Abatacept Shows Long-Term Efficacy for JIA

BY MITCHEL L. ZOLER

COPENHAGEN — Long-term treatment with abatacept was safe and effective in patients with juvenile idiopathic arthritis in a study with 153 patients.

The best response rate was in patients who were maintained on continuous abatacept treatment for up to 31 months. In this subgroup of 58 patients, 75% had an American College of Rheumatology (ACR) 70 response after 2 years of treatment, 57% had an ACR 90 response, and 43% had inactive disease, Dr. Nicolino Ruperto said at the annual European Congress of Rheumatology. Response rates were higher in these patients than in patients who briefly stopped abatacept or those who didn't respond to abatacept early, said Dr. Ruperto, a pediatric rheumatologist at the Pediatric Rheumatology International Trials Organization of the IRCCS (Istituto di Rivovero e Cura a Carattere Scientifico) in Genoa, Italy.

Children were just as likely to achieve ACR 70 response regardless of whether they took the drug continuously or went off it for 4 months to serve as the placebo group (75%).

The findings support continuing abatacept treatment of patients with juvenile idiopathic arthritis (JIA) once the regimen starts, in order to optimize the response rate and give every opportunity for late responses among patients without an early response.

The study was funded by Bristol-Myers Squibb Co. (BMS), the company that markets abatacept (Orencia). Dr. Ruperto said that he has received research support from BMS but has no other relationships with the company. Several of his coauthors also reported relationships with BMS and with other drug companies, and some coauthors were employees of BMS.

The long-term assessment in the new report involved most of the 190 patients who participated in a double-blind, placebo-controlled comparison of abatacept and placebo. The enrolled JIA patients failed prior treatment with at least one disease-modifying antirheumatic drug. Patients were an average age of 12 years old (range, 6-17 years), and they had been diagnosed with JIA for an average of 4 years. In the study, patients received either 10 mg/kg IV abatacept or placebo. Patients received treatment every 2 weeks for the first month, followed by monthly treatment. The study was conducted at 45 pediatric rheumatology centers in Europe, the United States, and Latin America.

Results from the first 4 months showed that abatacept significantly prolonged the time to an arthritis flare, the study's primary end point. Flares occurred in 12 of 60 (20%) patients on abatacept and in 33 of 62 (53%) control patients. The risk for a flare was cut by 69% in abatacept-treated patients, compared with those on placebo (Lancet 2008;372:383-91).

The long-term follow-up study involved 153 of the 190 patients. Of the 153, 58 began abatacept treatment in the study and continued without stopping; 59 started on abatacept and responded during an open-label, 4-month course, were withdrawn for 4 months as the placebo group for the initial study, and then went back on abatacept when the trial was over; and the 36 patients who did not respond to abatacept during the initial, open-label 4 months were put back on the drug later.

Of the 153 patients, 42 dropped out during extended abatacept treatment. Although the best response rates were in patients on continuous abatacept treatment, even those who at first did not respond to the drug showed notable responses, with 46% having an ACR 70 response, 18% having an ACR 90 response, and 5% attaining disease inactivity. (See box.)

Patients who responded to abatacept initially but who were taken off while they served as the placebo arm in the randomized phase had the same ACR 70 response rate as did patients whose treatment wasn't interrupted (75%). But fewer patients who missed 4 months of abatacept treatment achieved complete disease inactivity during follow-up (23%, compared with 43% among those on uninterrupted abatacept).

Serious adverse events occurred in 23 patients (15% of the 153) on extended abatacept treatment. Five of these patients had a serious infection, but no patient had an opportunistic infection, tuberculosis, pneumonia, or malignancy. Overall, long-term abatacept was safe and well tolerated, Dr. Ruperto said. ■

Uninterrupted Abatacept Gives Best JIA Outcome

Patient subgroups	ACR 30	ACR 50	ACR 70	ACR 90	Inactive Disease
Continuous abatacept treatment (n = 58)	90%	88%	75%	57%	43%
Initial abatacept responder, then placebo for 4 months, then back to abatacept (n = 59)	87%	83%	75%	40%	23%
Initial abatacept nonresponder, then put back on the drug (n = 36)	73%	64%	46%	18%	5%

Note: Based on an average 2 years' follow-up.
Source: Dr. Ruperto

ELSEVIER GLOBAL MEDICAL NEWS

Data Confirm 3-Year Efficacy, Safety of Tocilizumab in JIA

BY DIANA MAHONEY

COPENHAGEN — The anti–interleukin-6 receptor monoclonal antibody tocilizumab represents "a major breakthrough" in the treatment of systemic-onset juvenile idiopathic arthritis, according to Dr. Shumpei Yokota, speaking at the annual European Congress of Rheumatology.

New data from an open-label extension trial of patients with systemic juvenile idiopathic arthritis (sJIA) who previously participated in phase II and phase III trials of the biologic agent confirmed the results of the earlier studies; the data demonstrated significant improvement in clinical responses among children who were refractory to conventional therapy, reported Dr. Yokota, professor of pediatrics at Yokohama (Japan) City University.

In addition, the findings from the extension study showed that the "acceptable safety profile" of tocilizumab therapy is maintained up to 3 years, he said.

In the double-blind, withdrawal phase III trial reported last year, 56 children (aged 2-19 years) with sJIA who didn't respond to conventional treatment received three doses of tocilizumab (8 mg/kg every 2 weeks) during a 6-week, open-label lead-in phase.

Patients who achieved an American College of Rheumatology (ACR) Pediatric 30 response and had a C-reactive protein concentration (CRP) of less than 5 mg/dL were then either randomized to placebo or continued on tocilizumab treatment for a 12-week, double-blind phase.

Patients responding to tocilizumab during the double-blind phase of the study who needed further treatment were enrolled in an open-label extension phase for up to 3 years (Lancet 2008;371:998-1006).

"At the end of the open-label lead-in phase, ACR Pedi 30, 50, and 70 were achieved by 91%, 86%, and 68% patients, respectively," Dr. Yokota said. Of the 43 patients who continued to the double-blind phase and were included in the efficacy analysis, significantly more patients in the tocilizumab group, compared with the placebo group, maintained an ACR Pedi 30 response and a CRP level less than 1.5 mg/dL (80% vs. 17%, respectively). By week 48 of the open-label extension phase, 100%, 95%, and 90% of the patients achieved ACR Pedi 30, 50, and 70, respectively, he said.

During long-term treatment, 77% of the 67 patients had their corticosteroid dose reduced at week 168; 8 patients achieved remission and were able to stop tocilizumab.

To evaluate the longer-term efficacy and safety of the treatment, Dr. Yokota and colleagues analyzed the outcomes of 67 patients who previously participated in the phase II and phase III trials who were eligible to receive tocilizumab.

"Safety end points included the incidence of serious adverse events and death, and efficacy end points were the ACR Pedi 30, Pedi 50, Pedi 70, and Pedi 90 criteria," he said.

Of the 67 patients included in the 3-year analysis of continuous tocilizumab therapy, 9 patients discontinued treatment, including 4 who experienced serious adverse events, 4 who developed anti-tocilizumab antibodies, and 1 in whom the treatment was no longer effective, Dr. Yokota said.

The median duration of tocilizumab treatment was 185 weeks, he noted.

In the 3-year analysis, the overall rate of serious adverse events—including anaphylactic reaction, gastrointestinal hemorrhage, bronchitis, and gastroenteritis—was 35.5 per 100 patient-years, Dr. Yokota reported, noting that "there were no cases of opportunistic infections, malignancies, autoimmune diseases, or reported deaths."

Among the frequently observed nonsevere adverse events were nasopharyngitis, upper respiratory tract infection, and gastroenteritis, he said.

Regarding efficacy, 96%, 96%, 88%, and 73% of patients, respectively, achieved ACR Pedi 30, 50, 70, and 90 by at week 168. "During the long-term treatment, 77% of them had reduced doses of corticosteroids at week 168 and tocilizumab was ceased in eight patients because of continuous remission," said Dr. Yokota.

The findings indicate that tocilizumab produces "favorable levels of clinical improvements in the signs and symptoms of systemic juvenile idiopathic arthritis with acceptable safety" up to 3 years, Dr. Yokota concluded.

Dr. Yokota disclosed no financial conflicts of interest with respect to his presentation. Chugai Pharmaceutical Co. sponsored the phase III trial. ■