-dose prednisone, local injection of glucocorticoid, rehabilitation support, and analgesics. Although adequate pain relief is an important goal with a chronic disease such as RA, every effort should be made to avoid narcotic analgesic dependency.

Given the chronic waxing and waning course of RA, a longitudinal treatment plan needs to be developed, and the patient should be involved in developing the plan. The discussion should address disease prognosis and treatment options, taking into account the costs, adverse effects, expected time for response, the patient's risk factors and comorbid conditions, monitoring requirements of pharmacologic agents, and the patient's preferences. Expectations for treatment and potential barriers to carrying out the recommendations should be discussed. Psychosocial factors, such as illness beliefs and perceived self-efficacy, have been shown to affect patient outcomes and treatment adherence (10–12). Education and cognitive–behavioral interventions, such as the Arthritis Self-Management Program, can improve health status and decrease health care utilization (13–17).

Initial evaluation of RA

The initial evaluation of the patient with RA should document symptoms of active disease (i.e., presence of joint pain, duration of morning stiffness, degree of fatigue), functional status, objective evidence of dis-

Table 2. Dosages, costs, and approximate time to benefit of disease-modifying antirheumatic drugs used in the treatment of rheumatoid arthritis

Drug	Approximate time to benefit	Usual maintenance dose	Annual drug cost (cost of generics), dollars*
Hydroxychloroquine	2–6 months	200 mg twice a day	1,056 (559)
Sulfasalazine	1–3 months	1,000 mg 2–3 times a day	509–763 (205–308)
Methotrexate	1–2 months	Oral 7.5–20 mg/week; injectable 7.5–20 mg/week	697–1,859 (259–691); 419–806 (42–81)
Leflunomide	4–12 weeks (skewed earlier)	20 mg/day in a single dose, if tolerated; otherwise, 10 mg/day†	2,938
Etanercept	A few days to 12 weeks	25 mg subcutaneously twice a week	15,436
Infliximab plus oral and subcutaneous methotrexate	A few days to 4 months	3–10 mg IV every 8 weeks or 3–5 mg IV every 4 weeks‡	13,940–30,287 or 28,040–36,694§
Azathioprine	2–3 months	50–150 mg/day	579–1,737 (471–1,414)
D-penicillamine	3–6 months	250–750 mg/day	865–2,595 (398–1,194)
Gold, oral	4–6 months	3 mg twice a day	1,622
Gold, intramuscular	3–6 months	25–50 mg intramuscularly every 2–4 weeks¶	198# (142)
Minocycline	1–3 months	100 mg twice a day	2,592 (582)
Cyclosporine	2–4 months	2.5–4 mg/kg/day**	4,432–8,859 (3,512–7,022)
Staphylococcal protein A immunoadsorption	3 months	Weekly for 12 weeks	20,433††

* Annual drug costs are provided for comparison purposes only. Values are based on costs from the 2001 Red Book (except where indicated otherwise) and on the usual maintenance dose or range of maintenance doses for a 70-kg individual. Values in parentheses represent lower-cost generics. These values do not include either physicians' office visit fees or laboratory costs associated with monitoring.
† The recommended loading dose for leflunomide is 100 mg/day for 3 days.
‡ Start infusions at the first visit (week 0), followed by infusions at weeks 2 and 6, and then every 8 weeks thereafter. Can consider increasing the frequency of infusions from every 8 weeks to every 4–6 weeks if there is an incomplete response. IV = intravenous.
§ Costs for infliximab are based on costs from the 2001 Red Book and on the Medicare reimbursement rates for outpatient procedures. They include the costs associated with the infusion, but not the cost of the weekly methotrexate that is recommended.
¶ Start with a 10-mg intramuscular test dose, followed by a loading dose of 50 mg intramuscularly every week until a cumulative dose of 1,000 mg is reached.
# Does not include the cost of administering the intramuscular injections.
** Start at 2.5 mg/kg/day in 2 divided doses taken 12 hours apart, and increase the dosage by 0.5 mg/kg/day every 2–4 weeks until a clinical repsonse is noted or a maximum dosage of 5 mg/kg/day is reached.
†† Costs for the staphylococcal protein A immunoadsorption treatments are based on Medicare reimbursement rates for outpatient procedures.

ease activity (i.e., synovitis, as assessed by tender and swollen joint counts, and the ESR or CRP level), mechanical joint problems (i.e., loss of motion, crepitus, instability, malalignment, and/or deformity), the presence of extraarticular disease, and the presence of radiographic damage (Table 1). The presence of comorbid conditions should also be assessed. The patient's and physician's global assessments of disease activity and a quantitative assessment of pain using a visual analog scale or other validated measure of function or quality of life are useful parameters to follow during the course of the disease (18,19). This baseline information greatly facilitates assessment of disease progression and response to treatment.

Baseline laboratory evaluations (Table 1) should include a complete blood cell count (with white blood cell differential and platelet counts), rheumatoid factor (RF) measurement, and measurement of ESR or CRP. Evaluation of renal and hepatic function is necessary, since many antirheumatic agents cause renal or hepatic toxicity and may be contraindicated if these organs are impaired. Since the hands and feet are so frequently involved in RA, radiographs of these joints as well as other affected joints establish a baseline for future assessment of structural damage. Arresting and preventing structural damage is a primary goal of therapy, and radiographic studies of major involved joints may be needed periodically.

Selection of the treatment regimen requires an assessment of prognosis. Poor prognosis is suggested by earlier age at disease onset, high titer of RF, elevated ESR, and swelling of >20 joints (20,21). Extraarticular manifestations of RA, such as rheumatoid nodules, Sjögren's syndrome, episcleritis and scleritis, interstitial lung disease, pericardial involvement, systemic vasculitis, and Felty's syndrome, may also indicate a worse prog-

Table 3. Assessment of disease activity in rheumatoid arthritis

At each visit, evaluate for subjective and objective evidence of active disease
Degree of joint pain (by visual analog scale)
Duration of morning stiffness
Duration of fatigue
Presence of actively inflamed joints on examination (tender and swollen joint counts)
Limitation of function
Periodically evaluate for disease activity or disease progression
Evidence of disease progression on physical examination (loss of motion, instability, malalignment, and/or deformity)
Erythrocyte sedimentation rate or C-reactive protein elevation
Progression of radiographic damage of involved joints
Other parameters for assessing response to treatment (outcomes)
Physician's global assessment of disease activity
Patient's global assessment of disease activity
Functional status or quality of life assessment using standardized questionnaires

nosis. Studies have shown that patients with active, polyarticular, RF-positive RA have a >70% probability of developing joint damage or erosions within 2 years of the onset of disease (21–26). Since studies have demonstrated that treatment with DMARDs may alter the disease course in patients with recent-onset RA (27–31), particularly those with unfavorable prognostic factors, aggressive treatment should be initiated as soon as the diagnosis has been established (25–27).

Assessment of disease activity

At each followup visit, the physician must assess whether the disease is active or inactive (Table 3). Symptoms of inflammatory (as contrasted with mechanical) joint disease, which include prolonged morning stiffness, duration of fatigue, and active synovitis on joint examination, indicate active disease and necessitate consideration of changing the treatment program. Occasionally, findings of the joint examination alone may not adequately reflect disease activity and structural damage; therefore, periodic measurements of the ESR or CRP level and functional status, as well as radiographic examinations of involved joints should be performed. Functional status may be determined by questionnaires such as the Arthritis Impact Measurement Scales (32) or the Health Assessment Questionnaire (33). It is important to determine whether a decline in function is the result of inflammation, mechanical damage, or both; treatment strategies will differ accordingly.

The American College of Rheumatology (ACR) has developed criteria for defining improvement (18) and clinical remission (9) in RA. These criteria have become accepted for outcome assessment in clinical trials, but have not been widely adopted for clinical practice. The ACR criteria for 20% clinical improvement (the ACR20) require a 20% improvement in the tender and swollen joint count, as well as a 20% improvement in 3 of the following 5 parameters: patient's global assessment, physician's global assessment, patient's assessment of pain, degree of disability, and level of acute-phase reactant. These criteria have been expanded to include criteria for 50% and 70% improvement measures (i.e., ACR50, ACR70). Other criteria, such as the Paulus criteria (34), have also been employed. More recently, radiographic progression (e.g., the Sharp score) (35,36) has been utilized as an outcome measure.

Nonpharmacologic treatment of RA

Optimal management of RA involves more than pharmacologic therapy. Early in the course of the disease, the patient needs to learn to accept that he or she will be living with RA and will need to become involved in the process of making decisions about treatment. If treatment does not fully control the disease, the patient may struggle emotionally as well as physically in adjusting to this chronic disease, its flares, and the concomitant loss of function. Rheumatologists, other physicians, and their office staff play important roles in educating the patient and the patient's family about the disease and providing longitudinal supportive care. The Arthritis Foundation is also an important source of educational material and/or programs. Other health professionals familiar with RA, including nurses, physical therapists, occupational therapists, social workers, health educators, health psychologists, and orthopedic surgeons, may also be involved in an interdisciplinary team approach to the comprehensive management of RA.

Instruction in joint protection, conservation of energy, and a home program of joint range of motion and strengthening exercises are important in achieving the treatment goal of maintaining joint function. Physical therapy and occupational therapy may help the patient who is compromised in activities of daily living. Regular participation in dynamic and even aerobic conditioning exercise programs improves joint mobility, muscle strength, aerobic fitness and function, and psychological well being without increasing fatigue or joint symptoms (37–40).

Pharmacologic treatment of RA

Pharmacologic therapy for RA often consists of combinations of NSAIDs, DMARDs, and/or glucocorti-

Table 4. Evidence of the efficacy of DMARDs in rheumatoid arthritis*

	Reference		
	Signs and symptoms of disease†	Function‡	Disease progression§
Monotherapy vs. placebo			
SSZ	55, 56, 58–62, 63	62, 63	62, 63
HCQ	29, 51–54	29	–
MTX	65–67, 71, 73, 75	70	63, 74, 75
Leflunomide	62, 75, 87	88, 89	63, 75
AZA	100–102	–	–
Minocycline	106–109	106–109	106, 110
Cyclosporine	111	111	–
Etanercept	90	–	–
Monotherapy vs. MTX or other DMARD			
AZA vs. MTX	120, 147	–	120, 147
SSZ or HCQ vs. MTX	62, 121, 122, 127	121, 122, 127	62
SSZ vs. leflunomide	62	–	63
MTX vs. leflunomide	62, 63, 75, 87–89	88, 89	63
MTX vs. etanercept	96, 97	97	96
Cyclosporine vs. gold	148, 149	148, 149	148, 149
Cyclosporine vs. MTX	150	–	–
Cyclosporine vs. AZA	151	151	–
Cyclosporine vs. HCQ	152	–	–
Combination therapy			
Initial combination			
MTX + SSZ	121, 122, 125, 128	121, 122, 125, 128	–
MTX + HCQ	128	128	–
MTX + SSZ + HCQ	125, 126, 128	125, 126, 128	–
MTX + leflunomide	130, 131	132	–
MTX + infliximab	91–93, 95	91	93
Step-up combination			
MTX + etanercept	94	94	–
Cyclosporine + HCQ	152	152	–
Cyclosporine + MTX	153	153	–
MTX + SSZ	128	128	–
MTX + HCQ	128	128	–
MTX + SSZ + HCQ	125	125	–

* DMARDs = disease-modifying antirheumatic drugs; SSZ = sulfasalazine; HCQ = hydroxychloroquine; MTX = methotrexate; AZA = azathioprine.
† For example, the swollen and/or tender joint counts, visual analog scale of pain, patient's global assessment of disease activity, and physician's global assessment of disease activity, or a combination of clinical features, such as those in the American College of Rheumatology 20%, 50%, and 70% criteria for improvement (9,18).
‡ For example, the Health Assessment Questionnaire or the Arthritis Impact Measurement Scales.
§ For example, radiographic evidence of erosions.

coids. The dosing schedules, efficacy, and toxicity of these medications are summarized in Tables 2, 4, and 5, respectively. Additional information on monitoring the toxicity of NSAIDs and older DMARDs is available in the ACR guidelines for monitoring drug therapy in RA (8), which also provide information on the effects of antirheumatic therapy on pregnancy, lactation, and fertility.

NSAIDs. The initial drug treatment of RA usually involves the use of salicylates, NSAIDs, or a selective cyclooxygenase 2 (COX-2) inhibitor to reduce joint pain and swelling and to improve joint function. These agents have analgesic and antiinflammatory properties but do not alter the course of the disease or prevent joint destruction. Thus, they should not be used as the sole treatment for RA.

Choice of available agents is based on considerations of efficacy, safety, convenience, and cost. Some salicylates and all available nonsalicylate NSAIDs inhibit the production of prostaglandins by inhibiting one or both of the cyclooxygenase enzyme isoforms, COX-1 and COX-2. COX-1 is produced constitutively and is present in many cells, including platelets, cells of the gastric and intestinal mucosa, and endothelial cells. Production of COX-2 can be increased many times over, particularly by cells at sites of inflammation. Data sug-

Table 5. Monitoring of toxicities of drugs used to treat rheumatoid arthritis*

Drug/category	Toxicities requiring monitoring†	Baseline evaluation	Systems review/examination	Laboratory
Salicylates; nonsteroidal antiinflammatory drugs	GI ulceration and bleeding	CBC, creatinine, LFTs	Dark/black stool, dyspepsia, nausea/vomiting, abdominal pain, edema, shortness of breath	CBC yearly, LFTs‡
Hydroxychloroquine	Macular damage	None unless patient is over age 40 or has previous eye disease	Vision changes, funduscopic and visual fields every 12 months	None
Sulfasalazine	Myelosuppression	CBC and LFTs in patients at risk, G6PDH	Myelosuppression,§ photosensitivity, rash	CBC every 2–4 weeks for first 3 months, then every 3 months thereafter
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis	CBC, creatinine, LFTs, alk. phos., chest radiograph within previous year, hepatitis B and C serology in high-risk patients	Myelosuppression,§ shortness of breath, nausea/vomiting, lymph node swelling. Potentially teratogenic.	CBC, creatinine, LFTs monthly for the first 6 months; every 1–2 months thereafter. For minor elevations in AST or ALT (<2-fold ULN), repeat testing in 2–4 weeks. For moderate elevations in AST or ALT (>2-fold but <3-fold ULN), closely monitor, with LFTs every 2–4 weeks and dosage reduction as necessary. For persistent elevations in AST or ALT (>2- or 3-fold ULN), discontinue MTX and perform liver biopsy as necessary.
Leflunomide	Diarrhea, alopecia, rash, headache, theoretical risk of immunosuppression infection	Hepatitis B and C serology in high-risk patients, CBC, creatinine, LFTs	Diarrhea, alopecia, intercurrent liver, gallbladder, and renal disease, pregnancy or delayed menses. Known teratogen.	CBC, creatinine, LFTs monthly for the first 6 months; every 1–2 months thereafter. For minor elevations in AST or ALT (<2-fold ULN), repeat testing in 2–4 weeks. For moderate elevations in AST or ALT (>2-fold but <3-fold ULN), closely monitor, with LFTs every 2–4 weeks and dosage reduction. For persistent elevations of AST or ALT (>2- or 3-fold ULN), discontinue leflunomide and eliminate with cholestyramine therapy¶; perform liver biopsy as necessary. Patients also taking MTX should have LFTs at least monthly.
Etanercept	None recognized	Assess for infections or risk factors for infections	Acute or chronic infections	Monitor for injection site reactions
Infliximab plus methotrexate	None recognized	Assess for infections or risk factors for infections	Acute or chronic infections	Monitor for infusion reactions and see Methotrexate above
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	CBC, creatinine, LFTs	Myelosuppression§	CBC every 1–2 weeks with changes in dosage, and every 1–3 months thereafter
D-penicillamine	Myelosuppression, proteinuria	CBC, creatinine, urinary protein (dipstick)	Myelosuppression§, edema, rash	CBC, urinary protein (dipstick) every 2 weeks until dosage stable, then every 1–3 months
Gold, intramuscular	Myelosuppression, proteinuria	CBC, creatinine, urinary protein (dipstick)	Myelosuppression§, edema, rash, oral ulcers, diarrhea	CBC, urinary protein (dipstick) every 1–2 weeks for first 20 weeks, then at the time of each (or every other) injection

Table 5. *(Cont'd)*

Drug/category	Toxicities requiring monitoring†	Baseline evaluation	Systems review/examination	Laboratory
Gold, oral	Myelosuppression, proteinuria	CBC, urinary protein (dipstick)	Myelosuppression§, edema, rash, diarrhea	CBC, urinary protein (dipstick) every 4–12 weeks
Minocycline	Hyperpigmentation, dizziness, vaginal yeast infections	None	Hyperpigmentation, dizziness, vaginal yeast infections	None
Cyclosporine	Renal insufficiency, anemia, hypertension	CBC, creatinine, LFTs, uric acid, BP	Hypertrichosis, paresthesia, nausea, gingival hyperplasia, edema, BP every 2 weeks until dosage stable, then monthly thereafter	Creatinine every 2 weeks until dosage is stable, then monthly; periodic CBC, LFTs, and potassium
Glucocorticoids (oral, ≤10 mg/day of prednisone or equivalent) (last)	Hypertension, hyperglycemia, osteoporosis	BP, blood chemistries panel, bone densitometry in high-risk patients	Polyuria, polydipsia, edema, shortness of breath, vision changes, weight gain, fracture, BP at each visit	Urinalysis for glucose yearly
Staphylococcal protein A immunoadsorption	Anemia, hypotension during procedure	CBC, creatinine, BP	Joint pain, fatigue, lightheadedness, infection at catheter site, BP	CBC

* GI = gastrointestinal; CBC = complete blood cell count (hematocrit, hemoglobin, white blood cell count, including white blood cell differential and platelet counts); LFTs = liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin); G6PDH = glucose-6-phosphate dehydrogenase; alk. phos. = alkaline phosphatase; ULN = upper limit of normal; MTX = methotrexate; BP = blood pressure.
† Potential serious toxicities that may be detected by monitoring before they have become clinically apparent or harmful to the patient. Toxicities that occur frequently enough to justify monitoring are shown here. Patients with comorbidity, concurrent medications, and other specific risk factors may need further studies to monitor for specific toxicities.
‡ The package insert for diclofenac (Voltaren; Novartis, East Hanover, NJ) recommends that AST and ALT be monitored within the first 8 weeks of treatment and periodically thereafter. Monitoring of serum creatinine should be performed weekly for at least 3 weeks in patients receiving concomitant angiotensin-converting enzyme inhibitors or diuretics.
§ Symptoms of myelosuppression include fever, symptoms of infection, bruising, and bleeding.
¶ Cholestyramine at a dosage of 4–8 gm 3 times a day for 5 days is generally adequate for washout, unless pregnancy is desired, in which case a longer washout is needed.

gest that although selective COX-2 inhibitors have a significantly lower risk of serious adverse gastrointestinal (GI) effects than do nonselective NSAIDs (41,42), they are no more effective than nonselective NSAIDs and may cost as much as 15–20 times more per month of treatment than generic NSAIDs.

Patients with RA are nearly twice as likely as patients with osteoarthritis to have a serious complication from NSAID treatment (43). Risk factors for the development of NSAID-associated gastroduodenal ulcers include advanced age, history of ulcer, concomitant use of corticosteroids or anticoagulants, higher dosage of NSAID, use of multiple NSAIDs, or a serious underlying disease (44). Advanced age is defined as 75 years or older. The following approaches may be considered for patients with RA who would benefit from an NSAID but who are at increased risk of serious adverse GI effects: use of low-dose prednisone instead of an NSAID, use of a nonacetylated salicylate, use of a highly selective COX-2 inhibitor, or use of a combination of an NSAID and a gastroprotective agent. Gastroprotective agents, which are effective in decreasing NSAID-associated gastroduodenal ulceration, include high-dose H_2 blockers (45), proton-pump inhibitors (46,47), and oral prostaglandin analogs (48).

While symptoms of dyspepsia are often improved by treatment with H_2 blockers, one study showed that asymptomatic patients with RA who were receiving both NSAIDs and low-dose H_2 blockers were at higher risk of GI complications than those receiving NSAIDs alone (49). Therefore, routine use of H_2 blockers to prevent dyspepsia or to protect against NSAID-induced gastropathy is not recommended.

In two recent large trials comparing highly selective COX-2 agents with traditional NSAIDs, the patients in the selective COX-2 agent group had significantly fewer GI events (41,42). There are several caveats, however. If antiplatelet therapy is indicated (e.g., as risk reduction for cardiovascular disease), an agent such as low-dose aspirin should be used because, unlike nonselective NSAIDs, the selective COX-2 inhibitors have no effect on platelet adhesion or aggregation (41). The

addition of low-dose aspirin may partially ameliorate the benefit of less GI toxicity associated with highly selective COX-2 agents (42). Moreover, the use of a highly selective COX-2 agent has been reported to be associated with a higher rate of thrombotic events (including more myocardial infarctions) compared with traditional NSAIDs (41). Use of NSAIDs and selective COX-2 inhibitors should be avoided in conditions associated with diminished intravascular volume or edema, such as congestive heart failure, nephrotic syndrome, or cirrhosis, and in patients with serum creatinine levels $\geq$2.5 mg/dl (50).

DMARDs. All patients with RA are candidates for DMARD therapy. Although NSAIDs and glucocorticoids may alleviate symptoms, joint damage may continue to occur and to progress. DMARDs have the potential to reduce or prevent joint damage, preserve joint integrity and function, and ultimately, reduce the total costs of health care and maintain economic productivity of the patient with RA. The initiation of DMARD therapy should not be delayed beyond 3 months for any patient with an established diagnosis who, despite adequate treatment with NSAIDs, has ongoing joint pain, significant morning stiffness or fatigue, active synovitis, persistent elevation of the ESR or CRP level, or radiographic joint damage. For any untreated patient with persistent synovitis and joint damage, DMARD treatment should be started promptly to prevent or slow further damage.

The DMARDs commonly used in RA (summarized in Table 2) include hydroxychloroquine (HCQ), sulfasalazine (SSZ), methotrexate (MTX), leflunomide, etanercept, and infliximab. Those used less frequently include azathioprine (AZA), D-penicillamine (D-Pen), gold salts, minocycline, and cyclosporine. Many studies have demonstrated the benefit of DMARD therapy in RA. The outcomes of these trials include control of the signs and symptoms of joint involvement, changes in functional status and quality of life, and retardation of radiographic evidence of erosions. The studies cited in Table 4 were randomized controlled clinical trials that showed improvement in outcomes for DMARDs given either as monotherapy or combination therapy, compared with either placebo or one or more other DMARDs. There are only a few studies comparing one DMARD with another.

Many factors influence the choice of DMARD for the individual patient (see Tables 2, 4, and 5). Patients and their physicians must select the initial DMARD(s) based on its relative efficacy, convenience of administration, requirements of the monitoring program, costs of the medication and monitoring (including physician visits and laboratory costs), time until expected benefit, and the frequency and potential seriousness of adverse reactions. The physician should also assess patient factors, such as likelihood of compliance, comorbid diseases, severity and prognosis of the patient's disease, and the physician's own confidence in administering and monitoring the drug. Because of these many considerations, input from a rheumatologist is often an essential component of the overall management plan when initiating DMARD therapy. Detailed descriptions of drug toxicity and recommendations for monitoring are provided in Table 5.

For women of childbearing age, effective contraception is required when most DMARDs are prescribed (8). The drug regimen will need to be modified if pregnancy or breastfeeding is contemplated (8).

Based on considerations of safety, convenience, and cost, many rheumatologists select HCQ or SSZ first, but for the patient with very active disease or with indicators of a poorer prognosis, MTX or combination therapy would be preferred. If a patient with RA has not achieved remission or a satisfactory response to the initial trial of DMARD(s), and if a rheumatologist has not yet been involved in the patient's care, a rheumatology consultation should be obtained. MTX as monotherapy or as a component of combination therapy should be instituted in patients whose treatment has not yet included MTX. For patients in whom MTX is contraindicated or has failed to achieve satisfactory disease control either because of lack of efficacy (in doses up to 25 mg/week) or intolerance, treatment with biologic agents or with other DMARDs, either alone or in combination, is indicated.

HCQ and SSZ. In the last decade, a number of studies have documented the symptomatic benefit of HCQ and SSZ, particularly for patients with early, milder disease (27–29,51–63). Although HCQ alone does not slow radiologic damage, early treatment with HCQ has a significant impact on long-term patient outcome. Rash, abdominal cramps, and diarrhea are infrequent adverse effects. HCQ is generally well tolerated and requires no routine laboratory monitoring, although patients need periodic ophthalmologic examinations for early detection of reversible retinal toxicity (64). The risk of retinal toxicity is increased when the dose exceeds 6 mg/kg. The length of time to benefit may vary from 1 month to as long as 6 months.

SSZ may act more quickly than HCQ, with benefit sometimes as early as 1 month after beginning therapy. More importantly, SSZ has been shown to

retard radiographic progression of RA (63). SSZ is usually well tolerated, with most side effects, which include nausea and abdominal discomfort, occurring in the first few months of therapy. The incidence of these side effects is lessened by starting at a low dosage and then gradually increasing the dosage. Leukopenia is an occasional, more serious side effect that may occur at any time, and periodic laboratory monitoring is therefore necessary. Clinical response should be apparent within 4 months, and the need for a change in therapy may be determined at that time.

MTX. Many rheumatologists select MTX as the initial DMARD, especially for patients whose RA is more active. Because of its favorable efficacy and toxicity profile, low cost, and established track record in the treatment of RA, MTX has become the standard by which new DMARDs are evaluated. Randomized clinical trials have established the efficacy of MTX in RA, particularly in patients with more severe disease (64–70). Longitudinal observational studies and randomized controlled trials show that MTX retards the progression of radiographic erosions (63,71–75).

Observational studies indicate that more than 50% of patients who take MTX continue the drug beyond 3 years, which is longer than any other DMARD (76–80). RA patients taking MTX are more likely to discontinue treatment because of adverse reactions than because of lack of efficacy (71). Stomatitis, nausea, diarrhea, and perhaps, alopecia caused by MTX may decrease with concomitant folic acid (81,82) or folinic acid (83) treatment without significant loss of efficacy. Relative contraindications for MTX therapy are preexisting liver disease, renal impairment, significant lung disease, or alcohol abuse.

Since the most frequent adverse reaction to MTX is elevation of liver enzyme levels, liver function must be monitored, but the risk of liver toxicity is low (84). Based on the ACR guidelines for monitoring liver toxicity in patients receiving MTX (84), a liver biopsy should be performed in patients who develop abnormal findings on liver function studies that persist during treatment or after discontinuation of the drug. Rare but potentially serious and even life-threatening pulmonary toxicity may occur at any time with any dosage of MTX. Lymphoproliferative disorders may rarely occur in patients taking MTX (85), but the relationship to the medication is unclear; some of these cases have regressed or resolved with discontinuation of MTX. Since MTX is potentially teratogenic, appropriate contraceptive measures during MTX treatment are recommended (8).

Leflunomide. Several randomized controlled clinical trials have established leflunomide as an alternative to MTX as monotherapy, especially for patients who cannot tolerate MTX or are experiencing an inadequate response to MTX (62,63,75,86–89). The reduction in RA disease activity and in the rate of radiologic progression achieved by leflunomide appears to be equivalent to that of a modest dosage of MTX. Leflunomide is also beneficial as combination therapy with MTX, in the absence of a complete clinical response with full doses of MTX.

Five percent of patients receiving leflunomide and up to 60% of patients receiving MTX plus leflunomide have elevated liver enzyme levels (75,87). Since enterohepatic recirculation plays a large role in leflunomide metabolism, leflunomide has a long half-life. Without the recommended washout protocol with cholestyramine resin, elimination of the drug would take as long as 2 years. Leflunomide is a potent teratogen, and women taking leflunomide who wish to conceive must discontinue leflunomide and undergo cholestyramine washout before attempting conception. Obstructive biliary disease, liver disease, viral hepatitis, severe immunodeficiency, inadequate birth control, and rifampin therapy (which raises leflunomide serum levels) are all contraindications to the use of leflunomide.

Anti–tumor necrosis factor α (anti-TNFα) therapy. The development of genetically engineered biologic agents that selectively block cytokines (anticytokine therapy) in the short term represents a major advance in the treatment of RA. The most clinically effective anticytokine agents studied to date are antagonists to TNFα, an essential mediator of the cytokine inflammatory cascade in RA. Two anti-TNFα agents are available in the US: etanercept, a recombinant soluble TNF-Fc fusion protein; and infliximab, a chimeric (mouse–human) anti-TNF monoclonal antibody.

Randomized double-blind, placebo-controlled trials have demonstrated the efficacy of etanercept and infliximab in improving clinical symptoms and signs in patients with RA, according to the ACR20, ACR50, and ACR70 improvement criteria (90–96). Patients with early RA (96) and those with active RA in whom previous DMARD therapy had failed (90) showed improvement with etanercept therapy. Both etanercept (94) and infliximab (92,93,95) have been shown to be beneficial when used in combination with MTX in patients with ongoing active RA despite adequate doses of MTX alone. Infliximab is currently recommended for use only with concomitant MTX therapy.

In these trials of etanercept and infliximab, many patients improved rapidly, even during the first 2 weeks

of treatment. Randomized trials have demonstrated that patients treated with etanercept alone or with infliximab plus MTX have less radiographic progression after 1 year than patients treated with MTX alone (93,96). In the trial of patients with early RA (96), the symptoms and signs of RA improved more rapidly with etanercept treatment than with MTX treatment over the first 6 months, with comparable efficacy of the two agents at 12 months.

Although data from randomized trials have not shown an increased frequency of serious adverse effects, such as serious infections or malignancies, for either anti-TNFα agent, concerns about the short-term and long-term safety of these agents continue. TNFα plays an important role in host protection against infection and tumor genesis. Postmarketing experience with etanercept and infliximab shows hospitalizations and deaths from serious infections in patients treated with these agents. Many of the patients who died while being treated with anti-TNFα had significant chronic infections or risk factors for infection. Anti-TNFα agents should therefore be used with caution in patients with any susceptibility to infection or a history of tuberculosis, should be avoided in patients with significant chronic infections, and should be discontinued temporarily in all patients with acute infection.

Postmarketing surveillance has yielded reports of sepsis, tuberculosis, atypical mycobacterial infections, fungal infections, other opportunistic infections, demyelinating disorders, and aplastic anemia. Risk of latent tuberculosis should be assessed prior to initiation of a TNFα antagonist. While the followup period with these new agents is still relatively short, thus far there have been no demonstrated increases in the incidence of malignancy in patients treated with etanercept or infliximab compared with the expected rates in the general population (97). At this time, there appears to be no need for routine laboratory monitoring with the anti-TNFα agents, but patients should be alerted to report any signs or symptoms of infection.

In addition to the absence of long-term safety data, the disadvantages of anti-TNFα agents are the need for parenteral administration and the high cost of these medications. Not all patients with RA respond to anti-TNFα therapy, and disease flares occur after therapy is discontinued.

Older DMARDs. AZA, a purine analog myelosuppressant, has demonstrated benefits in controlling RA, but it is rarely used (98–102). D-Pen is effective (98,99,103,104), but its use is limited, in part, by an inconvenient dosing schedule (i.e., slow increases in the dosage) and rare, but potentially serious, complications, including autoimmune diseases, such as Goodpasture's syndrome and myasthenia gravis. Intramuscular gold treatment is effective (98,99,105), but injections are required every week for 22 weeks before less-frequent maintenance dosing is initiated. Although oral gold is more convenient than injectable gold, there is a long delay (up to 6 months) before benefits are evident, and it is less efficacious (98,99).

Tetracyclines. Recently, randomized double-blind, placebo-controlled trials have demonstrated the efficacy of minocycline in improving the clinical parameters of RA (106–109). Importantly, one trial showed long-term benefit of minocycline and a decrease in radiographic progression in a subset of patients who were positive for the HLA shared epitope (HLA–DR4+) (110). Further research is necessary to define the exact role of tetracyclines in the treatment of RA.

Cyclosporine. Cyclosporine is beneficial as monotherapy (111,112), and has short-term efficacy similar to that of D-Pen (113). The use of cyclosporine, however, has been limited by its toxicity, especially hypertension and dose-related loss of renal function (114,115). The ~20% loss of renal function with cyclosporine appears to be largely, but not entirely, reversible with discontinuation of the drug (115,116). Dose calculation to avoid renal toxicity is more critical with cyclosporine than with any other DMARD. Many medications may increase cyclosporine levels and thus increase the risk of nephrotoxicity. Therefore, cyclosporine treatment is primarily confined to patients with refractory RA.

Staphylococcal protein A immunoadsorption. Extracorporeal immunoadsorption of plasma against a staphylococcal protein A column (Prosorba; IMRE Corporation, Seattle, WA) was reported to be efficacious in a portion of patients with severe refractory RA (117). Given the difficulty and cost of administering weekly treatments for 12 weeks, the limited duration of the response, and the high frequency of side effects, this treatment should be considered only for patients with refractory RA in whom treatment with several DMARDs has failed.

Combination DMARD therapy. Conventional treatment with a single DMARD often fails to adequately control clinical symptoms or to prevent disease progression. As a result, rheumatologists are increasingly prescribing combination DMARD therapy (118). Controversy remains about whether to initiate this type of treatment in a sequential "step-up" approach in patients with persistently active disease in whom single agents have failed or whether to initiate combination

therapy early in the disease course and then apply a "step-down" approach once adequate disease control is attained (119). In either case, rheumatology referral is strongly recommended for patients being considered for initiation of combination therapy.

Early open-label studies showed promising results (120), but often there was increased toxicity without clear demonstration of a synergistic effect of the multiple DMARDs. However, a number of these studies either had insufficient statistical power to detect differences between treatment groups, used DMARDs that were subsequently found to be weakly active as single agents, or used suboptimum dosages (119,121,122).

Cyclosporine plus MTX was found to be more effective than MTX alone, but long-term followup revealed the development of hypertension and elevated creatinine levels (123,124). A randomized controlled clinical trial has demonstrated that the triple-DMARD combination of MTX, HCQ, and SSZ has substantially increased efficacy compared with MTX alone and with the combination of HCQ plus SSZ, without increased toxicity (125). The efficacy of this 3-DMARD combination without the occurrence of additional toxicity was confirmed in another randomized trial (126). In this latter trial, patients with early disease were studied, and the treatment regimen included low-dose prednisolone in a subset of patients. Recently, the triple-DMARD combination of MTX, SSZ, and HCQ has been shown to be superior to the double-DMARD combinations of MTX plus SSZ or MTX plus HCQ in both early (127) and more advanced (128) RA.

Using a "step-down" approach, a recent randomized controlled trial compared SSZ alone or in combination with a 6-month tapering dosage of high-dose, short-term prednisolone and MTX in patients with early disease (129). Patients who took triple therapy had less radiographic progression, fewer withdrawals because of either toxicity or lack of efficacy, and lower disease activity scores than did patients who took SSZ alone.

The studies cited above all predate the introduction of leflunomide and biologic agents and their use in combination with other DMARDs. The combinations of infliximab, etanercept, or leflunomide with MTX have all been studied in patients who had a partial response to MTX, and the combinations were found to be beneficial (93,94,130–132).

Over the last several years, combination DMARD therapy has played a significant role in improving our ability to control RA. The role of combination DMARD therapy continues to evolve.

Glucocorticoids. Low-dose oral glucocorticoids (<10 mg of prednisone daily, or the equivalent) and local injections of glucocorticoids are highly effective for relieving symptoms in patients with active RA. A patient disabled by active polyarthritis may experience marked and rapid improvement in functional status within a matter of days following initiation of low-dose glucocorticoids. Frequently, disabling synovitis recurs when glucocorticoids are discontinued, even in patients who are receiving combination therapy with one or more DMARDs. Therefore, many patients with RA are functionally dependent on glucocorticoids and continue them long-term.

Recent evidence suggests that low-dose glucocorticoids slow the rate of joint damage and, therefore, appear to have disease-modifying potential (133). Joint damage may increase on discontinuation of glucocorticoids (134).

The benefits of low-dose systemic glucocorticoids, however, should always be weighed against their adverse effects. The adverse effects of long-term oral glucocorticoids at low doses are protean and include osteoporosis, hypertension, weight gain, fluid retention, hyperglycemia, cataracts, and skin fragility, as well as the potential for premature atherosclerosis. These adverse effects should be considered and should be discussed in detail with the patient before glucocorticoid therapy is begun. For long-term disease control, the glucocorticoid dosage should be kept to a minimum. For the majority of patients with RA, this means ≤10 mg of prednisone per day.

RA is associated with an increased risk of osteoporosis independently of glucocorticoid therapy. Patients taking glucocorticoids at dosages as low as 5 mg/day have an increased risk of osteoporosis, and densitometry to assess bone loss should be performed at regular intervals for the duration of glucocorticoid treatment (135). Glucocorticoid-treated patients should receive 1,500 mg of elemental calcium per day (including diet and supplements) and 400–800 IU of vitamin D per day (136,137). Hormone replacement therapy should be considered for postmenopausal women in whom such treatment is not contraindicated (137). Antiresorptive agents, especially bisphosphonates, prevent bone loss, and these agents should also be considered at the time glucocorticoid therapy is initiated (137).

Glucocorticoid injection of joints and periarticular structures is safe and effective when administered by an experienced physician. Injecting one or a few of the most-involved joints early in the course of RA may provide local and even systemic benefit. The effects are sometimes dramatic, but temporary. The prompt im-

provement from an intraarticular injection of glucocorticoids helps to instill confidence that treatment can be effective. A patient who has disease flare in only one or a few joints can be treated successfully by injecting the particular joint(s), without requiring a major change in the prescribed treatment regimen. Local glucocorticoid injections may also allow the patient to participate more fully in rehabilitation programs to restore lost joint function.

Not all joint flares in RA patients are caused by the disease. Joint infection or microcrystalline arthritis must be considered and ruled out before local glucocorticoid injections are given. In general, the same joint should not be injected more than once within 3 months. The need for repeated injections in the same joint or for injections in multiple joints indicates the need to reassess the adequacy of the overall treatment program.

Surgical treatment of RA

In patients who have unacceptable levels of pain, loss of range of motion, or limitation of function because of structural joint damage, surgical procedures should be considered. Surgical procedures for RA include carpal tunnel release, synovectomy, resection of the metatarsal heads, total joint arthroplasty, and joint fusion. New prosthetic materials and cements for fixing joint prostheses have greatly advanced the prevention of aseptic loosening and have increased the longevity of total joint prostheses in patients with RA (138–142).

Preoperative functional status is an important determinant of the rate of recovery of functional independence after surgery. Strategies for increasing functional recovery include optimization of preoperative functional status and early surgical intervention (143). The pre- and postoperative team should include health care professionals who have performed large numbers of the particular surgical procedure and are experienced in the care of patients with RA.

Responsibilities of primary and specialty care physicians

Depending on the health care setting, the majority of the care of patients with RA may be provided by a single physician (primary care physician or rheumatologist who also provides primary care) or the responsibility may be shared. The role of the primary care physician is to recognize and diagnose RA at its onset and to ensure that the patient receives timely treatment before permanent joint damage has occurred. The rheumatologist should provide support and consultation to the patient and his or her primary care physician in the diagnosis and treatment of the RA.

Since the level of training and experience in diagnosing and managing RA varies among primary care physicians, the responsibility for accurate diagnosis and monitoring of RA activity and/or drug toxicity may appropriately be assigned to a rheumatologist. If the care of a patient with RA is to be shared, an explicit plan for monitoring RA disease activity (Table 3) and/or drug toxicity needs to be formulated. The patient's preference may be the most important factor in deciding which physician(s) assumes responsibility for care.

A general health maintenance strategy should be developed, and responsibility for this strategy should be coordinated among the patient's health care providers. Routine prevention measures, such as screening for hypertension or cancer, should be recommended and risk factors modified.

Cost considerations

RA has significant economic implications for the individual patient as well as for society. Individuals with RA have 3 times the direct medical costs, twice the hospitalization rate, and 10 times the work disability rate of an age- and sex-matched population (144). A recent study has shown annual medical costs for a patient with RA to be approximately $8,500 (145). Annual costs rise as the duration of disease increases and as function, measured by the Health Assessment Questionnaire, declines. Indirect costs related to disability and work loss have been estimated to be 3 times higher than the direct costs associated with disease.

Responsibility for the direct medical costs often falls to the third-party payor and, in part, to the patient, whereas the majority of indirect costs are borne by the government or by employers. In a variety of health care financing systems, the fragmentation of these financial risks and incentives, the frequent turnover of patients into different risk pools and health care delivery systems, and the relatively slow disease course may all adversely affect access to appropriate care.

For many years, relatively low-cost options have been available for the treatment of RA. However, the advent of COX-2 inhibitors, newer DMARDs, including biologic agents, and the increasing use of combination therapy have all brought cost considerations to the forefront. The majority of guidelines have generally avoided cost issues by limiting their scope to an evidenced-based review of the literature followed by

optimum treatment recommendations. However, the committee thought that ignoring financial considerations would inadequately reflect the impact on daily treatment decisions.

Despite promising short-term results for newer DMARDs that have demonstrated significant effects on functional status and radiographic progression, there are, at present, insufficient longitudinal data to determine whether such an increased expenditure will eventually be offset by lower total costs of the disease. A recent analysis has examined the relative cost-effectiveness of 6 different treatment options for RA patients in whom MTX therapy has failed (146): etanercept monotherapy, etanercept plus MTX, cyclosporine plus MTX, triple therapy with HCQ, SSZ, and MTX, continued MTX monotherapy, and no second-line agent. Triple therapy was the most cost-effective option, as determined by the ACR20 improvement criteria or a weighted proportion of patients achieving ACR20, ACR50, and ACR70 improvement. However, as with all cost-effectiveness analyses, there were assumptions which may limit the applicability of the results. For example, the time horizon for this model was limited to the first 6 months of therapy. In addition, only a limited number of treatment options were considered in the model. Neither leflunomide nor infliximab was considered. More data about the impact of newer DMARDs on outcomes such as work capacity and radiographic progression are also needed.

In today's cost-constrained environment, whenever the efficacy and toxicity of treatment options are equivalent, the lower-cost agent is likely to be used. However, practitioners are increasingly facing situations in which therapies are no longer equivalent, there is only a partial response to treatment, treatment toxicity or comorbid conditions contraindicate the use of more traditional agents, or high-risk or severe disease requires the use of newer agents, either alone or in combination. Providers with sufficient numbers of RA patients in their practice and with longitudinal experience in treating this disease will, in consultation with their patients, be the best qualified to balance these delicate cost issues with the frequently progressive and debilitating natural course of this disease.

Summary

RA is a chronic progressive polyarthritis (with varying systemic features) associated with substantial disability and economic losses. Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease-modifying agents. The goal of treatment is to arrest the disease and to achieve remission. Although remission occurs infrequently, patients may benefit from nonpharmacologic, pharmacologic, and if necessary, surgical interventions. Optimal longitudinal treatment requires comprehensive coordinated care and the expertise of a number of health care providers. Essential components of management include systematic and regular evaluation of disease activity, patient education/rehabilitation interventions, use of DMARDs, possible use of local or low-dose oral glucocorticoids, minimization of the impact on the individual's function, assessment of the adequacy of the treatment program, and general health maintenance.

Addendum. Since the time these guidelines were completed and accepted for publication, anakinra, a recombinant human form of interleukin-1 receptor antagonist (IL-1Ra), was approved for use in RA. IL-1β is a cytokine that, along with TNFα, is thought to play an essential role in the synovial inflammation and joint destruction seen in RA. IL-1Ra acts to block the binding of IL-1α and IL-1β to the IL-1 receptor, thus preventing the activation of target cells. Randomized, double-blind, controlled trials of anakinra, at a dosage of 150 mg administered as a once-daily subcutaneous injection, showed it to be superior to placebo in improving the clinical signs and symptoms of RA, as assessed by the ACR20 criteria (154). Anakinra also improved the Health Assessment Questionnaire score (154) and reduced radiographic progression (155) compared with placebo. A recent study demonstrated that combination treatment with anakinra, at a dosage of 1.0 mg/kg or 2.0 mg/kg, plus MTX was more beneficial than treatment with MTX alone (156).

Anakinra is approved for use in RA as a 100-mg self-administered subcutaneous daily dose. Injections are simplified with the use of a specially designed injector device that is provided by the manufacturer. Injection site reactions were the most common adverse effect reported. These most often occur during the first 4 weeks and may disappear in days to weeks. At times, such reactions may lead to discontinuation of the drug. As with other biologic therapies, there is concern about the risk of serious infections and malignancy, but the available safety data are limited. Patients with asthma/chronic obstructive pulmonary disease had a higher rate of pulmonary infections; thus, anakinra should be used with caution in patients with these comorbid conditions. Anakinra should not be given to patients with active infections of any type. Anakinra fits into the management of RA along with the other biologic therapies.

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