Rheumatoid arthritis is a chronic autoimmune disease of uncertain cause associated with symmetric polyarthritis and, in some patients, with extra-articular manifestations. Patients with rheumatoid arthritis experience a chronic, fluctuating course that may result in joint damage, disability, deformities, and even a shortened life span. The goals of treatment are to control pain and inflammation and to avoid, to the extent possible, progressive joint destruction.

In recent years, studies comparing immediate with delayed treatment with disease-modifying antirheumatic drugs (DMARDs) have shown that early treatment with these drugs is associated with improved outcomes for signs and symptoms and slower progression of damage to joints (1). Currently available DMARDs fall into 2 broad categories: synthetic DMARDs, including sulfasalazine, hydroxychloroquine, methotrexate, and leflunomide, and biological DMARDs, including tumor necrosis factor–blocking agents, anakinra, abatacept, and rituximab. Pharmacologic treatment for patients with rheumatoid arthritis typically consists of synthetic DMARDs, alone or in combination, or a biological DMARD, either alone or in combination with 1 or more synthetic DMARDs. Biological DMARDs are not generally used in combination with other biological DMARDs because several of these combinations have shown increased toxicity (2, 3).

Given the multiplicity of effective DMARDs, clinicians need an up-to-date, comprehensive summary of the evidence to help them choose 1 DMARD over another for an individual patient and, when a single agent fails to control disease activity, decide which combinations of DMARDs to consider. The report by Donahue and colleagues in this issue (4) addresses this need by reporting the results of a systematic review of the literature comparing the benefits and harms associated with different DMARDs, used alone or in combination. The authors include head-to-head randomized trials, prospective cohort studies, and meta-analyses for 11 drug therapies in their review.

Their review provides evidence for the following important conclusions: there is no evidence that any synthetic DMARD is more effective than another; combinations of synthetic DMARDs can be effective in patients who continue to have active disease despite monotherapy with a synthetic DMARD; the clinical response to monotherapy with tumor necrosis factor blockers compared with that of methotrexate is similar, but radiographic outcomes are better with tumor necrosis factor blockers, and clinical outcomes are better when methotrexate is combined with a biological DMARD than when methotrexate is administered alone.

These general conclusions are well supported by the evidence and are clinically useful. However, the authors offer a few caveats. First, they note that several of the studies used a lower methotrexate dose than is typically used in the United States (7.5 to 15 mg/wk vs. 7.5 to 25 mg/wk) (5, 6), which limits the lessons we can draw from studies that compare methotrexate and other synthetic DMARDs.

Second, most studies were short-term efficacy studies conducted in selected populations. Many of the randomized trials in rheumatoid arthritis were conducted to demonstrate efficacy of products for registration with the U.S. Food and Drug Administration, and they typically use placebo as a comparator. Consequently, head-to-head comparisons of some important drugs have never been done. For example, no published randomized head-to-head trial compares the available biological DMARDs with each other. These shortcomings of the evidence notwithstanding, Donahue and colleagues have provided an evidence base for comparing outcomes of many currently available therapies.

How do the conclusions of this review compare with current recommendations? The American College of Rheumatology offered guidelines for managing rheumatoid arthritis in 2002 (7). These guidelines emphasize the importance of establishing the diagnosis early, documenting the baseline level of disease activity and existing joint damage, and estimating the prognosis. Most patients should start taking a DMARD within 3 months of diagnosis. In addition to DMARDs, physicians should consider treating with a nonsteroidal anti-inflammatory drug; using local or low-dose corticosteroids; and initiating nonpharmacologic interventions, including physical therapy and occupational therapy. Physicians should assess patients regularly (approximately every 3 months) for a response to treatment. For patients with active disease despite treatment with a DMARD, the guidelines recommend 1 of the following strategies: a trial with methotrexate, if the patient has not yet received it; adding another synthetic DMARD (combination therapy); switching to monotherapy with another synthetic DMARD; and biological DMARD therapy, alone or in combination with synthetic DMARDs. Thus, the American College of Rheumatology guidelines seem generally consistent with the findings of Donahue and colleagues.

Many patients continue to live with active rheumatoid arthritis despite DMARD treatment and the availability of many effective regimens. What can be done to improve the care of patients with rheumatoid arthritis? Two approaches may help guide future research. One is to compare different treatment strategies, rather than comparing individual study drugs, as exemplified by the FinRACo (Finnish Rheumatoid Arthritis Combination Therapy), BeST, and TICORA (Tight Control for Rheumatoid Arthritis) studies (8–10). In these 3 randomized trials of patients with early rheumatoid arthritis, treating physicians monitored disease activity at regular intervals (every 3 months) and adjusted therapy as needed to attain a target low level of...
disease activity. All 3 studies used strategies associated with high rates of remission at 18 to 24 months, based on the disease activity score (a standardized measure of disease activity). Patients in these studies had good clinical outcomes, which suggests that treating to the target of low disease activity by using a standardized sequence of graded treatment regimens (the empirical approach) is a sound treatment strategy. In the future, it may be possible to define biomarkers that identify patients who are most likely to respond to a particular treatment and those who are most prone to developing toxicity (11). Hopefully, with a mix of different strategies, we can find a way to target the best treatment to patients with rheumatoid arthritis.

In summary, many disease-modifying agents are effective, both as monotherapy and in combination, for treating rheumatoid arthritis. By following the American College of Rheumatology guidelines for monitoring disease activity and selecting pharmacologic and nonpharmacologic treatment (12–14), clinicians can optimize the care of their patients with rheumatoid arthritis.

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