Abatacept Improves Life When Methotrexate Fails

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Concomitant use of abatacept can significantly improve physical and mental health and physical functioning in patients with rheumatoid arthritis who have had an inadequate response to methotrexate treatment, reported Dr. Anthony Russell of the University of Alberta, Edmonton.

Dr. Russell and his colleagues analyzed health-related quality of life data from the Abatacept in Inadequate responders to Methotrexate (AIM) trial, a 1-year, randomized, double-blind, placebo-controlled, phase III trial conducted at 116 sites worldwide.

The AIM trial was designed to evaluate once-monthly abatacept as an adjunct to methotrexate (MTX) for treatment of rheumatoid arthritis (RA) in patients who continued to have active disease despite MTX therapy. An earlier report describes the primary efficacy and safety results of the AIM study (Ann Intern Med 2006;144:865-76). The AIM study population consisted of RA patients who had persistent, active disease despite treatment with MTX for at least 3 months.

Participants also were required to be at least 18 years old; to have had RA for at least 1 year since diagnosis; to have functional status I, II, or III disease; and to have active disease, defined as 10 or more swollen joints, 12 or more tender joints, and C-reactive protein levels of 10 mg/L or higher. Patients were required to maintain a steady dose of MTX for at least 28 days before enrollment.

Combined abatacept and methotrexate produced significant improvements across a wide range of quality of life measures in patients with RA.

Patients were not allowed to take any other disease-modifying antirheumatic drugs (DMARDs) during the study, and patients were required to undergo washout of other DMARDs at least 28 days before randomization.

Patients were randomized 2:1 to receive a fixed dose of abatacept (approximately 10 mg/kg) or placebo by intravenous infusion on days 1, 15, and 29 for the first month and every 28 days thereafter for up to 12 months. All patients remained on MTX at a weekly dose of 15 mg or greater throughout the study.

A total of 652 patients participated in the trial, with 433 in the abatacept-MTX group and 219 patients in the placebo-MTX group. The mean age of the patients was 51.5 years, and the mean disease duration was 8.6 years.

Health outcomes were assessed using the Medical Outcomes Study Short Form (SF)-36 Health Survey, consisting of eight scales covering physical and mental health, and the Health Assessment Questionnaire (HAQ), designed to assess physical functioning. Both questionnaires were self-administered. Patients completed the SF-36 at baseline and at months 1, 3, 6, and 12. Patients completed the HAQ at baseline, at days 15 and 29 within the first month of treatment, and every 28 days thereafter.

"[T]he physical functioning of these patients is comparable to that of patients with congestive heart failure in the general U.S. population," wrote Dr. Russell. In both treatment groups mean baseline scores were approximately one standard deviation below the U.S. population norm for most of the eight subscales of the SF-36.

The mean physical component summary (PCS) scores of the SF-36 were 30.6 for the abatacept-MTX group and 30.7 for the placebo-MTX group at baseline, approximately two SD below the U.S. population norm of 50. Baseline mean scores in the mental component summary (MCS) of the SF-36 were 41.8 in the abatacept-MTX group and 40.8 in the placebo-MTX group, approximately one SD below the U.S. population norm of 50.

Differences between the two treatment groups in quality-of-life measures emerged within the first month of treatment. Relative to the placebo-MTX group, the abatacept-MTX group showed significant improvement by day 29 for five of the eight SF-36 subdomains: self-reported bodily pain, role physical, general health, vitality, and social functioning.

"After 3 months of treatment, the difference between abatacept and placebo widened for all of the SF-36 domains," reported Dr. Russell (Ann. Rheum. Dis. 2007 [Epub doi: 10.1136/ard.2006.057018]).

For each of the various health outcome categories, investigators calculated the proportion of patients in each treatment group whose score improved by at least 0.5 SD over the 12-month study period. Significant differences were observed in the abatacept-MTX group relative to the placebo-MTX group after 12 months in the proportion of patients who showed improvement in PCS (67.2% vs. 51.1%, respectively) and in HAQ (72.4% vs. 55.2%, respectively).

"Combined abatacept and MTX treatment produces significant improvements across a wide range of health-related quality of life domains in patients with RA," concluded Dr. Russell.

The project was supported financially by Bristol-Myers Squibb, makers of Orencia (abatacept). ■

Symptoms Begin Within Weeks

Pain *from page 1*

44% reported AI-related joint tenderness. Knees and fingers were the joints most often affected. Roughly two-thirds of patients with AI-related arthralgias rated their symptoms as moderate to severe.

The risk of joint symptoms was unrelated to age, the AI used, or the duration of therapy. The strongest predictor of AI-related joint symptoms was taxane chemotherapy, which was associated with a 4.3-fold increased risk. Patients who were overweight or had a history of prior tamoxifen therapy were less likely to report AI-associated joint problems.

After completing the course of acupuncture, two-thirds of the patients indicated they would be willing to pay out of pocket to continue treatments.

The third-generation aromatase inhibitors anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are quickly replacing tamoxifen as the adjuvant endocrine therapy of choice in postmenopausal women with hormone receptor–positive breast cancer, based on randomized trial evidence of superior disease-free survival and other advantages. Updated practice guidelines recommend preferential use of third-generation AIs in this population.

However, the success of AI therapy depends on patient adherence—and in this regard joint symptoms are emerging as a significant and as-yet poorly understood impediment.

After noticing that consecutive patients were complaining of severe musculoskeletal pain within weeks after starting on an AI, Dr. Leilani Morales and coworkers at the Catholic University of Leuven (Belgium) decided to look at the problem in depth using MRI and ultrasound.

Dr. Morales reported on a series of 12 consecutive nonmetastatic breast cancer patients who developed musculoskeletal pain and stiffness that became severe and debilitating a median of 8 weeks after starting on letrozole or exemestane.

The most common complaint was early-morning stiffness and hand/wrist pain that made it difficult to completely close and extend the fingers. Carpal tunnel syndrome and trigger finger were the most common findings. All 12 patients reported that the condition interfered with activities of daily living and/or work. Six ultimately discontinued AI therapy as a result.

The patients consistently exhibited tenosynovial imaging abnormalities, in some cases accompanied by abnormal joint findings. Ultrasound demonstrated fluid in the tendon sheath surrounding the digital flexor tendons. On MRI all 12 patients showed enhancement and thickening of the tendon sheath. These pathologies haven't previously been reported in association with musculoskeletal pain related to AI therapy, according to Dr. Morales.

C-reactive protein levels and erythrocyte sedimentation rates were within the normal range in all patients, the physician added.

Most participants in Dr. Crew's survey reported moderate to near-complete relief with nonsteroidal anti-inflammatory agents and/or exercise. Acupuncture also showed promise in a 21-patient pilot study presented by Dr. Crew's Columbia coinvestigator Dr. Arlyn Apollo.

Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function subscale improved from a mean baseline of 454 to 289 following 6 weeks of twice-weekly 45-minute acupuncture sessions, which included auricular and full-body acupuncture.

Functional Assessment of Cancer Therapy–General (FACT-G) physical well-being scores also improved significantly, from 19.9 at baseline to 24.4, as did scores on the Brief Pain Inventory–Short Form.

After completing the course of acupuncture, two-thirds of the patients indicated they would be willing to pay an average of $50 per session out of pocket to continue the treatments.

Based on these encouraging results, a larger randomized trial featuring a sham acupuncture control arm was started, Dr. Apollo said in an interview.

Andrea LaFountain, Ph.D., presented the largest-ever study of adherence to adjuvant AI therapy among women with early-stage breast cancer. The study showed that roughly one in four women taking anastrozole was nonadherent in the first year. By the end of the third year, this rate had increased to nearly one in two.

The study involved more than 12,000 anastrozole-treated patients with early breast cancer in the large national United Healthcare, Blue Cross/Blue Shield, and MarketScan databases.

Patients were deemed adherent if they took the medication on at least 80% of days.

Among the nonadherants, 18%, filled only one monthly prescription over the first year, and 36% filled three or fewer, according to Dr. LaFountain of AstraZeneca Pharmaceuticals, Wilmington, Del.

AI nonadherence results were similar to rates found in an earlier study of adjuvant tamoxifen in New Jersey breast cancer patients, she added.

The studies presented by Dr. Crew and Dr. Apollo were supported by grants from the Lance Armstrong Foundation. ■

Free Fact Sheet on Pain Management

The Substance Abuse and Mental Health Services Administration has published a new fact sheet on providing pain management while keeping a patient from becoming psychologically dependent on opioids.

To order free copies of "Pain Management Without Psychological Dependence: A Guide for Healthcare Providers," contact the National Clearinghouse for Alcohol and Drug Information by calling 800-729-6686. ■