Rheumatoid Arthritis: Emerging Treatments

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Rheumatoid arthritis (RA) affects 1% of adults during their most productive years and can result in significant disability. The goals of therapy are to reduce pain, limit joint destruction, and preserve function.

In recent years, the armamentarium of agents that combat RA has greatly expanded. New biologic therapies that specifically target the immune response are now available. Although disease-modifying antirheumatic drugs (DMARDs) such as methotrexate remain the standard of care, these newer agents can be added to the regimen when monotherapy fails.

In this article, I offer general guidelines for selecting the safest and most effective regimens for your patients with RA. I also describe how to make best use of the newer therapies.

OVERVIEW

Epidemiology. Women are affected by RA about 3 times as often as men. The presence of estrogen receptors on synovial cells and T cells suggests an important hormonal relationship. Estrogens influence both T-cell survival and cytokine production. This relationship between estrogen and immune disease may explain the increased prevalence of RA in women.

RA appears to be genetically linked, with higher concordance in monozygotic than dizygotic twins. One genotype of HLA-DRB chains appears to be a marker for RA. Approximately 10% of patients with RA have an affected first-degree relative.

Pathophysiology. RA is characterized by synovial inflammation and progressive erosion of cartilage and bone. The process begins with the activation of T cells, which results in proliferation of synovial cells, activation of proinflammatory cells from the bone marrow, and secretion of cytokines (including interleukin [IL]-1 and tumor necrosis factor α [TNF-α]) by macrophages and fibroblast-like synovial cells. Many therapies for RA-including corticosteroids and TNF and IL-1 antagonists-directly inhibit proinflammatory cytokine activities.

Disease progression. Symptoms of RA typically develop between the third and sixth decades of life. Significant joint abnormality and disability occur within the first few years of disease. Eighty-three percent of patients with RA experience joint-space narrowing, and 67% have joint erosions within the first 2 years. After 5 years, joint erosions can be seen radiographically in 73% of patients. After 18 years, all patients have joint-space narrowing, 97% have joint erosions, and 41% have malalignment.

Economic impact. Patients with RA begin to incur significant costs early in the course of illness. A study of patients with newly diagnosed active RA that evaluated costs during the first 6 months of illness showed that medical costs averaged $200 a month. Patients lost an average of 3.8 workdays monthly, at an indirect cost of $281. Eighteen percent became work-disabled during the first 6 months of illness. Work disability increased to about 60% after 10 years of illness.
INITIAL EVALUATION The American College of Rheumatology (ACR) classification criteria (Table 1) can help guide clinical diagnosis. Laboratory testing is also useful in diagnosis, as well as in assessing prognosis and in monitoring the response to therapy. Rheumatoid factor-autoantibodies found in most patients with RA may also be present in other rheumatologic conditions (eg, lupus erythematosus and Sjögren syndrome) and infectious illnesses (eg, malaria and rubella). A high rheumatoid factor titer in patients with RA is associated with more aggressive disease, greater joint destruction, and greater functional disability. The Creactive protein (CRP) level and erythrocyte sedimentation rate (ESR) are markers of the acute phase response. Elevations in CRP level and ESR also correlate with bone destruction.

Evaluation includes an assessment of comorbid illness and lifestyle factors that may aggravate RA (Algorithm). Frequently associated comorbid conditions that may be exacerbated by either the pathophysiologic mechanisms that underlie RA or by its treatment include infection, renal insufficiency, cardiovascular disease, chronic pulmonary disease, peptic ulcer disease, and lymphoproliferative disease. Psychological distress also increases disability associated with RA; symptoms of anxiety, depression, and hopelessness need to be identified and treated. Cigarette smoking is associated with an increased risk of RA. Longer duration of smoking is linked to greater risk, and heavier use is associated with more serious symptoms and bony erosions. Obesity is also a risk factor, since adipose tissue releases proinflammatory substances, including IL-6, TNF-α, and CRP.
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- Physical examination of the joints
- Measurement of serum inflammatory markers
- Radiographs
- Functional assessment questionnaires

**Patient education**
- Education about the disease process and medications
- Physical therapy
- Occupational therapy
- Rheumatology consultations

**Medication**
- Symptomatic analgesics (eg, NSAIDs and corticosteroids)
- Disease-modifying antirheumatic drugs
  - Mild disease: hydroxychloroquine, sulfasalazine
  - Moderate or severe disease: methotrexate, new biologics

Adapted from Goroll AH et al, eds. Primary Care: Office Medicine
**DISEASE MANAGEMENT** Treatment involves a combination of patient education, physical and occupational therapies, consultations with a rheumatologist, and medical management (Table 2). Because the standard of care is moving from a more conservative to a more aggressive approach that involves early use of DMARDs, referral to a rheumatologist is recommended at initial diagnosis. Following the initial rheumatology consultation, both the primary care provider and rheumatologist should be actively involved in disease management. In general, consult a rheumatologist when patients present with persistent joint inflammation, require more intensive therapy, or manifest one or more of the following indicators of poor prognosis: genotype HLA-DRB1 *04/04, high serum titer of rheumatoid factor, extra-articular manifestations, a large number of involved joints, age less than 30 years, female sex, or systemic symptoms.

Regularly monitor patients with evidence of active disease, such as joint inflammation, stiffness, and fatigue. Patients require periodic measurement of serum inflammatory markers (e.g., ESR or CRP) and radiographs. Functional assessments may also be performed with the Arthritis Impact Measurement Scales or the Health Assessment Questionnaire. The latter is a good predictor of long-term mortality. Patients in remission, as defined by the ACR criteria (Table 3), may be seen every 6 months. All patients need to be followed indefinitely for disease flares, progression, and comorbid illness.

Medications include both symptomatic analgesics and DMARDs. Early, aggressive management of RA and consistent use of DMARDs may result in reduced long-term disability. NSAIDs and corticosteroids have no effect on disability. Unfortunately, drug therapy does not reduce the higher mortality seen in patients with RA.
**PHARMACOTHERAPY** The goals of pharmacotherapy are to reduce joint destruction and inflammation and limit disease progression. Initial treatment of all patients with active RA is essential because joint destruction begins early in the course of the disease. Clinical and serologic activity has been linked to increasing morbidity, loss of function, and mortality. Therefore, rapid control translates into better long-term outcomes, particularly in patients with a large number of affected joints, early loss of function, and elevated inflammatory markers. Although combination therapy, new biologics, and monitoring costs are more costly than traditional modalities, the higher cost must be weighed against the long-term expense of poorly controlled RA, which often necessitates arthroplasty and hospitalization.

Therapy is generally initiated with an NSAID and a DMARD. If patients fail to respond, consider adding a second DMARD or a low-dose oral glucocorticoid (10 mg or less of prednisone daily). When remission occurs, NSAIDs and glucocorticoids may be discontinued. DMARDs, however, are continued for the long term. Treat RA flares with the addition (or increased dosage) of oral glucocorticoids. Change to another DMARD may also be considered. RA flares that involve only a small number of joints may also be treated with intraarticular glucocorticoids.

**NSAIDs.** Although effective for pain relief and reduction of inflammation, these agents do not prevent joint destruction. They are used only as adjunctive therapy for patients with active RA. Long-term use of high doses of NSAIDs may result in significant organ toxicity. This risk is increased when patients use combinations of analgesics. Commonly prescribed NSAIDs include aspirin, celecoxib, and rofecoxib.

**DMARDs.** These agents reduce or prevent joint destruction and subsequent disability. They include hydroxychloroquine, sulfasalazine, methotrexate, gold, and D-penicillamine. All patients with active RA, even those who have achieved adequate analgesic relief from NSAIDs, are candidates for DMARD therapy. Rheumatoid factor-negative patients with mild disease may use hydroxychloroquine or sulfasalazine. In patients with severe RA, therapy is initiated with methotrexate. Patients who do not achieve an adequate response with methotrexate may use a combination of DMARDs or alternative DMARDs, such as gold, which are usually prescribed by a consulting rheumatologist. Periodic monitoring is recommended for most RA therapies (Table 4).
dizziness, bruising, bloody stools

D-Penicillamine
- Rash
- Coombs negative, platelets, uric acid for proteinuria

Hydroxychloroquine
- Skin reaction, visual disturbance, GI distress
Sulfasalazine

Infection, bruising, bleeding, swelling, diarrhea

Methotrexate

Elevated blood pressure, polyuria/polydipsia, swelling, shortness of breath, weight gain, visual disturbance

Corticosteroids, liver function, creatinine

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In the Early RA Study, patients undergoing DMARD therapy were followed for 5 years. In the Early RA Study, patients undergoing DMARD therapy were followed for 5 years.\(^{35}\) Initially, 9% reported marked functional loss and 33% had normal functioning. During the study period, 84% required the addition of second-line DMARD therapy, 10% required a wheelchair or home adjustment, 17% underwent orthopedic surgery, and 8% had a major joint replacement. The study concluded that about 16% of patients treated with conventional drug therapy function poorly after 5 years of treatment, 40% function normally, and the remaining patients range in function between marked disability and normal.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Extent of response</th>
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<tbody>
<tr>
<td>ACR 20</td>
<td>20%*</td>
</tr>
<tr>
<td>ACR 50</td>
<td>50%</td>
</tr>
<tr>
<td>ACR 70</td>
<td>70%</td>
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*An ACR 20 response is a reduction of at least 20% in the number of tender and swollen joints plus an improvement of at least 20% in 3 or more of these 5 criteria:
- Patient's assessment of pain.
- Patient's assessment of disease activity.
- Physician's assessment of disease activity.
- ESR.
- CRP.

CBC, complete blood cell; TB, tuberculosis.
TARGETED NEW BIOLOGIC THERAPIES  New therapies are typically used in conjunction with methotrexate for patients who fail to achieve adequate benefit from this agent alone or in patients who have been inadequately helped by or cannot tolerate other DMARDs. The most effective new treatments are a class of biologics that include TNF-α antagonist therapies.\textsuperscript{36} Response to treatment is rated using ACR criteria (Table 5). Overall, these medications are well tolerated. However, as with all immunosuppressive therapies, there is a theoretical increased risk of lymphoproliferative disease.

**TNF-α antagonist therapy.**  
\textit{Etanercept}, one of 2 recently introduced agents, is a soluble receptor protein that binds to circulating TNF-α. It is effective whether used alone (25 mg SC twice weekly) or in combination with methotrexate.\textsuperscript{36,37} According to the package labeling, more than 60% of patients treated with etanercept achieved an ACR 20 response, and 40% achieved an ACR 50 response. The respective rates among placebo recipients were 23% and 5%.

Etanercept is well tolerated; local injection-site reaction is the most common side effect. In postmarketing reports, however, a small number of serious adverse events have been noted, including infections, sepsis, and death. The package insert carries a strong caution on the use of etanercept in patients with a history of recurring infections or with underlying conditions that may predispose to infection, such as advanced or poorly controlled diabetes. Other adverse reactions include pyelonephritis and osteomyelitis.

\textit{Infliximab} is a chimeric monoclonal antibody that binds circulating TNF-α. In a study of patients who failed to achieve an adequate response with methotrexate, the addition of infliximab (3 to 10 mg/kg IV every 4 to 8 weeks) resulted in an ACR 20 response in 50% of the treated patients (compared with 20% in the placebo group), and an ACR 50 response in 27% (vs 5% in the placebo group).\textsuperscript{38} Some studies showed that neutralizing antibodies develop in 40% of patients using infliximab alone.\textsuperscript{39} Antibody production is reduced by combining infliximab with methotrexate.\textsuperscript{40} The most common side effects of infliximab are GI distress and fatigue. However, as with etanercept, a small number of serious infections have been reported; use caution in prescribing this agent to patients who have chronic infection or a history of recurring infections.\textsuperscript{40} Although the number of cases of infection is small, tuberculosis and other opportunistic infections have been observed in patients taking infliximab. Before beginning treatment, patients must be tested for tuberculosis if they are at significant risk for exposure.

**Pyrimidine synthesis inhibition.**  Pyrimidine is required for mitogeninduced proliferation of T cells, and inhibition of pyrimidine synthesis is an important step in RA. Leflunomide is a reversible inhibitor of de novo pyrimidine synthesis, with active metabolites that inhibit the rate-limiting step in pyrimidine synthesis and also inhibit IL-1 and TNF-α.\textsuperscript{41} Response to leflunomide, 20 mg PO daily, is similar to that achieved with methotrexate, 7.5 to 15 mg weekly.

In one study, an ACR 20 response was seen in 52% of patients taking leflunomide, compared with 46% of patients taking methotrexate and 26% of patients taking placebo.\textsuperscript{42} An ACR 50 response was seen in 34% of the leflunomide group, compared with 23% of the methotrexate patients and 26% of the placebo group. Leflunomide is also effective in combination with methotrexate.\textsuperscript{43} Leflunomide may be associated with elevated liver enzyme levels; regular monitoring is thus required, especially when this agent is used in combination with methotrexate. The most common side effects associated with leflunomide are diarrhea and alopecia, which occur in a minority of patients.

**IL-1 agonist therapy.**  The newly approved agent anakinra is an exogenous recombinant human IL-1 receptor antagonist that augments diminished levels of naturally occurring IL-1Ra, as a counterbalance to the detrimental effects of the diseaseheightened activity of IL-1 in bone resorption, erosion, and joint cartilage destruction. Anakinra binds to IL-1 receptors, thus preventing receptor activation.

In one study, 43% of patients treated with anakinra, 150 mg SC, had an ACR 20 response, compared with 27% of placebo-treated patients.\textsuperscript{44} Anakinra-treated patients also experienced a 41% reduction
in radiographic bone destruction over 24 weeks, compared with the placebo group. Anakinra is well tolerated; injection site reaction is the most common side effect. The package labeling states that anakinra is associated with an increased incidence of serious infection. Treatment should be discontinued if a serious infection develops. Assessments of neutrophil counts should be made before treatment initiation, monthly for the first 3 months of treatment, and annually thereafter.

TNF-α and IL-1 function independently in the pathogenesis of RA. However, the combination of anakinra and TNF receptor type I in rodents results in synergistic inhibition of inflammation. These data suggest the need for research in human clinical trials to evaluate the clinical effects of combination therapy. Because preliminary data in humans treated with a combination of anakinra and a TNF blocking agent indicate a high rate of serious infection, combination therapy is not recommended at this time.

References:

22. Karlson EW, Lee IM, Cook NR, et al. A retrospective cohort study of cigarette smoking and risk of


FOR MORE INFORMATION:


Updated information about RA may be obtained on several Web sites:

- [www.hopkins-arthritis.som.jhmi.edu](http://www.hopkins-arthritis.som.jhmi.edu) Excellent information about RA diagnosis, pathophysiology, and treatment options.
- [www.rheumatology.org](http://www.rheumatology.org) American College of Rheumatology Web site, which includes a search feature to find a local rheumatologist.
- [http://my.webmd.com/condition_center/rha](http://my.webmd.com/condition_center/rha) WebMD provides good general information about RA.
- [http://www.nih.gov/niams/healthinfo/juvarthr.htm](http://www.nih.gov/niams/healthinfo/juvarthr.htm) Comprehensive information on juvenile RA.

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