Current Treatments for Rheumatoid Arthritis

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The goals of treatment for rheumatoid arthritis (RA) are to alleviate pain, prevent or limit joint damage, maximize quality of life, and improve or preserve function.[1] Available treatments include analgesics/nonsteroidal anti-inflammatory drugs, glucocorticoids, and both traditional and newer biologic disease-modifying antirheumatic drugs.

CURRENT TREATMENT APPROACHES

The current thinking regarding treatment of RA is that an aggressive approach early in the course of the disease is needed to prevent irreversible joint damage and to spare patients years of pain and discomfort. This represents a change from the "stepped therapy" or "therapeutic pyramid" approach by which RA was historically managed—start with nonpharmacologic therapies and NSAIDs and move on to "aggressive" treatments only if inflammation is persistent or joint erosions have been demonstrated radiographically.

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Furthermore, it is now apparent that combination regimens, which have been studied for at least the past 2 decades, are generally more effective than any single therapy. For example, the BeSt Study[2] showed that treatment with either initial combination DMARD therapy along with high-dose prednisone or the combination of methotrexate plus a tumor necrosis factor alpha (TNF-α) inhibitor was associated with earlier functional improvement and less joint damage compared with sequential monotherapy or step-up combination therapy. In addition, patient-reported outcomes from the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) revealed better function, quality of life, and satisfaction with treatment among patients given a combination of a TNF-α inhibitor and methotrexate than either drug as monotherapy.[3]

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Analgesics and NSAIDs

Analgesics (acetaminophen, opioids, tramadol) reduce pain but not inflammation or joint destruction. NSAIDs (aspirin, celecoxib, diclofenac, ibuprofen, ketoprofen, naproxen, piroxicam, etc.) reduce pain and—at higher doses—inflammation, but do not slow joint damage. Because they do not prevent disease progression, these drugs are no longer recommended as sole treatment for RA, though they are still useful adjuncts.[1] Narcotic analgesics can be habit-forming and toxic with chronic use and therefore must be used judiciously.

Although many analgesics and NSAIDs are available over-the-counter and are generally perceived as benign, they are not free of risk. With chronic use, NSAIDs often cause fluid retention (which can exacerbate heart failure and hypertension), gastrointestinal irritation, and rash and can be renally toxic. Acetaminophen does not cause gastrointestinal irritation, but it can cause severe hepatotoxicity, particularly with overdose or in patients with preexisting liver dysfunction, and it potentially interacts with warfarin. Concomitant use of proton pump inhibitors, or misoprostol during treatment with NSAIDs reduces the frequency of NSAID-induced ulcers.[4]

Cyclooxygenase-2 (COX-2) inhibitors were developed because their more-specific activity was expected to control signs and symptoms of arthritis with less risk of gastrointestinal complications. Although 3 COX-2 inhibitors were approved in the United States, only celecoxib is still available. Newer COX-2 inhibitors have been approved in other countries, and others are in development.

Glucocorticoids

Oral glucocorticoids are used to control pain, inflammation, and stiffness, and they have recently been shown to stop or slow progression of joint damage.[5,6] Originally perceived as "miracle drugs" when introduced as treatment for RA, these agents are now recognized as having significant adverse effects, especially with long-term use at high doses. As a result, their role is now usually limited to short-term treatment of very active and aggressive RA, usually in combination with NSAIDs and DMARDs. They are often tapered when the disease is under control.

Some of the side effects of glucocorticoids are changes in appetite and weight, glucose intolerance/hyperglycemia, infection, osteoporosis, mood and sleep disturbances, hypertension, suppression of the hypothalamic-pituitary axis, and interference with wound healing.

Injection of glucocorticoids into joints can provide dramatic, though temporary, results in patients who have a disease flare in a single joint or just a few joints.[1] Although X-rays have shown that oral steroids can slow progression of joint damage, it is unclear whether intra-articular steroids have a similar effect. Most clinicians feel that no more than 1 injection in any 3-month period should be made in a given joint. The need for repeated injections suggests that the overall treatment plan requires reevaluation.[1]

Standard DMARDs

DMARDs are currently the mainstay of treatment for RA because they can modify various aspects of the immune and inflammatory responses, thereby potentially controlling signs and symptoms of the disease and slowing its progression. Extensive clinical studies of DMARDs have demonstrated reductions in joint damage, preservation of joint function, and higher rates of productivity.

At one time reserved for patients with signs of joint damage, DMARDs are now used earlier and are considered first-line therapy for all patients with newly diagnosed RA.[1] In contemporary practice, it is considered a standard of care to initiate DMARD therapy within the first 3 months for patients with established RA who, despite adequate treatment with NSAIDs, have ongoing joint pain, significant morning stiffness or fatigue, active synovitis, evidence of active inflammation (eg, persistent elevation of the erythrocyte sedimentation rate or C-reactive protein level in a patient with a number of swollen joints), or radiographic joint damage.[1]

Methotrexate is the most commonly used DMARD, a result of its simple (oral, once-weekly) administration, well-defined safety profile, demonstrated efficacy, and low cost.[1] Hydroxychloroquine and sulfasalazine tend to be used in people whose disease is milder or is progressing more slowly. These drugs are also used in combination with methotrexate for aggressive disease. Leflunomide was shown in several phase III trials to offer comparable efficacy to methotrexate and sulfasalazine against active RA.[7] Other drugs in this class (azathioprine, D-penicillamine, parenteral or oral gold), though shown to be effective in older clinical trials, are now less commonly used, largely because of tolerability issues.[1]

In chemotherapy, methotrexate works presumably by specifically blocking dihydrofolate reductase, thereby inhibiting cell division. However, in RA, the mechanism of action of methotrexate is thought to be related more to its inhibition of inflammation, by increasing the local release of adenosine. Its efficacy has been demonstrated in many randomized clinical trials,[8,9] and other trials have shown that it may slow the progression of joint erosions seen on radiography.[10,11] Clinical response can take 6 to 8 weeks to be seen. The mean dose used among RA patients worldwide is about 17.5 mg per week, although many clinicians initiate therapy at lower doses to help ensure tolerability. Most clinicians consider 25 mg per week to be a maximum dose. Commonly, parenteral administration is given at doses higher than 15 mg per week because of more predictable absorption. Many RA patients take methotrexate for years, which attests to its efficacy and safety.[1]

Leflunomide is a prodrug that after oral administration is actively metabolized to A77 1726. This active metabolite inhibits dihydroorotate dehydrogenase, which in turn interferes with pyrimidine synthesis and ultimately leads to inhibition of activated T cells and other cells. To minimize toxicity, many physicians are forgoing the initial 3-day 100-mg/d loading dose and initiating treatment with the maintenance dose of 20 mg/d orally, which can be reduced to 10 mg if side effects are poorly tolerated.

Although DMARDs represent a major advance in the management of RA, they are not without risks and limitations. Methotrexate is associated with rare but serious side effects, including bone marrow suppression, hypersensitivity pneumonitis, and hepatotoxicity. It can also slightly increase the risk of infection. It must be used with caution in patients with preexisting liver disease, renal impairment, significant pulmonary disease, or alcohol abuse.[1] Less serious but common side effects of methotrexate include stomatitis, gastrointestinal effects, headache, fatigue, and liver transaminase elevations. Folic acid supplementation can prevent many of the minor side effects.

Leflunomide produces liver transaminase elevations in 2% to 4% of patients, with a smaller risk of severe liver injury.[12] Other side effects of leflunomide include weight loss (eg, 20% of body weight), hypertension, diarrhea, reversible alopecia, and myelosuppression.[12] Leflunomide inhibits cytochrome P450 (CYP) 2C9, so there is a theoretical potential for interactions with other drugs that are also CYP2C9 substrates.[12]

Both leflunomide and methotrexate necessitate regular monitoring of liver enzymes and complete blood counts at regular intervals. Treatment should be stopped for any persistent or severe abnormalities.

Gastrointestinal intolerance, rash, pruritus, and hair loss are also common side effects of many DMARDs. Although antimalarial drugs (eg, hydroxychloroquine) have been reported to cause ocular toxicity, with current dosages and preparations this is extremely rare. Sulfasalazine can cause cutaneous adverse events (eg, urticaria, maculopapular rash, photosensitivity) and hematologic side effects. Use of cyclosporine has been limited by its toxicity, which can cause headache, tremors, hypertension, and renal insufficiency. Patients taking cyclosporine require frequent monitoring of blood pressure and serum creatinine. Some DMARDs (eg, azathioprine, chlorambucil, cyclophosphamide) may promote the development of secondary malignancies. Some DMARDs are teratogenic and abortifacient and therefore should not be used during pregnancy or breastfeeding and should be discontinued for at least 3 months before any attempts to conceive.

Since DMARDs can take 2 to 6 months to reach full effect, NSAIDs and sometimes glucocorticoids can be used in the interim to reduce pain and swelling. The duration of DMARD use can be limited by loss of efficacy or development of toxicity.

Biologic Response Modifiers

Improved understanding of the immunopathogenesis of RA has led to the introduction of a newer class of antirheumatic drugs that inhibit various components of the immune system and inflammatory response central to the pathogenesis of RA. These biologic response modifiers ("biologics") can be further subclassified according to their specific target or mechanism.

Three of the currently available biologics are inhibitors of TNF-α: adalimumab, etanercept, and infliximab. Use of TNF-α inhibitors in combination with methotrexate is the current "gold standard" for RA. These agents are also highly effective in treating other disease states, including ankylosing spondylitis, psoriatic arthritis, psoriasis, and Chron disease.

The success of TNF-α inhibitors represents proof-of-concept that inhibition of a single key cytokine can ameliorate symptoms of RA. Most RA patients respond to TNF-α inhibitors with a reduction in signs and symptoms, improved quality of life, and preservation of functional status; some even achieve clinical remission of disease.[13] Radiographic evidence shows that TNF-α inhibitors also significantly slow disease progression, to an extent not seen with any previous agents.[14-16] One recent study even suggests that anti–TNF-α therapy reduces aortic stiffness, a cardiovascular risk factor caused by RA.[17] Even though their acquisition costs are higher than for the older, traditional DMARDs, TNF-α inhibitors are notably clinically efficient, so their cost-effectiveness is comparable to that of other accepted medical practices.[18] In early clinical trials, and in clinical practice, TNF-α inhibitors were used most often in patients with chronic refractory disease. After more clinical experience with these agents, it was suggested that use of TNF-α inhibitors earlier in the course of the disease might bring about even better results. This has indeed been shown to be the case with all 3 TNF-α inhibitors.[3,14,19] There may actually be a window of opportunity in early RA during which maximum benefit of TNF-α inhibitors can be achieved.

From an immunologic standpoint, TNF-α inhibitors do not represent a cure, and maintenance of clinical efficacy almost always requires continued therapy, certainly for patients with longstanding RA. Two- to 4-year and longer studies of anti–TNF-α therapy suggest that response is well maintained.[14,15,20] However, some patients do either fail to respond or eventually lose response. Other biologic agents can be effective for patients who fail anti–TNF-α therapy. All the biologics differ in terms of their mechanisms, method of delivery, and side effects, so a patient who does not respond to or cannot tolerate one may still have a good outcome with another. Although they are commonly used in combination with methotrexate, biologics are generally not given in combination with each other, since this approach can potentially increase risk without much benefit.

Three other FDA-approved biologics target different pathophysiologic mechanisms of RA: (1) anakinra is a subcutaneously (SC) administered interleukin-1 (IL-1) receptor antagonist; (2) rituximab is a monoclonal antibody that eliminates B cells by targeting CD20, a molecule expressed by these cells; and (3) abatacept is a selective modulator of T-cell costimulation. A number of new biologics are being investigated for RA, including new inhibitors of IL-1, IL-6, IL-15, and IL-18, as well as antibodies against proteins needed for B-cell function/survival.

Anakinra showed statistically significant clinical and radiographic benefits in placebo-controlled trials.[21,22] However, it is used less frequently than other biologics because it appears to be associated with lower response rates, although head-to-head comparisons have not been made. Abatacept or rituximab is usually administered after failure of TNF-α inhibitors. In patients with active RA who failed one or more anti–TNF-α therapies, rituximab significantly reduced signs/symptoms, as well as fatigue, disability, and health-related quality of life.[23] Abatacept has been shown to improve signs and symptoms and physical function and to reduce progression of joint damage in methotrexate-resistant RA.[24] Similarly, it has improved signs and symptoms, physical function, and health-related quality of life in RA refractory to TNF-α inhibition.[25]

With more than 1.5 million patients now treated with TNF-α inhibitors, physicians can be guardedly optimistic regarding their long-term safety. Because biologics interfere with the immune system, they potentially increase the risk of both minor and serious infections, as well as secondary malignancies. Because biologics require paren-

teral administration—either SC injections (adalimumab, anakinra, etanercept) or intravenous infusions (abatacept, infliximab, rituximab)—they are less convenient than oral drugs and can be associated with administration reactions, such as injection site or infusion reactions.[26,27]

CONCLUSIONS

There is no cure for RA. However, with available agents applied appropriately, clinical remission is now the goal of therapy, and a realistic expectation for some patients. When remission is not achieved, the rheumatologist must seek the most effective combination of therapies to alleviate pain, maintain function, and maximize quality of life. Methotrexate is still the mainstay of long-term care, but newer biologic DMARDs provide additional benefits. The role of biologic agents is still evolving. Their use is often reserved for patients who fail to respond to methotrexate. However, recent trends are toward earlier use of these agents. NSAIDs and glucocorticoids are useful as "bridge" therapy in patients with acute symptoms, especially while waiting for DMARDs to reach their maximum effect. Patients should be evaluated periodically for evidence of disease activity and progression, as well as for drug toxicity. The management strategy should be changed if there is progressive joint damage or evidence of ongoing activity after 3 months of maximal treatment, or if treatment is poorly tolerated.

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