



Arthritis & Rheumatology Clinics of Kansas PATIENT EDUCATION

RHEUMATOID ARTHRITIS

Introduction: RA is not a generic term for just *any* type of arthritis. It also is not a term applied to any form of severe arthritis. It is a specific type of arthritis that begins in the soft tissue around the joint known as the *synovium* (sin-O-vee-um). RA affects 1% of the U.S. population, with women outnumbering men 2:1 to 4:1. While the peak age of onset is in the 30's to 50's, RA can begin at any age. It is a disease that progresses most rapidly within the first two years of onset, and those afflicted with RA have twice the mortality rate of individuals of the same age in the general population.

Features of RA: The basic problem in RA is inflammation of the synovium, causing swelling, pain, and morning stiffness, and which can lead to irreversible joint damage and loss of function. The joints most often affected are the wrists and the small joints of the hands, usually the first and second row of knuckles past the wrists. Other commonly affected joints include those in the balls of the feet, the ankles, the knees, the elbows, and the shoulders. While neck involvement is common, the lower back is typically spared. The pattern of arthritis has a strong tendency to be symmetrical, affecting the same joints on both sides of the body.

When joints become affected in RA, they don't simply hurt; they become progressively damaged. The inflamed synovium, when not properly treated, can invade the bone and cartilage surrounding the joint and result in irreversible damage and loss of function. This may result in not only pain, but also limited mobility, deformity, and difficulty using the impaired joint. This process does not discriminate according to age, race or gender; all affected with RA are at risk for complications.

While the joint disease is the most striking manifestation of RA, the inflammation will often affect other organs. Up to 40% of RA patients will have abnormalities in lung function, which are often subtle and may go unnoticed. Many patients, however, can experience serious lung damage requiring more aggressive therapy. Roughly 25% of patients will have dry eyes and dry mouth known as secondary Sjögren's syndrome (see section on Sjögren's), and about 20% will have inflammation that may cause irritation of the eyes, or less commonly, vision loss. A condition known as Felty's syndrome causes low blood counts and frequent enlargement of the spleen, and rheumatoid vasculitis (inflammation of the blood vessels) may result in rash, skin ulcers, or less commonly damage to the nerves or other organs. Both of these conditions are infrequently encountered in RA (about 1% of patients).

In recent years, the risk of cardiovascular disease in RA has been a focus of several studies. It is likely that the aforementioned increase in mortality seen in RA vs. the general population is in large part due to the increased rate of heart disease in RA patients, which is nearly twice that of age-matched individuals without RA. This risk appears to be due in large part to the effect inflammation has on the lining of blood vessels, resulting in plaque buildup, narrowing of blood vessels, and an increased tendency for these vessels to clot. The good news is that many studies would suggest treating the inflammation of RA aggressively and at an earlier stage will reduce these risks.

Diagnosis: RA is predominantly diagnosed by a thorough review of a patient's symptoms and physical examination. While laboratory studies help in the evaluation, no laboratory test can either establish or rule out a diagnosis of RA. The rheumatoid factor (RF), markers of inflammation, and a newer antibody known as anti-CCP are useful studies and are often used to predict the severity of RA in individual patients. X-rays are also useful diagnostic tools, particularly films of the hands and feet, and can be used to monitor disease progression by assessing the degree of joint damage.

Because RA may be difficult to identify at its earliest stages, and because prompt intervention has resulted in improved outcomes in several studies, the American College of Rheumatology (ACR) is in the process of revising criteria for diagnosis of this disease. Patient within the first year of the onset of symptoms may demonstrate findings on physical examination or laboratory testing that are less specific than those with well established disease, leading to delays in diagnosis and therapy. The new criteria are designed to help physicians recognize RA in patients who would have previously been labeled "undifferentiated." More advanced imaging techniques such as ultrasound or magnetic resonance imaging (MRI) have also been advanced as methods for demonstrating joint inflammation not detectable on physical examination or damage not apparent on plain x-rays.

Treatment (see *Medications section*): Therapy in RA has two goals: reducing symptoms and preventing joint damage and disability. We have more tools available to treat RA today than ever before, and studies have documented that early treatment with specific medications has a long-term impact on the course of the disease. While all therapies have potential side effects, the consequences of *not* treating RA are generally much greater. Your doctor will work carefully with you to select the right medications for you as an individual.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin) and *simple analgesics* such as acetaminophen (Tylenol) or even narcotic-strength pain relievers have a role in treating RA. These therapies, however, are limited to their effects on reducing day-to-day symptoms and have no effect on the long-term course of the

disease. Many of these medications may be given in combination with other RA therapies to reduce pain in inflamed joints.

Corticosteroids such as prednisone may be very effective in rapidly reducing pain and swelling in inflamed joints, both when given orally and injected directly into a joint. Some evidence suggests that these medications may even slow down joint damage. Long-term side effects, however, limit the use of corticosteroids in RA. Generally speaking, steroids should be used for disease flares, for brief periods of time, or in low doses to avoid these complications (see Medications section).

Disease-modifying anti-rheumatic drugs (DMARDs) should be the mainstay of therapy for most patients with RA. Generally speaking, the sooner they are started after the onset of symptoms, the more effective they are at treating the disease. Ideally, DMARDs should be initiated within three months of disease onset to achieve an optimal response. Because patients are individuals, your doctor will work with you to determine which DMARD is appropriate for the severity and stage of your disease.

All of the agents listed below fall under this category and can be further subdivided into *traditional DMARDs* and *biologic DMARDs*. These latter agents are specifically designed to attack key targets in the inflammatory processes involved in RA. Because of the cost and potential side effects of these agents, biologic DMARDs are typically reserved for patients who fail to respond adequately to traditional DMARDs or in patients with highly active disease who are at high risk for progressive damage and/or disability. Careful monitoring of disease activity under the supervision of an experienced physician is necessary to assist in making the decision to advance or to withdraw therapy. An effort has been made by many specialists in rheumatology in recent years to more carefully monitor disease activity and adjust medications accordingly.

Traditional DMARDs

Anti-malarial drugs are generally among the safest of the DMARDs but are generally utilized to treat milder RA. Hydroxychloroquine (HCQ), marketed under the trade name Plaquenil, takes 3 to 6 months to begin working and can be used either by itself or in combination with other DMARDs. The only potential complication requiring monitoring is that of damage to the retina, the layer in the back of the eye, which can potentially impair color vision. While this is of concern, it occurs in only one of 1,000 people taking the drug and is detectable before serious damage occurs if monitored by your eye doctor every 6-12 months. HCQ doses of less than 6.5 mg/kg/day generally have a very low incidence of retinal damage.

Sulfasalazine (SSZ) was developed many decades ago to treat RA and is also commonly used to treat Crohn's disease, an inflammatory intestinal disorder. SSZ takes effect in 1 to 3 months and seems to have a modest effect on slowing down joint damage

in RA. This drug also seems to be more effective in patients who are “seronegative” (with a negative RF). The most common side effect of SSZ is stomach upset, which may be eliminated by using a coated preparation of the drug. Allergic reactions are also no unusual. Serious problems, such as a drop in the white blood cells or acute damage to the liver, are unusual and typically occur early in the course of therapy, if at all. Blood tests to monitor for these complications will generally pick up any problems before they become severe.

Methotrexate (MTX) is perhaps the most popular and most commonly prescribed DMARD among rheumatologists, and for good reason. MTX slows joint damage, improves symptoms and physical functioning in RA patients, and has an onset of action of 1 to 3 months after starting the medication. It is taken once weekly in the form of pills or injections, with injections being associated with better availability of the medication and often less side effects. Nausea, mouth sores, thinning of the hair, lowering of blood counts, susceptibility to infection, and liver damage are among the more common side effects and can be reduced by taking folic acid or folinic acid (Leucovorin) supplementation. Rarely, acute lung injury may occur that can resemble pneumonia. Despite these potential side effects, problems with MTX can generally be detected with regular lab monitoring every 1 to 2 months. Most importantly, patients with RA taking MTX have a mortality rate that is only 40% of the mortality rate of RA patients not taking the drug. This finding seems to indicate that for most patients, the trade-off between benefit and side effects is very good.

Leflunomide (LEF), marketed under the trade name Arava, is a relatively new drug used to treat RA. It is taken orally once daily and begins to take effect in 1 to 3 months. The efficacy of LEF is similar to that of MTX, and it does seem to slow down the development of joint damage. LEF can result in nausea, diarrhea, hair loss, and liver damage, but the incidence of lowered blood counts and infection are lower than with MTX.

Miscellaneous drugs that are less commonly used to treat RA but which may be useful in certain individuals include minocycline, azathioprine (Imuran), injectable gold, and D-penicillamine.

Minocycline is an antibiotic that is also used to treat acne and other skin diseases. Like HCQ, minocycline is usually used to treat milder RA, but one study showed that if started within one year of disease onset and continued for one year, up to 40% of patients went into remission. Other than nausea, dizziness, and sun sensitivity in some individuals, minocycline is usually very well tolerated.

Imuran is a medication that suppresses the immune system and may be effective at reducing the inflammation in the joints of RA patients as well as in other organ

systems, such as the lungs. Increased infection rates, lowered blood counts, and liver damage are potential side effects.

Injectable gold is given once weekly in the doctor's office and must be monitored closely, including blood and urine tests with each visit to screen for low blood counts and protein in the urine. Rashes, damage to the liver, and lung damage are also potential side effects. While effective in treating RA, the inconvenience, toxicity, and delayed onset of action (4 to 6 months) have made gold a less popular choice among rheumatologists and patients.

D-penicillamine, a drug also used to bind toxic levels of heavy metals in the body, has a therapeutic effect in RA. The toxicity of this agent, however (blood cells, kidneys, liver, secondary autoimmune diseases), has led to less frequent use in treating RA patients.

Biologic DMARDs

TNF antagonists are perhaps the most exciting class of medications to be recently introduced for the treatment of RA. Currently, there are now 5 available medications in this class: etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), Certolizumab pegol (Cimzia), and Golimumab (Simponi). Enbrel is given as a once weekly injection, Remicade is given as an intravenous infusion every 4-8 weeks, Humira is administered as an injection every 2 weeks, Cimzia as an injection given every 2-4 weeks, and Simponi as an every 4 week injection. Each of these medications inhibits a substance known as tumor necrosis factor (TNF) in one way or another. TNF is known to play a key role in inflammation in inflammation and joint damage in RA, and for this reason these medications are highly effective in controlling both the symptoms of the disease and the joint damage. In fact, some studies suggest that these medications actually **halt** joint damage in RA patients.

Each of the TNF antagonists may begin working within a few weeks of starting therapy. While individual patients may respond more favorably to one agent over another, all of these drugs seem to have similar efficacy. Disadvantages of these therapies include cost, inconvenience of injections or infusions, injection site or infusion reactions, and suppression of the immune system. Respiratory infections occur in increased frequency in patients treated with TNF antagonists, and those exposed to tuberculosis may experience reactivation of their disease. For this reason, a TB skin test is recommended prior to starting therapy. Patients with multiple sclerosis or severe congestive heart failure may experience worsening of their disease and therefore should not take these medications. Thus far, cancer rates have not been clearly shown to be increased in RA patients taking TNF antagonists versus other RA patients, but the data is somewhat confusing. Recently, the press has publicized an increased rate of a cancer known as lymphoma in patients taking these medications, but this was compared to the

normal population. Because RA patients as a whole have an increased risk of lymphoma, it is not clear if the medications themselves or the **disease** accounts for this increased rate.

On the whole, we have found these medications to be well worth the cost and the potential side effects and have seen them virtually eliminate signs of active disease in patients resistant to many of our standard therapies. Currently, we are using TNF antagonists mostly in patients who have inadequately responded to MTX or other therapies. Most often, these drugs are added to MTX and may be more effective when used in this manner but may also be used alone. Use of TNF antagonists earlier in the course of the disease is being investigated and may be recommended for certain patients in the future. Despite the efficacy of these medications, there remains a subset of patients (about 30% in most studies) who respond inadequately to each of the TNF antagonist drugs. Switching to a different TNF antagonist is often effective in such patients, although some physicians prefer to use another biologic drug with a different mechanism of action, and these medications will be discussed further.

Abatacept (Orencia) is a biologic DMARD that works to block the activation of a subset of white blood cells known as T-lymphocytes, cells that are involved in causing joint inflammation in RA. Orencia is given intravenously every 4 weeks, but while this drug requires more frequent administration than Remicade, the infusion time is typically no longer than one hour, about half the time it would take to administer Remicade. This drug is typically given in combination with MTX. Not only has Orencia been shown to be effective in patients responding inadequately to traditional DMARDs, it also may be effective in patients with a less than ideal response to TNF antagonists. Like TNF antagonists, this drug appears to significantly slow joint damage by x-rays as well. The onset of action for Orencia is often more delayed than what is noted for TNF antagonist medications and may not be observed for several months after starting the drug.

Like TNF antagonists, Orencia is associated with an increased risk for infections, and careful observation is again warranted in patients receiving this drug. Infusion reactions, while less commonly seen than with other biologic drugs, can also occur with Orencia. Finally, a few studies have raised the concern that patients with chronic obstructive pulmonary disease (COPD, or emphysema) may experience worsening of symptoms, and caution should be exercised when using this drug in patients with this illness.

Rituximab (Rituxan) is an antibody against another type of white blood cell known as B-lymphocytes, which also have a role in generating inflammation in the joints of patients with RA. This drug was originally developed for the treatment of lymphoma, or a tumor of the lymph nodes, but has been adapted to the treatment of RA and is being investigated for use in other autoimmune diseases. While also given intravenously, Rituxan only needs to be administered in two sets of infusions every 6 months, with each

set of infusions being two weeks apart. Each infusion, however, requires 4-6 hours to complete. The onset of action for Rituxan, as with Orenzia, is typically not seen for several months after the initial infusion but may actually increase with subsequent rounds of infusions. The majority of patients taking Rituxan, as with other biologic drugs, continue to use concurrent MTX therapy. Like other biologic drugs, Rituxan both reduces signs and symptoms of the disease and appears to significantly slow joint damage. With continued use of Rituxan some patients can be maintained with longer intervals between sets of infusions than the typical 6 months. Under current Food and Drug Administration (FDA) guidelines, Rituxan can only be prescribed when another biologic drug has failed to produce an adequate response or if side effects have developed to that drug.

Infusion reactions may also occur with Rituxan but are typically less frequent and less severe when the drug is used for the treatment of RA than when it is used to treat patients with lymphoma. Infections occur more frequently in Rituxan treated patients, and vaccinations given after the administration of this drug may have less protective effect due to the suppression of the normal immune response. A rare and fatal infection of the brain known as progressive multifocal leukoencephalopathy (PML) has been described in isolated patients treated with Rituxan, predominantly in patients treated with this drug for illnesses other than RA and when used in combination with other immunosuppressive drugs. It is noteworthy that this complication had also been reported in the setting of autoimmune diseases prior to the introduction of Rituxan as well.

Tocilizumab (Actemra), is the most recently approved biologic drug for the treatment of RA and is targeted against interleukin-6 (IL-6), another chemical playing a central role in the inflammation of RA. Like Orenzia, Actemra is given as an intravenous infusion every 4 weeks, and the response may be fairly rapid in many patients initiating therapy. Actemra has been well studied in early RA, in MTX inadequate responders, and in patients experiencing an inadequate response to TNF antagonists and it is effective in all of these settings. This agent may be used alone but is more often given in combination with MTX, as with other biologic drugs, and it too appears not only to improve disease activity but also to slow the progression of joint damage.

Like other biologic drugs, Actemra is associated with an increased risk for infection and some potential for infusion reactions. In addition, suppression of white blood cell counts, elevation of liver enzymes, and an increase in cholesterol levels have all been observed in some patients treated with Actemra. With proper monitoring, problems with white blood cells and liver enzymes can be minimized, and the significance of the elevated cholesterol levels is not yet known, since there is also an elevation of the HDL (so-called “good cholesterol”), which may balance out any possible negative effects of cholesterol elevation. Monitoring of cholesterol levels while on therapy with Actemra is prudent.

Anakinra (Kineret) is an injectable drug given once daily and inhibits a substance known as interleukin-1 (IL-1). While effective in a subset of RA patients, responses to therapy are generally less dramatic than those seen with TNF antagonists. A somewhat increased infection rate and injection site reactions are the most commonly observed side effects.