CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Rheumatoid arthritis: More aggressive approach improves outlook

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ABSTRACT

As recently as 10 years ago, many patients with rheumatoid arthritis would receive only a nonsteroidal anti-inflammatory drug and low-dose corticosteroids until damage to their joints was documented. Now, despite risks of toxicity and adverse effects, a disease-modifying antirheumatic drug such as methotrexate is given as early as possible to retard disease progression and help prevent new erosions. Other agents can be added to or used in place of methotrexate, such as a biologic response modifier that regulates the proinflammatory cytokine tumor necrosis factor-alpha.

A 55-YEAR-OLD WOMAN with a 6-month history of rheumatoid arthritis complains of several hours of daily morning stiffness, tenderness, swelling, and difficulty performing her activities of daily living. She has polyarthritis that affects her hands, wrists, elbows, knees, and feet. Her sedimentation rate is 85, and she tests positive for rheumatoid factor. What do you do?

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This paper discusses therapies that are investigational or are not approved by the US Food and Drug Administration for the use under discussion.

Fifty years ago, the crippling course of rheumatoid arthritis was considered inevitable. Just a decade ago, you would have given this patient a low-dose corticosteroid and watched for the first signs of joint destruction. Now, however, therapies have evolved to the point that rheumatoid arthritis can be treated using targeted drugs that can lead to significant improvement in disease response.[1] Gone is the "pyramid" approach, which started patients on a nonsteroidal anti-inflammatory drug (NSAID) and a low-dose cortico-steroid. The physician then watched over several years for the appearance of structural joint damage, and only then would intervene with a disease-modifying antirheumatic drug (DMARD). Now, as soon as the diagnosis is established, we start patients on a DMARD—usually methotrexate—often in addition to an NSAID and a corticosteroid. The goal of this more aggressive therapy is to prevent joint damage.

Consider giving a DMARD at the time of diagnosis

RHEUMATOID ARTHRITIS: A SYSTEMIC INFLAMMATORY DISEASE

Rheumatoid arthritis is a systemic, chronic, inflammatory disease that affects mainly the synovial joints. The erosions, joint space narrowing, subluxation, and osteopenia that result from this multicellular process can be seen radiographically as early as the first 6 months of the disease.

A profusion of proinflammatory cytokines (eg, tumor necrosis factor-alpha [TNF-alpha], interleukin-1 [IL-1]) and a dense inflammatory infiltrate of T cells and B cells occur in the synovium. TNF-alpha, produced by synovial cells and macrophages, stimulates the production of other inflammatory cytokines and metalloproteinase and is also an important

A historical perspective: From gold to whiskey

Some of the treatments tried in the past are now considered to be of limited value, or even harmful. They include intramuscular injections of gold, bed rest in the open air, a full and varied diet, a small quantity of whiskey or gin with the evening meal, iodine, quinine, vaccination, colonic lavage, arsenic, protein shock, and baths. Most of these treatments have fallen from favor, but quinine is still used in the form of the antimalarial drug hydroxychloroquine, and the new anti-TNF drugs are proteins made by recombinant DNA technology.

In 1925, corticosteroids were discovered, and for the next 60 years they dominated the treatment of rheumatoid arthritis. Dr. Philip Hench at the Mayo Clinic received the Nobel Prize in medicine for his pioneering work on the use of corticosteroids in rheumatoid arthritis.[2] During World War II, the United States Department of War funded research on corticosteroids and found that they led to a dramatic improvement in the disease process. Other compounds studied have included nitrogen mustard and azathioprine.

The 'squeeze test' helps separate rheumatoid arthritis from osteoarthritis or fibromyalgia

factor in the fatigue associated with rheumatoid arthritis. It remains unclear what starts this cascade and the accompanying invasion of synovium into bone. There may be a polygenic genetic component.

Rheumatoid arthritis is generally a disease of young and middle-aged people, usually beginning to carve its path to deformity and disability between ages 25 and 50.[1] About 2 million Americans have the disease, which affects three times as many women as men. It has a worldwide prevalence of 1%. Only 10% of patients go into remission during the first year.

In addition to its obvious impact on quality of life, rheumatoid arthritis has enormous costs to the economy. Half of all people affected by rheumatoid arthritis are unable to work within 5 years of diagnosis, and the remaining half have functional disability. The direct cost to the economy in 1991 dollars was $4.76 billion.

SCREENING AND DIAGNOSIS

More than 90% of patients with rheumatoid arthritis have disease in the metacarpophalangeal joints. Indeed, observation of the patient's response to application of gentle pressure across these joints is a good initial screen for patients who complain of joint pain. This "squeeze test" helps differentiate rheumatoid arthritis from diseases such as fibromyalgia and osteoarthritis.

The diagnosis is typically established on the basis of the physical examination and clinical history, further supported by detecting rheumatoid factor. It is important to remember that a positive test for rheumatoid factor is not diagnostic of rheumatoid arthritis. It can be found in other conditions that can cause arthritis, such as hepatitis C infection and sarcoidosis.

TREATMENT TODAY: METHOTREXATE AND BEYOND

In 1972, rheumatologist Dr. Hoffmeister of Spokane, Wash., observed that weekly doses of methotrexate appeared to be beneficial to patients with rheumatoid arthritis.[3] In 1985, my colleagues and I at Harvard found low-dose methotrexate to be effective in a randomized, controlled clinical trial.[4] Controlled studies have since shown that weekly doses of methotrexate attenuated the progression of joint narrowing, slowed the formation of new erosions, improved functional status, and reduced the need for NSAIDs and corticosteroids.

DMARDs were once reserved for only the most severe cases because of concerns about their toxicity and lack of effectiveness, as well as the misguided belief that rheumatoid arthritis was a benign disease. However, two Dutch studies[5,6] showed that they improve functional outcome and slow disease activity more than NSAIDs or corticosteroids alone. They decrease the tenderness and swelling of joints, may decrease acute-phase reactants, regulate

the disease process, and may prevent now-uncommon extraarticular complications of the disease.

More patients stay on methotrexate in the long term than on other older DMARDs. It is easy to dose, its toxic effects can be monitored with standard laboratory tests and offset with folic acid or leucovorin, and it is cost-effective ($1,000 to $1,500 for 1 year, vs $13,000 per year for biologic response-modifying DMARDs).

COMBINATION THERAPY

In addition to being the "anchor drug," methotrexate is also used as "background" therapy in combination drug treatment (ie, other DMARDs are added on with methotrexate as the background). There are a number of treatment combinations to choose from. A common triple regimen is methotrexate combined with sulfasalazine and hydroxychloroquine.[7] Other options include methotrexate with leflunomide (Arava), azathioprine, or agents that inhibit TNF-alpha.

BEYOND METHOTREXATE

Even though methotrexate is the first choice among DMARDs, the drug of choice for individual patients depends on disease activity, functional status, and response to therapy. Patients who do not tolerate methotrexate can be switched to the pyrimidine inhibitor leflunomide. This drug has been shown to have an efficacy comparable to that of methotrexate and is sometimes used with it. Patients who do not respond to leflunomide can try biologic response modifiers, such as those that down-regulate the proinflammatory cytokine TNF-alpha: these include infliximab, etanercept, and adalimumab, with or without methotrexate.

TNF-alpha inhibitors have been shown to significantly reduce disease activity, especially in patients in whom methotrexate has failed. FDA-approved TNF-alpha inhibitors are the monoclonal antibodies infliximab and adalimumab, and etanercept, a soluble receptor for TNF-alpha. These agents work remarkably quickly: it can take 4 to 6 weeks to see results with a therapeutic dose of methotrexate (ie, 15 to 20 mg per week), whereas improvement can sometimes be seen with 1 week of the TNF-alpha inhibitors. These drugs are also being used or studied for use in nonrheumatic diseases, including asthma, inflammatory eye disease, psoriasis, lymphoma, and sarcoidosis.

Infliximab

Infliximab (Remicade) is FDA-approved for use in Crohn disease and rheumatoid arthritis.

The ATTRACT trial[8] studied patients taking infliximab in addition to methotrexate as background therapy in the United States and Europe. It showed a 60% response rate with high-dose therapy, a 50% response rate with lower-dose therapy, a significant 17% improvement compared with placebo, and a remarkable radiographic response. This study was important in establishing the ability of TNF-alpha inhibitors to improve functional status and limit radiographic progression in patients with 10 years of disease duration.

Etanercept

Etanercept (Enbrel) was studied as combination therapy with methotrexate in a 24-week randomized trial of about 90 subjects with 13 years of disease activity.[9] Subjects who received etanercept plus methotrexate had a 70% response rate compared with 27% with placebo plus methotrexate.

Methotrexate is still the gold standard treatment

Etanercept is the only biologic response modifier to be compared directly with methotrexate. In one study, subjects who had rheumatoid arthritis for less than 3 years received etanercept injections twice weekly or received methotrexate in a rapid-dose escalation to 20 mg per week. By 6 months, patients who had received etanercept achieved superior improvement in signs and symptoms over patients who received methotrexate. After 12 months, there was no significant difference between the two groups, and both had achieved a 65% improvement. However, fewer new erosions were seen in patients who received etanercept than with methotrexate, and the difference in the number of erosions became even greater in the second year.

Adalimumab

Adalimumab (Humira) produced a 66% response rare in a clinical trial of patients taking 40 mg of adalimumab every 2 weeks plus methotrexate.[10] Results for radiographic joint space erosion and narrowing were similar to those achieved with etanercept and methotrexate.

ADVERSE EFFECTS OF DISEASE-MODIFYING AGENTS

Both methotrexate and the TNF-alpha inhibitors are fairly well tolerated. However, they both have some adverse effects that need to be taken into account.

Methotrexate

The side effects of methotrexate include gastrointestinal intolerance, pulmonary toxicity, birth defects, lymphoma, bone marrow toxicity, thinning of the hair, and stomatitis. Some side effects, such as hair-thinning, bone marrow toxicity, and gastrointestinal intolerance, can often be attenuated with supplemental folic acid. The degree of effect on the liver is not as severe as was reported in patients who had psoriasis and were taking methotrexate.[11] This difference may be due to more vigorous monitoring of transaminase and albumin levels, the quantity of alcohol consumed by patients with rheumatoid arthritis compared with those with psoriasis, or different liver pathologic factors in each patient group.

All patients should be screened for latent tuberculosis before starting TNF-alpha inhibitors

TNF-alpha inhibitors

TNF-alpha inhibitors are rarely associated with infection, demyelinating syndromes, aplastic anemia, lupus-like syndromes, and lymphoma. (The risk of lymphoma may be slightly higher relative to the healthy population; however, patients with rheumatoid arthritis are at higher risk of developing lymphoma than are healthy controls.) These drugs need to continue to undergo long-term testing before their safety, efficacy, and dosing regimens can be fully established.

Infection. There is a link between TNF-alpha inhibitors and infection. This phenomenon is particularly true of mycobacterial organisms. In experimental models including knockout of TNF-alpha in rodents, there is a reduction of granuloma formation. Without granulomas to encapsulate acid-fast bacilli, these bacilli proliferate. Deaths have been reported as a result of such infections in patients, and physicians need to be vigilant about this possibility. For example, swift identification of the causative organism is essential in a patient taking a TNF-alpha inhibitor who has a fever. If the organism cannot be identified, the patient probably should be hospitalized for treatment with broad-spectrum antibiotics until the organism is identified through specimen culture.

Worldwide, 300 cases of tuberculosis in patients taking these agents have been reported. Many of these cases involved extrapulmonic infections. On the basis of the timing of these cases (ie, within several weeks after starting a TNF-alpha inhibitor), it has been suggested that most of these cases occurred as a result of reactivation. Therefore, all patients should be screened with a purified protein derivative for latent tuberculosis *before* starting TNF-alpha blockade, regardless of whether they are taking these drugs for the treatment of rheumatoid arthritis or for another disease.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Over 50% of patients seek out some sort of complementary therapy on their own. If patients ask about these therapies, I tell them that the only alternative therapies with established benefits are fish oil and evening primrose oil, which have been shown to have some anti-inflammatory properties.

Other interventions

The management of rheumatoid arthritis is not limited to pharmacologic intervention. It requires a team approach that involves physical and occupational therapists and orthopedic surgeons. In addition, studies have shown that patients who work with both a primary care physician and a rheumatologist have a better outcome than those who receive care exclusively from a primary care physician.[12]

On the other hand, patients with rheumatoid arthritis should not be seen solely by their rheumatologist, because they need basic screening and health maintenance that is often better provided by a primary care physician.

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