Low-Dose Infliximab Effective In Active Ankylosing Spondylitis

BY NANCY WALSH
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Mont Tremblant, Que. — Low-dose infliximab effectively reduced the signs and symptoms of active ankylosing spondylitis over 12 weeks in a double-blind, placebo-controlled trial, and response was maintained in a small group through 50 weeks, according to data from a randomized controlled trial.

In ankylosing spondylitis (AS), infliximab is generally given in doses of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. If the drug could be given in 3 mg/kg, as is the case in rheumatoid arthritis, patients and the health care system stand to save a substantial amount of money, Dr. Robert D. Inman reported at the annual meeting of the Canadian Rheumatology Association.

In the CANDLE (Canadian Evaluation of Low-Dose Infliximab in Ankylosing Spondylitis) trial, 76 patients aged 18 years and older were randomized to receive a 3-mg/kg dose of infliximab or placebo intravenously at weeks 0, 2, and 6. The primary end point was the proportion of patients achieving an ASAS (Assessment in Ankylosing Spondylitis Working Group) 20 response at week 12.

About 80% of patients were male. Mean time since the first symptoms appeared was 19 years, and mean time since diagnosis was 11 years. In all, 73% were HLA B27 positive, approximately 10% had a history of inflammatory bowel disease, 34% had a history of uveitis, and 7% had a history of psoriasis.

At week 12, the percentage of patients achieving an ASAS 20 score was 54% in patients receiving infliximab versus 31% in patients receiving placebo.

Additionally, 41% and 21% of infliximab patients achieved ASAS 50 and ASAS 70 responses, respectively, compared with 6% and none of the placebo patients, according to poster presentation results presented by Dr. Inman, professor of medicine and immunology at the University of Toronto.

At week 12, the blind was broken and the infliximab group continued to receive the active treatment, while patients originally in the placebo group began infliximab therapy (3 mg/kg) at weeks 16, 18, 22, and every 8 weeks until week 46.

By week 50, 83% of patients in the original infliximab group and 80% of those who had been randomized to placebo but subsequently switched to the active drug had achieved an ASAS 20 response.

Additionally, 64% and 28% of the original infliximab group had achieved ASAS 50 and 70 responses, respectively, as had 69% and 40% of the original placebo group.

At week 12, patients in the infliximab group reported greater improvement in various domains of the Medical Outcomes Study SF-36 (short form–36), including body pain, vitality, social functioning, and mental health, and significant improvements in all eight domains were reported at weeks 22 and 50.

Most of the adverse events reported in the study were classified as unlikely to be related to the study medication. Only one patient discontinued the study because of an adverse event, Dr. Inman noted.

During the unblinded phase of the study, patients with an inadequate clinical response were permitted to have an increase in dose to 5 mg/kg. At week 22, 38% of patients previously in the placebo group required dose titration, as did 62% of those in the infliximab group.

By week 38, 67% of patients previously in the placebo group and 84% of those in the infliximab group required an increase in their infliximab dose, according to Dr. Inman, who dislcosed that he has served as consultant to Schering-Plough Corp., the study sponsor.

Although most patients did need the higher dose over time, a subset of patients will respond to induction and maintain response at 50 weeks with low-dose infliximab, Dr. Inman wrote.

A subanalysis in CANDLE included 32 patients who underwent spinal MRI at baseline and 12 weeks to evaluate the effects of low-dose infliximab on spinal inflammation as measured by the SPARCC (Spondyloarthritis Research Consortium of Canada) MRI index.

At baseline, the mean SPARCC score was 18.03 in the placebo group and 17.63 in the infliximab group. Three patients had no spinal inflammation evidence at baseline.

At week 12, the mean SPARCC score remained at 18.03 in the placebo group but fell to a mean of 6.22 in the infliximab group, which was a statistically significant difference.

Lack of Overall Rates of Malignancy Is 'Reassuring'

Abatacept *from page 1*

maker of abatacept, sponsored the postmarketing surveillance study. The analysis included safety data from two phase II RA trials and five phase III studies, as well as the cumulative abatacept experience of a total of 4,134 patients representing approximately 8,400 person-years of exposure, according to Dr. Lacaille of the University of British Columbia, Vancouver.

Six cohorts that together contained about 94,000 DMARD-treated patients from across the world were used as a reference population for the study.

Six cohorts containing approximately 94,000 DMARD-treated patients from across the world were used as a reference population, she said during a poster presentation. Dr. Lacaille and her colleagues derived rates of malignancy in the U.S. general population from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.

The observed incidence of overall malignancies (excluding nonmelanoma skin cancer) per 100 patient-years was 0.59 in the double-blind trials and 0.61 in the ongoing cumulative abatacept experience. The corresponding standardized incidence ratio (SIR) among DMARD-treated patients, calculated by dividing the number of observed cancers by the number of expected cancers adjusted for age, gender, and duration of exposure, was 0.68. In the U.S. general population, the corresponding SIR was 0.8.

For lung cancer, the observed incidence was 0.24 in the abatacept trials and 0.15 in the abatacept surveillance data; the SIRs were 1.07 in the DMARD-treated patients and 1.5 in the general population.

The lymphoma rates were identical, 0.06, in the trials and the cumulative experience with abatacept; the corresponding SIRs were 0.89 in the DMARD cohorts and 2.2 in the general population. For the RA cohorts, the confidence intervals for the incidence rates and SIRs overlap.

Finally, the breast cancer rates were 0.06 in the trials and 0.08 in the surveillance data, with corresponding SIRs of 0.42 for the DMARD cohorts and 0.4 for the general population

With this longer exposure than in the double-blind studies, the observed incidence rates for malignancies remain unchanged, said Dr. Lacaille. Moreover, overall and individual malignancy SIRs are consistent with what would be expected in an RA population and, when compared with the U.S. general population, are consistent with the literature, she added.

"I think it's reassuring to see that the SIRs are certainly not increased for cancer overall or for lymphoma or particularly for lung cancer among abatacept-treated patients, when compared with the DMARD cohorts," she said.

The overall safety of abatacept will continue to be monitored in this surveillance program.

Physicians Propose Knee Surgery to More Men Than Women

BY HEIDI SPLETE
Senior Writer

Physicians were four times more likely to recommend total knee arthroplasty to men than to women, based on data from 67 physicians.

Total knee arthroplasty has been underused in women, according to population-based survey data. Although 93% of physicians in one Canadian survey said that a patient's sex does not impact their decision to recommend total knee arthroplasty, the researchers conducted a study to test for gender bias in clinical practice.

In this study, Cornelia M. Borkhoff, Ph.D., of the child health evaluative sciences program at the Hospital for Sick Children in Toronto, and her colleagues, recruited one man and one woman with moderate knee osteoarthritis to serve as standardized patients. Each visited 38 family physicians and 33 orthopedic surgeons between August 2003 and October 2005. The physicians were blinded to the patients' status and told that they were taking part in a study of clinical decision making (Can. Med. Assoc. J. 2008;178:681-7 [Epub doi:10.1503/cmaj.071168]). Four of the orthopedic surgeons requested their data not be included in the results.

The patients memorized identical clinical presentation protocols. Both patients were 67 years of age and their identical disease severity was confirmed by two orthopedic surgeons not participating in the study. The patients described their primary complaint as "I've had pain in my right knee now for the past 6 months. Is there anything I can do for some relief?"

Overall, 67% of physicians recommended total knee arthroplasty to the male patient vs. 33% who recommended it to the woman. And 42% recommended surgery to the man but not the woman, while 8% recommended it to the woman but not the man.

Female and male physicians had similar recommendation rates—67% of both male and female physicians recommended surgery to the men, and 42% of the female physicians and 31% of male physicians recommended surgery to the women.

Because only 12 of the physicians in the study were women, the researchers could not evaluate the impact of the doctor's sex on the clinical decision. But of the 12 women physicians, 5 recommended knee surgery to the man but not the woman, 3 recommended surgeries to both patients, 2 recommended surgeries to the woman but not the man, and 2 did not recommend surgery for either patient.

Although the study was limited by the use of only two standardized patients, the patients were well trained and any subtle differences in their presentations to different doctors were unlikely to impact the surgery recommendation rates, the researchers said.

One family physician detected the standardized male patient and another family physician detected both patients as standardized, but removing the data from these three visits did not change the results, they noted.

Possible explanations for the findings include a physician tendency to attribute a woman's symptoms to emotional, rather than physical causes, unconscious gender bias, or gender differences in the patients' clinical presentations, they wrote.

None of the researchers disclosed any conflicts of interest.