Methotrexate Plus Biologic More Effective in RA

Federal report on rheumatoid arthritis therapies praised as a good summation of years of literature.

BY DOUG BRUNK
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"Evidence is insufficient to draw firm conclusions."

"We did not find any head-to-head randomized controlled trials."

Those are phrases that commonly appear in a 151-page report, based on a literature review and released by the Agency for Healthcare Research and Quality, titled "Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults."

"The gaps in information for specific [rheumatoid arthritis] therapies are substantial," wrote the researchers of the RTI International–University of North Carolina Evidence-Based Practice Center, under contract to AHRQ, a part of the U.S. Department of Health and Human Services.

Despite the paucity of data, the researchers draw some conclusions from the best available medical literature about the benefits and harms of three classes of medications for rheumatoid arthritis (RA) and psoriatic arthritis: synthetic formulations of disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and corticosteroids.

For example, they found that combining the synthetic DMARD methotrexate with one of the biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, or rituximab) works better to lessen joint damage than does using methotrexate or one of the biologic DMARDs alone.

In addition, they found that methotrexate works as effectively as adalimumab and etanercept for patients with early RA. "Radiographic outcomes, however, were statistically significantly better in patients treated with biologic DMARDs than [in] patients treated with methotrexate," the researchers wrote.

"How such intermediate outcomes translate to the long-term clinical progression of the disease remains unclear."

Dr. Steven B. Abramson, director of the division of rheumatology at New York University Medical Center, called the report "very comprehensive and useful" and "reflective of what I think is our common practice. It tries not to tilt toward one therapy or another. It's a good summation of several years of literature."

Dr. Craig Leonardi, a dermatologist in private practice in St. Louis, Mo., called the report a "good start" and acknowledged the challenge researchers faced in assembling a document "when there is such precious little data comparing therapies directly.

"That's always a limitation of any of these studies, yet clinicians are forced to make these comparisons all the time," according to Dr. Leonardi.

The team of researchers, led by Dr. Katrina E. Donahue of the department of family medicine at the University of North Carolina at Chapel Hill, reviewed 156 articles in the medical literature based on 103 studies of synthetic DMARDs, biologic DMARDs, and corticosteroids. Of these, 50% were supported by pharmaceutical companies, 20% were supported by government or independent funds, 11% had a combination of pharmaceutical and government funding, and the source of funding could not be determined in the remaining 19% of studies.

Most of the studies were found to be of fair quality, which was defined as susceptible to some bias but probably not sufficient to invalidate their results. Only one-quarter of the studies were rated good quality, which was defined as having the least bias and results that are considered to be valid.

Based on their literature review, the researchers found that combining prednisone with hydroxychloroquine, methotrexate, or sulfasalazine works better than using only a synthetic DMARD to reduce joint swelling and tenderness and to improve function. They also determined that there are no meaningful clinical differences between methotrexate and either leflunomide or sulfasalazine.

Other findings in the report include the following:

► There is not enough evidence to conclude that combining two biologic DMARDs is better than using one biologic DMARD.

► An estimated 17 out of every 1,000 people who take a biologic DMARD for 3-12 months develop serious infection. Combining biologic DMARDs increases this risk.

► Painful injection-site reactions occur more often among patients who take anakinra (67%), compared with those who take etanercept (22%) or adalimumab (18%).

Dr. Leonardi, who has helped run clinical trials of biologic DMARDs for psoriasis patients, said that while the current data on comparative treatments for RA and psoriatic RA might be limited, dermatologists "have a long way to go" in comparing biologic DMARDs for psoriasis. "We're left to try our own meta-analysis based on safety and efficacy and looking at the types of patients that come into the trials, [asking] how well did things perform? What were the comparable end points at 12, or 14, or 16 weeks? We try to make our own assessments as best as we can without those head-to-head trials. We just don't have that degree of sophistication yet."

In the report's conclusion, the researchers emphasized the need for long-term studies of arthritis medications, including head-to-head trials "assessing combination therapies involving synthetic DMARDs in comparison with those involving biologic DMARDs," they wrote. "Adequately powered, long-term [randomized clinical trials] must also examine different treatment strategies with and without corticosteroids, synthetic DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in patients with RA. Additionally, no head-to-head [randomized clinical trials] have compared one biologic DMARD with another; this is a significant hole in the literature that future research should fill. However, this is less likely to occur because of the expense of biologic DMARDs."

Dr. Abramson, who is also vice dean for education, faculty and academic affairs at New York University, New York, called the lack of head-to-head trials of biologic DMARDs "a weakness of this field. These are the studies that do need to get done, particularly with respect to x-ray progression."

To access the full report online, visit www.effectivehealthcare.ahrq.gov/reports/final.cfm. ■

Drug Side Effect Profiles Vary in Rheumatoid, Psoriatic Arthritis

BY DENISE NAPOLI
Assistant Editor

Methotrexate's adverse event profile in psoriatic arthritis was different from that in rheumatoid arthritis in a study of more than 1,000 "everyday" patients treated in 30 rheumatology clinics across 13 countries.

"We have suspected for some time that there is differential toxicity, but the studies have not been based in 'everyday practice,' so these data help," said lead investigator Dr. Philip Helliwell of the University of Leeds (England) in an interview.

In a study that sought to characterize both drug use patterns and side effect profiles in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) patients, Dr. Helliwell and his colleague, Dr. William J. Taylor, of the University of Otago, Wellington (New Zealand), looked at enrollees in the Classification Criteria for Psoriatic Arthritis (CASPAR) study, including 588 consecutive clinic attendees with PsA and 536 controls, who were also clinic attendees with some form of inflammatory arthritis, most often RA.

Details about drug therapy were unavailable for 12% of PsA and 2% of RA patients. However, in the cases where treatment was known, methotrexate (MTX) was the most often prescribed first-line therapy in both diseases, given as the initial therapy to 39% of patients with PsA and 29% of RA patients. The second most often prescribed first-line therapy was sulfasalazine in PsA and corticosteroids in RA (J. Rheum 2008 Jan. 15 [Epub before print]).

Of the 404 patients with psoriatic arthritis who were still taking pharmacotherapy at the study's conclusion, 23% were treated with combination therapy. The most frequent combinations were "MTX/sulfasalazine (33 cases), MTX/steroids (22 cases), and MTX/anti-TNF (16 cases)," wrote the researchers. Triple drug therapy was used in nine PsA patients.

Combination therapy was used in 45% of the 315 RA patients still taking drugs at the study's end, with the most often prescribed regimens being MTX/corticosteroids (74 cases), MTX/antimalarials (33 cases), MTX/sulfasalazine (22 cases), and MTX/anti-TNF (13 cases). Triple drug therapy was used in 26 cases.

Methotrexate monotherapy was used through the study's completion by "a majority . . . over 50%," said Dr. Helliwell.

According to Dr. Helliwell, methotrexate's popularity is despite the fact that it is prescribed "off-label" for both PsA and RA in the United Kingdom. "The people who make methotrexate have no incentive to seek regulatory approval because everybody is using it anyway, and [getting approval] is an expensive process," he said.

In the United States, methotrexate has Food and Drug Administration approval for the treatment of psoriasis and rheumatoid arthritis, including Polyarticular-Course Juvenile Rheumatoid Arthritis, and neoplastic diseases, according to a representative of the Center for Drug Evaluation for Research at the FDA.

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As for the second goal of the study—to ascertain the adverse event profile in each drug—the researchers found that while some events were common to both diseases, like renal problems with cyclosporine and gold salts, and skin problems with antimalarials and gold salts, "pulmonary toxicity seen with MTX was confined to the patients with RA," affecting 4% of RA patients vs. 1% of PsA cases. Also, "although MTX is infrequently discontinued for reasons of inefficacy in both diseases, it was more often discontinued in PsA compared to RA, primarily for reasons of toxicity."

Hepatic adverse events occurred in 7% of PsA cases vs. 4% of RA cases. "The problem of hepatotoxicity and methotrexate is of particular concern with psoriasis. Dermatologists seem to see much more hepatotoxicity than we as rheumatologists," said Dr. Helliwell.

"Treatment trials are constrained in ways that may detract from the use of the drug in everyday practice—patients entered into trials are often a very select group with little comorbidity, which confounds extrapolation of drug use to a wide spectrum of patients," wrote the authors.

Dr. Helliwell reported no conflicts of interest in relation to this study. ■