Two Additional Biologics Are Safe and Effective in JIA

BY NANCY WALSH
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BOSTON — Treatment options for children with juvenile idiopathic arthritis might soon expand, with safety and efficacy now having been demonstrated for two additional biologic agents—even in patients who have failed to respond to methotrexate or another biologic, Dr. Daniel J. Lovell reported at the annual meeting of the American College of Rheumatology.

The sole biologic approved for use in juvenile idiopathic arthritis (JIA) is the tumor necrosis factor (TNF) blocker etanercept, but not all patients respond to this drug. Randomized studies now have shown benefits for the T-cell costimulation modulator abatacept and for another anti-TNF agent, adalimumab.

Both of these drugs have been studied and used extensively in adults with rheumatoid arthritis, with approval for use in JIA pending from the Food and Drug Administration, Dr. Lovell said.

The phase III abatacept study included 190 patients who had previously failed other therapies, including methotrexate, etanercept, and anakinra.

"This was the first study in which we enrolled kids who had already received a biologic. They had exhausted our current therapies but still had active disease," said Dr. Lovell, who is associate director, division of rheumatology, Cincinnati Children's Hospital Medical Center, and professor of pediatrics, University of Cincinnati.

All patients initially received the drug as intravenous infusions of 10 mg/kg on days 1 and 15, and every 28 days thereafter in an open-label fashion for 4 months. They also were permitted (though not required) to receive methotrexate in doses of 10-30 mg/m^2 per week.

By the end of the open-label phase, the overall ACR pediatric 30 response rate was 65%, while the response rate among those who had previously failed on a biologic agent was 40%.

"Clearly this was a treatment that can work when other drugs have failed," Dr. Lovell said.

A total of 123 patients who achieved an ACR pediatric 30 response during the open-label phase were then invited to enter the double-blind portion of the trial; 122 did so.

In this phase of the study, patients were randomized to continue on the active drug or placebo for up to 6 months or until their JIA flared.

As in other blinded trials for JIA, as soon as patients flared they were placed back on the active drug, Dr. Lovell said.

JIA flared in 53% of patients in the placebo group and 20% of those in the active treatment group.

During the open-label phase of the study, six patients reported serious adverse events, three relating to the underlying disease. During the double-blind phase, no serious adverse events were reported in the abatacept group, and three were seen in the placebo group. Overall, the most common adverse events were influenza, bacteriuria, nasopharyngitis, upper respiratory tract infection, and pyrexia. The safety was similar to that seen with other biologics, he said.

An estimated 30% of kids on adalimumab reached ACR 100. 'I don't know what an ACR 100 feels like to patients—it's so new, I've never asked anyone to describe it.'

The adalimumab study was a phase III double-blind trial that included 171 patients ranging in age from 4 to 17 years.

"A unique aspect of this trial was that we enrolled patients who were already on methotrexate as well as patients who were earlier in the course of disease and had not yet received methotrexate. This was the first study in which a biologic agent was introduced independent of, or prior to, methotrexate," Dr. Lovell said.

This was done at the request of the Food and Drug Administration, and the results showed efficacy in both combination and methotrexate-naive groups, he said.

As in the abatacept trial, patients first entered an open-label phase during which they received 24 mg/m^2 adalimumab to a maximum dosage of 40 mg every other week for 16 weeks.

At week 16, 84% of patients had achieved an ACR pediatric 30 response, 77% achieved an ACR pediatric 50 response, 58% achieved an ACR pediatric 70 response, and 27% achieved an ACR pediatric 90 response.

Those who achieved at least an ACR pediatric 30 response were then randomized to continue adalimumab or placebo for 32 weeks or until disease flared. At week 48, ACR pediatric 30, 50, and 70 responses were achieved by 60%, 59%, and 56% of patients in the adalimumab group, respectively, compared with 35%, 35%, and 28% of patients in the placebo group.

The ACR pediatric responses represent a comprehensive picture of disease activity and impact, Dr. Lovell said in a press conference at the meeting.

For an ACR pediatric 30 response, a 30% improvement must be seen in three of six core disease parameters such as physician and parent global assessment and number of joints with active arthritis, and there can be a worsening of no more than 30% in one component.

"This system was developed back when we were just using methotrexate, when we found that if patients demonstrated a 30% response and remained at that level, their outcome was dramatically improved, compared with children who didn't reach that level of response. "It represented a clinically important difference, and it was what we could achieve most of the time with methotrexate," Dr. Lovell said.

But when etanercept was first evaluated in JIA, the bar was raised dramatically, with 80% of patients achieving an ACR pediatric 30 response.

"Now we're talking about ACR 70s and 90s, and in the adalimumab study we even had 30% reaching ACR 100," he said.

"With an ACR 70 response, patients report that the disease impacts their life only intermittently, maybe a few days each month, and with an ACR 90 the disease is almost nonexistent—they can do everything kids want to do.

"I don't know what an ACR 100 feels like to patients—it's so new I've never asked anyone to describe it," he said.

Decisions on approval for the two drugs are expected in the first quarter of 2008, he said.

Dr. Lovell disclosed that he has received consulting fees from Bristol-Myers Squibb Co. and Abbott Laboratories. ■

Long-Acting IL Inhibitor Promising in Systemic JIA

BY NANCY WALSH
New York Bureau

BOSTON — Data emerging from the open-label extension period of a phase II trial of rilonacept for systemic juvenile idiopathic arthritis are showing "obvious clinical benefits," despite disappointing results from the double-blind portion of the study, Dr. Daniel J. Lovell said at the annual meeting of the American College of Rheumatology.

Rilonacept is a long-acting inhibitor of both the interleukin (IL)-1α gene and IL-2β gene that has been shown to be "strikingly effective" in clinical studies of diseases known to be driven by IL-1 overexpression, such as familial cold autoinflammatory syndrome and Muckle Wells syndrome, Dr. Lovell said.

Uncontrolled studies have demonstrated clinical benefits with a short-acting IL-1 inhibitor in systemic juvenile idiopathic arthritis (JIA), suggesting that this cytokine plays a pivotal role in the disease.

The study, which was supported by Regeneron Pharmaceuticals Inc., is ongoing, and a phase III study is planned and will be funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, he said.

Dr. Lovell disclosed that he has received consulting fees from Regeneron.

The study included 24 patients aged 5-20 years who have active systemic JIA. Most were white females who had had either a fever or rash during the previous 2 weeks that was accompanied by functional limitations. They also had abnormal laboratory markers including elevated C-reactive protein, white blood cell counts, and platelets; and lower than normal hemoglobin levels.

At baseline, disease was assessed as very active on both physician and parent global assessment, the mean number of active joints was 16, and the mean childhood health assessment questionnaire score was 1.4. Patients were permitted to enroll if they had previously failed prior biologic therapies including the IL-1 receptor antagonist anakinra, said Dr. Lovell, a pediatric rheumatologist at Cincinnati Children's Hospital Medical Center, and professor of pediatrics, University of Cincinnati.

During the 4-week double-blind phase of the trial, patients received placebo or 2.2 mg/kg or 4.4 mg/kg of rilonacept subcutaneously once weekly. The number of patients in each of these groups was seven, eight, and nine, respectively.

Response was assessed according to the ACR Pediatric 30 criteria, which require a 30% improvement in at least three of the core disease components and a worsening of no more than 30% in one component. The core disease components in JIA include physician and parent global assessments, number of joints with active arthritis, number of joints with limited motion, childhood health assessment questionnaire score, and laboratory values such as C-reactive protein. An adapted version of the ACR Pediatric 30 response, targeted for use in systemic JIA, also includes the presence of fever or rash.

By the end of the double-blind phase, an ACR Pediatric 30 response had been reached by two (29%) patients in the placebo group, four (50%) of those in the 2.2-mg/kg group, two (22%) in the 4.4-mg/kg group, and a total of six (35%) in the two active-treatment groups combined.

These differences were not statistically significant. "So if this was the end of the story, we would go home and say rilonacept was not effective in this patient population. But that would be premature because of the small sample size—and also because the story is more complex than that. These patients went on to be treated with rilonacept for at least 52 weeks, and the data from the open-label extension are important for us to look at," Dr. Lovell said.

Ten of the 24 patients withdrew from the study for lack of efficacy, poor tolerance, or other unrelated reasons, and 3 continued with treatment but did not reach an ACR Pediatric 30 response. Among the remaining 11 patients, 10 demonstrated an ACR Pediatric 70 or greater response by week 52, and 1 additional patient reached an ACR Pediatric 30 response. Fever and rash had resolved in all patients, and laboratory parameters had improved substantially. "So in up to 48% of patients, there was an obvious clinical benefit that persisted through 52 weeks," he said.

Only four serious adverse events were seen in the trial, none of which was thought by the investigators to be related to the treatment.

Among the lessons learned from this study was that 4 weeks was not long enough to demonstrate full response to the drug in systemic JIA, according to Dr. Lovell. ■