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General principles of management of rheumatoid arthritis

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INTRODUCTION — The management of patients with rheumatoid arthritis (RA) is based upon an emerging understanding of the biology and natural history of the disease [1,2]:

- Although the etiology and pathogenesis remain unclear, recent data suggest that RA generally results from acute and chronic inflammation in the synovium associated with a proliferative and destructive process in joint tissues. Affected areas may either heal without lasting structural defects, or be irreversibly damaged or destroyed if inflammation is severe and does not remit. Measures aimed at identifying early active disease and ameliorating inflammation are therefore essential and may be highly effective in modifying disease outcome. (See "Pathogenesis of rheumatoid arthritis".)

- Much of the joint damage that ultimately results in disability begins early in the course of the disease [3,4]. In one study, for example, more than 80 percent of patients with RA of less than two years duration had joint space narrowing on plain radiographs of the hands and wrists, while two-thirds had erosions [4]. The use of more sensitive imaging techniques, such as magnetic resonance imaging (MRI) and high resolution ultrasonography is likely to identify even earlier damage [5]. Certain clinical features may help in predicting which patients with early arthritis will go on to develop progressive and erosive disease [6]. (See "Clinical features of rheumatoid arthritis".)

- Prior to the widespread use of methotrexate or the availability of targeted biologic agents, RA was associated with a high degree of economic loss, morbidity, and early mortality. As an example, almost 80 percent of patients in one center were severely disabled after 20 years of follow-up; an additional one third had died [7]. Patients with RA that require hospital care have at least a twofold increased mortality when compared to those without disease [8], and more severe RA is associated with higher mortality rates due to higher rates of myocardial infarction, infection, and certain malignancies. The excess mortality in severe RA (more than 30 involved joints) has been compared to that of three vessel coronary artery disease or stage IV Hodgkin lymphoma [9]. (See "Disease outcome and functional capacity in rheumatoid arthritis".)

An appreciation of the pathogenic mechanisms of RA and the poor outcomes with conventional therapy led to the concept of effective treatment of newly diagnosed or early aggressive disease to suppress ongoing inflammation and prevent joint injury [10,11]. By

comparison, the management of patients with end-stage disease in whom active inflammation is much less significant is focused principally upon the relief of pain and the improvement or maintenance of function.

An overview of the therapeutic approach to the patient with RA is presented here. This approach begins with an understanding of the stages of the disease and the assessment of disease activity and severity. This is followed by the prescription of both nonpharmacologic and pharmacologic modalities in an attempt to diminish inflammation and to preserve long-term function.

2008 ACR RECOMMENDATIONS — The 2008 American College of Rheumatology (ACR) recommendations for the use of nonbiologic and biologic disease modifying antirheumatic drugs (DMARDs) in RA addressed five main issues [12,13]:

- Indications for use of nonbiologic and biologic DMARDs
- Screening for tuberculosis for biologic DMARD use
- Monitoring for side effects
- Assessing the clinical response
- The roles of cost and patient preferences in decision making for biologic DMARDs

The recommendations were based on a systematic literature review and a structured group approach, representing consensus expert opinion, rather than being fully evidence based. The use of the term recommendations, rather than guidelines, was made explicitly to emphasize that their use required individualized patient assessment and the decision-making skills of experienced clinicians. The recommendations were not intended to be applied in a prescriptive manner or to limit the use of clinical judgment.

Treatment algorithms for initial therapy or resumption of a DMARD depended upon three factors: disease duration, disease activity, and prognostic factors. A limitation to the clinical utility of the guideline is that recommendations were not made on specific questions when consensus could not be reached, such as when treatment should be adjusted because of insufficient efficacy by switching or adding DMARDs in patients already on a DMARD [13]. The consensus was reached on the recommendation that biologic DMARD use should follow the failure of nonbiologic DMARDs.

The ACR recommendations can be accessed online at:

<http://www.rheumatology.org/practice/clinical/guidelines/recommendations.pdf> (accessed April 12, 2010)

STAGES OF DISEASE — The 2008 American College of Rheumatology (ACR) recommendations on the use of disease-modifying antirheumatic drugs (DMARDs) used the following definitions for classification according to duration of symptoms in patients with active RA who have not been treated with DMARDs [12]:

- Early (<6 months)
- Intermediate (6 to 24 months)
- Long or longer disease (>24 months)

Among patients with early RA, treatment is influenced by the activity of the disease (mild, moderate, or severe). In addition, some patients have persistently active disease despite initial pharmacologic therapies. Each of these issues is discussed separately in other topic reviews. (See "Treatment of early, mildly active rheumatoid arthritis in

adults" and "Treatment of early, moderately active rheumatoid arthritis in adults" and "Treatment of early, severely active rheumatoid arthritis in adults" and "Treatment of persistently active rheumatoid arthritis in adults".)

Another therapeutic issue, also presented elsewhere, is the management of end-stage RA. (See "Evaluation and medical management of end-stage rheumatoid arthritis".)

ASSESSMENT OF DISEASE ACTIVITY — The evaluation of disease activity in patients with RA is currently based upon the following factors:

- Patient and physician assessment of symptoms and functional status
- Evaluation of joint involvement and extraarticular manifestations
- Laboratory markers
- Radiographic studies

These factors are used both for initial assessment of disease activity and to monitor the response to therapy. Composite measures employing these variables have been developed for use in clinical research and practice, including:

- The Disease Activity Score derivative for 28 joints (DAS28)
- The Simplified Disease Activity Index (SDAI)
- The Clinical Disease Activity Index (CDAI)

These tools have been validated as being useful for defining remission, defining low, moderate, and high disease activity, and, in some cases, determination of the appropriate use of DMARDs [12]. (See "Assessment of rheumatoid arthritis activity in clinical trials and clinical practice", section on 'Composite indices for disease activity assessment'.)

Calculators for these measures are available:

- DAS28 (calculator 1)
- SDAI (calculator 2)
- CDAI (calculator 3)

Symptoms and functional status — The assessment of disease activity should include questions concerning the degree of joint pain, duration of morning stiffness, and the severity of fatigue [14]. In addition, evidence for and changes in extraarticular manifestations of RA should be actively sought, including systemic signs such as fever, anorexia, malaise, weight loss, and symptoms of cardiovascular disease.

Fever is not a common feature of RA in adults. Infection must be excluded before ascribing fever to RA.

A self-report questionnaire designed to give an assay of function is often helpful. The Stanford Health Assessment Questionnaire (HAQ) is one of the best known and tested of these questionnaires [15,16]; others include the Functional Independence Measure [17], the Arthritis Impact Measurement Scale (AIMS), the Short Form 36 (SF36), the Modified Health Assessment Questionnaire (MHAQ) [18], and by the DAS28 and SDAI instruments mentioned above for more definitive assessments. (See "Disease outcome and functional capacity in rheumatoid arthritis", section on 'Functional capacity'.)

Physical examination — A physical examination should be performed at regular intervals that vary with disease activity and severity. As an example, patients with severely active disease might be seen at four week intervals, while those with mildly active or well controlled disease could be seen every two to four months. At these visits, an examination should be performed to assess changes in previously affected joints or the appearance of inflammation in previously uninvolved joints. If the hands but not the feet are involved a 28 joint examination is appropriate [19]. Examined joints include the wrists, elbows, shoulders, and knees, and the metacarpophalangeal and proximal interphalangeal joints of the hands. If the feet but not the hands are involved, the metatarsophalangeal joints and proximal interphalangeal (PIP) joints of the feet can be assessed instead of the small joints of the hands. The joints should be evaluated for the presence of swelling, tenderness, loss of motion and deformity.

In addition to the articular examination, periodic examination of the skin for rheumatoid nodules or other dermal manifestations of RA, of the lungs for signs of pleural or interstitial disease, may detect evidence of systemic or extraarticular involvement. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis".)

Laboratory tests — Laboratory tests to assay disease activity should be selected from those that are abnormal in the individual patient during a period of significant disease activity, are sensitive to change, and are relatively inexpensive [1]. One or more of the following may be useful:

- **Acute phase reactants** — The serum C-reactive protein (CRP) concentration is a direct measure of the impact of interleukin-6 (IL-6) upon liver cells, is linear over a wide range, and is reproducible [20]. The erythrocyte sedimentation rate (ESR) has traditionally been used, but it is an indirect measure of acute phase reactants and its value is influenced by the red blood cell concentration and the presence of other proteins (eg, fibrinogen). Both the ESR and CRP reflect the degree of synovial inflammation. (See "Acute phase reactants" and "Clinically useful biologic markers in the diagnosis and assessment of outcome in rheumatoid arthritis".)
- **Hemoglobin** — Hemoglobin is generally less than normal but above 9.0 g/dL in active RA, unless there is concurrent blood loss from irritation of the gastrointestinal tract.
- **Serum albumin** — Serum albumin concentration is often decreased and correlates directly with disease severity.
- **Rheumatoid factor titers** — Rheumatoid factor (RF) titers rarely change with disease activity, and are not useful for following patients with RA, although whether or not rheumatoid factor is present is helpful in determining prognosis. (See "Clinically useful biologic markers in the diagnosis and assessment of outcome in rheumatoid arthritis", section on 'Rheumatoid factors'.)
- **Anti-citrullinated peptide antibody (ACPA) titers** — Antibodies with an affinity for peptides containing citrulline, a post-translationally modified amino acid created by deimination of arginine residues, may be as sensitive and more specific than assays for RF for the diagnosis of RA. In addition to use in diagnosis, the presence of ACPA, detected by assays for anti-cyclic citrullinated peptide (CCP) antibodies, may be a better predictor of progression to erosive joint disease than RF titers early in the course of RA [6,21,22].

However, antibody levels or serial measurements are not useful in ongoing assessment of disease activity. (See "Clinically useful biologic markers in the diagnosis and assessment of outcome in rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

- Platelet counts — Platelet counts are elevated in patients with very active disease, but serial platelet counts have not proven useful in sequentially following patients.

Imaging techniques — Early in the course of RA, it is appropriate to obtain plain radiographs of the hands and wrists (one film, PA view), and at least one AP view of both feet to include the metatarsophalangeal joints. These radiographs serve as a baseline for evaluating change in the joint during the next 6 to 12 months. If periarticular osteopenia, joint space narrowing, or bone erosions appear or worsen during this interval, current therapy may be deemed insufficient to restrain disease progression, and the regimen should be intensified. The physician must be aware that in hand radiographs of older patients, coexistent osteoarthritis may account, in part, for joint space narrowing noted near the joints involved with RA [23].

CT scanning, ultrasonography, computerized image analysis and magnetic resonance imaging (MRI) are more sensitive for the detection of cartilage and bone abnormalities, and their role in the process of making therapeutic decisions is presently under investigation [24-26].

Biologic markers — Although not generally available for routine use, novel urine and serum assays may provide additional information concerning cartilage and bone involvement or the extent of immune and cellular synovial activity. Most of these assays reflect recent findings concerning the pathogenesis of RA [1]. (See "Investigational biologic markers in the diagnosis and assessment of rheumatoid arthritis".)

ADVERSE PROGNOSTIC FACTORS — The 2008 ACR recommendations for the treatment of RA with DMARDs identified four adverse prognostic indicators as being clinically most important [12]:

- Functional limitation
- Extraarticular disease
- Rheumatoid factor positivity or presence of anti-cyclic citrullinated peptide (CCP) antibodies
- Bony erosions documented radiographically

Other factors associated with a worse prognosis include concurrent medical disorders, cigarette smoking, lack of formal education, and lower socioeconomic status [27]. (See "Epidemiology, risk factors for, and possible causes of rheumatoid arthritis".)

Some studies have derived models to estimate prognosis, such as persistent erosive disease [6]. However, these models have not been validated in other cohorts.

SEVERITY OF DISEASE — Using information obtained from the physical examination, laboratory data, and imaging studies, the patient's disease can be characterized as mild, moderate, or severe. This distinction is important clinically because treatment of RA varies with disease severity. (See "Treatment of early, mildly active rheumatoid arthritis in adults" and "Treatment of early, moderately active rheumatoid arthritis in adults" and "Treatment of early, severely active rheumatoid arthritis in adults".)

The following descriptions use many elements that are incorporated into measures of disease activity and estimates of prognosis, including evidence of joint injury.

(See 'Assessment of disease activity' above and 'Adverse prognostic factors' above.)

Two other factors are important in the following definitions. First, clear distinctions cannot always be made between mild and moderate disease and moderate and severe active disease. Second, the classification applies best to untreated patients.

Mild disease — Patients with mild disease meet the ACR criteria for RA (table 1) and typically have less than six inflamed joints, no extraarticular disease, and no evidence of erosions or cartilage loss on plain radiographs. (See "Diagnosis and differential diagnosis of rheumatoid arthritis", section on 'Classification criteria'.)

Severe disease — Patients with severe RA typically have more than 20 inflamed joints, an elevation in the ESR and/or serum CRP, and one or more of the following:

- Anemia of chronic disease and/or hypoalbuminemia
- Rheumatoid factor positivity (often in high titer) and/or anti-CCP antibodies
- Joint radiographs demonstrating rapid appearance of bony erosions and loss of cartilage
- Extraarticular disease

Moderate disease — Patients with moderate disease, by definition, do not fulfill criteria for either mild or severe disease. They typically have between 6 and 20 inflamed joints and have some combination of the following clinical features:

- Absence of extraarticular disease (most commonly)
- Elevation in the erythrocyte sedimentation rate (ESR) and/or serum C-reactive protein (CRP) concentration
 - Positive RF and/or anti-CCP antibodies
 - Evidence of inflammation on plain radiography, such as osteopenia and/or periarticular swelling; in addition, minimal joint space narrowing and small peripheral erosions may be observed.

These individuals may progress to severe disease after a period of inadequately controlled synovitis.

GENERAL MANAGEMENT STRATEGY — The recognition that destruction of affected joints due to active inflammation occurs early in the course of RA supports the view that every patient with established disease should be offered treatment with disease modifying antirheumatic drugs (DMARDs) as soon as possible after disease onset. Those with more severe active disease and/or poor prognostic signs should be treated more aggressively than those with milder disease. A reasonable goal is to escalate the intensity of treatment until evidence for synovitis and inflammation diminishes or disappears, or until drug-induced side effects become intolerable.

It is important to recognize that patients with RA form a heterogeneous group, ranging from those with very mild and undifferentiated disease, to early, established, and severe disease, to end-stage disease associated with little inflammation but severe functional disabilities.

Course — The course of RA varies considerably, and three broad patterns have been identified:

- Long clinical remissions — Almost 10 percent of patients have prolonged clinical remissions that may be associated with disappearance of rheumatoid factor positivity [1]. Some of these patients have an occasional flare, but the prognosis for good function is excellent.
- Intermittent disease — Approximately 15 to 30 percent of patients have an intermittent course characterized by partial to complete remissions, without need for continuous therapy [1]. The remissions last up to one year, and relapses are often marked by involvement of additional joints.
- Progressive disease — The majority of patients have progressive disease that can lead to joint destruction and disability.

Therapeutic options — Optimal therapy varies based upon individual patient characteristics and the response to previous treatment regimens.

- Nonpharmacologic and preventive treatments — These interventions serve as the foundation of therapy for every patient and include patient education, rest, exercise, physical, occupational and dietary therapy, and general measures to protect bone structure and function. (See "Nonpharmacologic and preventive therapies of rheumatoid arthritis".)
- Pharmacologic agents — Drug therapy is the mainstay of treatment for all patients except for those in clinical remission. Such therapy should be instituted with the goals of treating each patient sufficiently to induce a remission and prevent further loss of joint tissues or function in daily activities. These goals should be achieved without resulting in permanent or unacceptable side effects. We favor continuation of DMARD therapy at reduced doses for patients in remission. (See "Assessment of rheumatoid arthritis activity in clinical trials and clinical practice".)
- Surgery — Surgery is an option for those with functional abnormalities caused by proliferative synovitis (eg, tendon rupture) or by bone and joint destruction [28].

Importance of tight control — Tight control largely describes an approach in which the principal goal is to quickly achieve and maintain control of the disease. Treatment protocols based upon this general approach are associated with improved radiographic and functional outcomes compared to less aggressive approaches [29-37].

Taken together, studies that have compared tight control to less aggressive approaches support the following observations:

- Most patients should receive a DMARD as soon as possible. Achieving and maintaining low disease activity using a DMARD or DMARD combinations as quickly as possible improves long-term outcomes and is cost-effective compared with older, more gradual approaches to initiating DMARD therapy.
- Excellent treatment responses can be achieved with a wide variety of nonbiologic and biologic DMARDs and regimens that combine either nonbiologic DMARDs alone or nonbiologic DMARDs with a biologic agent.
- Escalation in the treatment regimen is needed for patients resistant to initial treatment;

both intraarticular and oral/intramuscular glucocorticoids help minimize disease activity until other medications are sufficient.

- Regular assessment with composite measures of disease activity are an important support to clinical decision-making. (See 'Assessment of disease activity' above.)

These observations are reflected in the ACR 2008 treatment recommendations and in recommendations based upon a 2010 systematic review and formal consensus process of an international task force [12,13,38,39]. Support for these conclusions is best illustrated by the following studies [29-35]:

- In the BeSt study, 508 patients with early active RA were randomly assigned to monotherapy (group 1), initial monotherapy with step-up combination therapy as required (group 2), combination therapy plus high dose prednisone (group 3), or combination therapy including infliximab (group 4) [29,30]. Regimens were adjusted based upon assessment of disease activity every 3 months. At 3 and 12 months, functional improvement was significantly better in those receiving initial combination therapy (groups 3 and 4). Significantly less radiographic progression was observed at two and four years in the combination groups compared with the initial monotherapy groups [30,36]. Remission at four years was achieved in 43 percent of all patients, and drug-free remission was seen in 13 percent.
- The FIN-RACo trial evaluated the outcomes of 199 patients randomly assigned to monotherapy or combination therapy for at least two years [32-34]. At follow-up at 11 years from the initial period of randomization, a significantly greater proportion of patients in the initial combination group had achieved minimal disease activity (63 versus 43 percent) and remission by ACR criteria (37 versus 19 percent) [34].
- In the TICORA study, 111 patients were randomly assigned to intensive or routine management [35]. Intensively managed patients had monthly visits, with calculation of disease activity scores, glucocorticoid injections of swollen joints, and every three month adjustment of their treatment regimen by a predefined protocol if moderate or highly active disease was present. Routinely managed patients were seen every three months, no formal measurement of disease activity was performed, and glucocorticoid injections and other treatment adjustments were made at the discretion of their rheumatologist. After 18 months, the patients receiving intensive management demonstrated a significantly greater reduction in their disease activity score compared with the routine management group (-3.5 versus -1.9), and a higher proportion achieved a good response by European League Against Rheumatism criteria (82 versus 44 percent).

The following sections will provide an overview of the nonpharmacologic, pharmacologic, and surgical therapies of patients with RA.

NONPHARMACOLOGIC AND PREVENTIVE THERAPIES — Nonpharmacologic and preventive therapies are important in the management of RA. The individual components include:

- Patient education and counseling
- Rest
- Exercise

- Physical therapy
- Occupational therapy
- Nutrition and dietary therapy
- Bone protection
- Atherosclerosis risk factor modification
- Vaccinations

These issues are discussed in detail elsewhere. (See "Nonpharmacologic and preventive therapies of rheumatoid arthritis".)

PHARMACOLOGIC THERAPY — Drugs form the mainstay of therapy in recent onset or active RA. The art to the management of such patients lies in the order in which different drugs are used, the dosages in which they are employed, and the combinations in which they may be usefully administered. Sequential evaluation permits assessment of the clinical response of the patient to the current therapeutic regimen.

It is not possible at the present time to predict which agent, or combination of drugs, will be most effective for an individual patient. However, because of the cost and the potential adverse effects of some therapies, efforts are being made to identify genetic or other patient-specific features that can be used to guide treatment [40,41]. This approach has not yet been validated for clinical practice.

Drug classes — Five main classes of drugs are currently used:

- **Analgesics** — Drugs that only provide analgesia, include topical (eg, capsaicin or diclofenac) and oral agents such as acetaminophen (paracetamol), propoxyphene, tramadol, and more potent opioids (eg, oxycodone, hydrocodone).
- **Nonsteroidal antiinflammatory drugs** — NSAIDs have both analgesic and antiinflammatory properties but do not alter disease outcomes. Selective cyclooxygenase 2 (COX-2) inhibitors may be substituted for nonselective NSAIDs in some patients who are at higher risk for adverse gastroduodenal effects. (See "NSAIDs: Therapeutic use and variability of response in adults" and "Overview of selective COX-2 inhibitors".)
- **Glucocorticoids** — Prednisone or prednisolone are most commonly used to suppress inflammation, and may be administered by oral, intravenous, or intraarticular routes. Oral doses equivalent to 7.5 mg/day or less of prednisolone are relatively safe for short duration (several months or less). Higher doses are more effective in relieving joint pain and tenderness and have a greater effect on these manifestations than do NSAIDs but also have a greater risk of side effects [42]. Doses higher than 7.5 mg/day should be used for the shortest time possible. (See "Use of glucocorticoids in the treatment of rheumatoid arthritis".)
- **DMARDs** — There are two classes of disease-modifying antirheumatic drugs (DMARDs): nonbiologic (traditional small molecule or synthetic) and biologic [12]. These drugs have the potential to reduce or prevent joint damage, preserve joint integrity and function.

The nonbiologic DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, and minocycline. There is no convincing evidence from head-to-head trials that there is a difference in efficacy or safety among methotrexate, leflunomide, or sulfasalazine [43]. However, the ACR 2008 recommendations, based upon a systematic literature review

and expert consensus, differentiate among these agents. Most important, methotrexate and leflunomide are preferred to sulfasalazine in patients with high disease activity and features associated with a poor prognosis [12]. (See 'Assessment of disease activity' above and 'Adverse prognostic factors' above.)

Biologic DMARDs, produced by recombinant DNA technology, generally target cytokines or their receptors or are directed against other cell surface molecules. These include anticytokine therapies, such as the tumor necrosis factor alpha inhibitors etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol, the interleukin (IL)-1 receptor antagonist, anakinra, and the IL-6 receptor antagonist, tocilizumab, and other biologic response modifiers such as abatacept (CTLA4-Ig) and the anti-CD20 B-cell depleting monoclonal antibody, rituximab. (See "Overview of biologic agents in the rheumatic diseases" and "T cell targeted therapies for rheumatoid arthritis", section on 'Abatacept' and "Rituximab and other B cell targeted therapies for rheumatoid arthritis", section on 'Rituximab'.)

Combination drug therapy — Various combinations of nonbiologic (traditional small molecule) DMARDs and of nonbiologic and biologic DMARDs have been used to treat both active early RA and established, moderate to severe disease. The results from randomized trials of combination therapies can be summarized as follows [44]:

- There is little conclusive evidence of sustained benefit from step-up, step-down, or parallel use of nonbiologic DMARDs in combinations, unless methotrexate is included in the regimen.
- Early use of glucocorticoids followed by rapid reduction in dose and then discontinuation, in combination with sustained use of a regimen of nonbiologic DMARDs that includes methotrexate is superior to monotherapy or step therapy with nonbiologic DMARDs.
- A combination of methotrexate with a tumor necrosis factor (TNF) inhibitor reduces both disease activity and the rate of radiographic progression of joint disease.

The supporting data from these trials are presented separately. (See "Randomized clinical trials of DMARDs in rheumatoid arthritis".)

Observational data suggest that in patients who do not tolerate methotrexate, the combination of a TNF inhibitor with another nonbiologic DMARD may be more effective in reducing disease activity than use of a TNF inhibitor alone [45,46].

In contrast, combinations of biologic DMARDs, such as a TNF inhibitor with either anakinra or abatacept, are NOT recommended since they are associated with an increased frequency of serious adverse events, including serious infections. Examples include:

- Combination of a TNF inhibitor and anakinra [47,48]
- Combination of a biologic DMARD and abatacept [49,50]

Baseline laboratory studies — Recommended screening prior to starting, resuming, or significantly increasing therapy with nonbiologic or biologic DMARDs includes [12]:

- All patients — Complete blood count and serum creatinine and aminotransferases

- Prior to methotrexate, leflunomide, or biologic DMARDs — Screening for hepatitis B and C should be performed in patients at increased risk, such as those with a history of intravenous drug abuse, multiple sex partners in the previous six months, and healthcare workers. (See "Hepatitis B virus reactivation associated with immunosuppression".)
- Hydroxychloroquine — A complete ophthalmologic examination within the first year of treatment, including examination of the retina through a dilated pupil and testing of central visual field sensitivity. Repeat examination should be performed annually in patients at higher risk (eg, liver disease, retinal disease, age ≥ 60 years) and at five years in patients who have none of these features.
- Testing for latent TB — The 2008 ACR guidelines recommended screening for latent tuberculosis (TB) with skin testing prior to all biologic DMARDs based upon evidence that TNF inhibitors increase the risk of mycobacterial infection [12]. A possible exception is rituximab, since there is no clear evidence of an increased risk of TB with this agent [51]. A chest radiograph is recommended in patients with a history of other risk factors for latent TB, and skin testing should be repeated in patients with new TB exposures. (See "Tumor necrosis factor-alpha inhibitors and mycobacterial infections" and "Diagnosis of latent tuberculosis infection in adults".)

The 2008 ACR guidelines did not make recommendations regarding screening with the interferon gamma release assay because of the lack of information regarding the sensitivity and specificity of this test in immunosuppressed patients. (See "Diagnosis of latent tuberculosis infection in adults".)

Monitoring and prevention of drug toxicity — Because of the potential risks of serious adverse effects and the frequency of common side effects of antirheumatic drugs, a careful balance must be struck between the risks and potential benefits of these agents [52,53]. The recommended strategy by the American College of Rheumatology (ACR) for drug monitoring in the treatment of RA is shown in Table 2 (table 2) [12,14,54].

If leflunomide and methotrexate are used together, monthly monitoring should be continued as long as this combination is used.

Some drugs used in the management of RA require dose adjustment in patients with impaired renal function that may be due to renal disease or drugs associated with RA or to concurrent renal disease unrelated to RA, which is more likely in elderly patients with significant comorbid conditions. (See "Renal disease in patients with rheumatoid arthritis".)

The serum creatinine alone may not provide an accurate estimate of glomerular filtration rate. As a result, estimation equations that take into account additional factors that affect muscle mass should be used when giving such drugs. (See "Assessment of kidney function: Serum creatinine; BUN; and GFR", section on 'Estimation equations'.)

We do NOT use chlorambucil since it has been associated with a high incidence of malignancy. Combination therapy involving methotrexate and azathioprine should also be avoided because of infrequent, but serious, toxic febrile reactions. In addition, one must be cautious in giving cyclosporine with a nonsteroidal antiinflammatory drug, since this combination may compromise renal function. (See "Pharmacology and side effects of cyclosporine and tacrolimus".)

Pregnancy — RA often improves or remits completely during pregnancy. Issues related to the pregnant woman with RA, including the use of immunosuppressive drugs, is discussed separately. (See "Rheumatoid arthritis and pregnancy" and "Use of antiinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation".)

Current approach — Specific therapy of RA varies with disease severity and the response to previous regimens. The treatment of each of the following RA categories is discussed in detail separately.

- Patients with early RA may have mildly, moderately, or severely active disease. (See "Treatment of early, mildly active rheumatoid arthritis in adults" and "Treatment of early, moderately active rheumatoid arthritis in adults" and "Treatment of early, severely active rheumatoid arthritis in adults".)
- Patients who do not respond completely to initial treatment within six months are considered to have persistently active disease. (See "Treatment of persistently active rheumatoid arthritis in adults".)
- Rheumatoid arthritis has many extraarticular manifestations. The treatment of these specific features, such as vasculitis, interstitial lung disease, and others. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis" and "Treatment of rheumatoid vasculitis", and see appropriate topic reviews).

DRUG THERAPY FOR FLARES — RA has natural exacerbations (also known as flares) and reductions of continuing disease activity. It is important to distinguish a disease flare, characterized by symptoms and physical and laboratory findings of increased inflammatory synovitis, from noninflammatory causes of local or generalized increased pain. (See 'Assessment of disease activity' above and "Clinical features of rheumatoid arthritis".)

The severity of the flare and background drug therapy influence the choice of therapies. The following is a brief summary of glucocorticoid therapy, which is discussed in detail separately. (See "Use of glucocorticoids in the treatment of rheumatoid arthritis".)

With respect to the severity of the flare:

- In patients with a single or few affected joints, intraarticular glucocorticoid injections may be effective and avoid the need for additional or prolonged systemic therapy.
- More widespread flares may be treated with an increase in the dose of oral glucocorticoid, with the intention of reducing the dose once the flare is under control. The magnitude of dose increase varies with the baseline dose and the severity of the flare. An alternative to increasing the oral dose is a single intramuscular injection of depot methylprednisolone acetate.
- Pulse intravenous methylprednisolone therapy, usually consisting of three daily infusions of up to 1000 mg is generally limited to severe flares, particularly those associated with systemic manifestations, such as rheumatoid vasculitis.

With respect to background drug therapy:

- Patients on methotrexate (MTX) who will tolerate a slower resolution of their flare may

respond to an increase in the dose of MTX or a switch from oral to subcutaneous therapy [55].

- Patients initially controlled with a regimen that includes [infliximab](#) may benefit from a decrease in the interval of infliximab dosing or from higher doses [56,57]. However, increasing the dose from 3 to 5 mg/kg was not beneficial in one well-designed study [58,59].

- Increases in doses of [etanercept](#) (greater than 50 mg weekly), or [adalimumab](#) (weekly rather than every two weeks), with or without MTX, do not appear to have greater efficacy [60,61].

- Patients who require multiple treatment courses with glucocorticoids for recurrent disease flares and whose medication doses have been increased to the maximally tolerated or acceptable level should be treated as patients with sustained disease activity. (See "Treatment of persistently active rheumatoid arthritis in adults".)

THERAPY OF END STAGE DISEASE — Despite the therapeutic interventions described in the sections above, some patients progress to disabling, destructive joint disease. The accurate evaluation of such patients is essential since deterioration associated with mechanical problems of the muscle or joint is treated much differently from ongoing inflammation or systemic manifestations of RA. Exacerbations and systemic toxicity are usually easily recognized by the presence of many inflamed joints, fever, anemia, or an elevated ESR or serum CRP concentration.

The goals of therapy in the patient with end-stage disease are:

- Pain relief
- Protection of remaining articular structures
- Maintenance of function
- Relief from fatigue and weakness

In the absence of inflammation, which requires antiinflammatory medications, treatments other than medications, such as the nonpharmacologic interventions mentioned above, are particularly important in management. (See "[Evaluation and medical management of end-stage rheumatoid arthritis](#)".)

The indications for surgical intervention in patients with RA include intractable pain or severe functional disability due to joint destruction, and impending tendon rupture. The timing of surgery is often critical. If one waits too long, there may be so much muscle atrophy from disuse that postoperative rehabilitation is unsuccessful. On the other hand, a decision about joint replacement should take into account the average life of the artificial joint (eg, 10 to 15 years for total hip replacement and less for knee or other joint replacement). (See "[Total joint replacement for severe rheumatoid arthritis](#)".)

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "[Patient information: Rheumatoid arthritis symptoms and diagnosis](#)" and "[Patient information: Rheumatoid arthritis treatment](#)" and "[Patient information: Disease modifying antirheumatic drugs \(DMARDs\)](#)" and "[Patient information: Complementary therapies for rheumatoid arthritis](#)".) We encourage you to print or e-mail these topics, or to refer patients to our public web site, www.uptodate.com/patients, which

includes these and other topics.

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American Rheumatism Association revised criteria for rheumatoid arthritis classification

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

Note: For classification purposes, a patient has RA if at least four of these criteria are satisfied (the first four must have been present for at least six weeks).

ACR recommended monitoring strategies for drug treatment of rheumatoid arthritis

Drugs	Ongoing monitoring via system review and physical examination	Ongoing monitoring via laboratory tests
Salicylates, nonsteroidal antiinflammatory drugs	Dark/black stool, dyspepsia, nausea/vomiting, abdominal pain, edema, shortness of breath	CBC yearly, LFTs, creatinine testing may be required•
Hydroxychloroquine	Visual changes, funduscopic and visual fields every 6 to 12 months	None after baseline
Sulfasalazine	Symptoms of myelosuppression*, photosensitivity, rash	CBC, aminotransferases and creatinine every 2 to 4 weeks for the first 3 months or after increasing the dose, every 8 to 12 weeks for months 3 to 6, then every 12 weeks
Methotrexate	Symptoms of myelosuppression*, shortness of breath, nausea or vomiting, lymph node swelling	CBC, aminotransferases and creatinine every 2 to 4 weeks for the first 3 months or after increasing the dose, every 8 to 12 weeks for months 3 to 6, then every 12 weeks
Leflunomide	Diarrhea, alopecia, intercurrent liver, gallbladder, and renal disease, pregnancy or delayed menses	CBC, aminotransferases and creatinine every 2 to 4 weeks for the first 3 months or after increasing the dose, every 8 to 12 weeks for months 3 to 6, then every 12 weeks
Minocycline	Hyperpigmentation, dizziness, vaginal yeast infections	None after baseline
Gold, intramuscular	Symptoms of myelosuppression*, edema, rash, oral ulcers, diarrhea	CBC, platelet count, urine dipstick every 1 to 2 weeks for first 20 weeks, then at the time of each (or every other) injection
Gold, oral	Symptoms of myelosuppression*, edema, rash, diarrhea	CBC, platelet count, urine dipstick for protein every 4 to 12 weeks
D-penicillamine	Symptoms of myelosuppression*, edema, rash	CBC, urine dipstick for protein every 2 weeks until dosage stable, then every 1 to 3 months
Azathioprine	Symptoms of myelosuppression*	CBC and platelet count every 1 to 2 weeks with changes in

<p>Glucocorticoids (oral ≤ 10 mg of prednisone or equivalent)</p>	<p>BP at each visit, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain</p>	<p>dosage, every 1 to 3 months thereafter Urinalysis for glucose yearly</p>
<p>Agents for refractory RA or severe extra-articular complications</p>		
<p>Cyclophosphamide</p>	<p>Symptoms of myelosuppression*, hematuria</p>	<p>CBC and platelet count every 1 to 2 weeks with changes in dosage, and every 1 to 3 months thereafter, urinalysis and urine cytology every 6 to 12 months after cessation</p>
<p>Chlorambucil</p>	<p>Symptoms of myelosuppression*</p>	<p>CBC and platelet count every 1 to 2 weeks with changes in dosage, every 1 to 3 months thereafter</p>
<p>Cyclosporine</p>	<p>Edema, BP every 2 weeks until dosage stable, then monthly</p>	<p>Creatinine every 2 weeks until dose is stable, then monthly; periodic CBC, potassium, LFTs</p>

* Symptoms of myelosuppression include fever, symptoms of infection, easily bruisability, and bleeding.

- Package insert for diclofenac (Voltaren) 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.

CBC: complete blood cell count (hematocrit, hemoglobin, white blood cell count) including differential cell and platelet counts; AST: aspartate aminotransferase; LFTs: liver function tests; BP: blood pressure. *Adapted from: Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Arthritis Rheum 1996; 39:723, American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the Management of Rheumatoid Arthritis 2002 Update. Arthritis Rheum 2002; 46:328, and Saag, KG, Teng, GG, Patkar, NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008; 59:762.*