Two Additional Biologics Are Safe and Effective in JIA

BY NANCY WALSH  
New York Bureau

BOSTON — Treatment options for children with juvenile idiopathic arthritis (JIA) may 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 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 171 patients ranging in age from 4 to 17 years. "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/m² 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 a biologic agent was 40%.

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

A total of 123 patients who achieved an ACR pediatric 30 response rate at 16 weeks were then randomized to continue on the active drug or placebo for up to 6 months or until their JIA flared. As in the abatacept trials for JIA, as soon as patients flared they were placed back on the active drug, Dr. Lovell said.

JIA flared in 5% of patients in the placebo group and 20% of those in the active treatment group.

During the double-blind phase of the study, six patients reported serious adverse events, three relating to the underlying disease. During the double-blind phase, reactions 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. Safety was similar to that seen with other biologics, he said.

The abatacept 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/m² 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 74% 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 the majority of patients in the abatacept 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 when we were just using methotrexate, Dr. Lovell said. 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 is almost nonexistent—maybe a few days each month, and with an ACR 90 the disease is almost nonexistent—the story is more complex. "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."

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-1 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 and IL-1β 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. ■

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