Biologics in Pipeline for Juvenile Idiopathic Arthritis

BY NANCY WALSH
New York Bureau

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 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%.

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 soon as patients flared they were placed on the active drug. 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.

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

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.

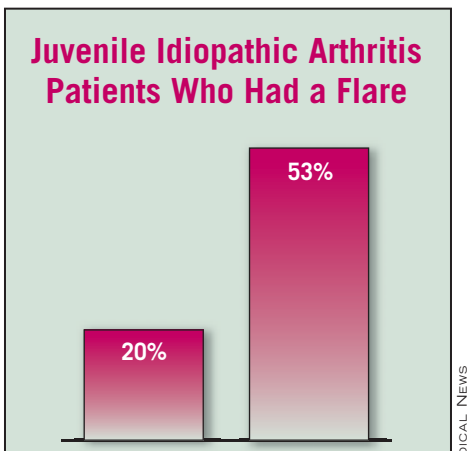
At week 16, 84% of patients had achieved an ACR pediatric 30 response, 77% achieved an ACR pediatric 50 response, 58% achieved an ACR pediatric 70 response, and 27% achieved an ACR pediatric 90 response.

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.

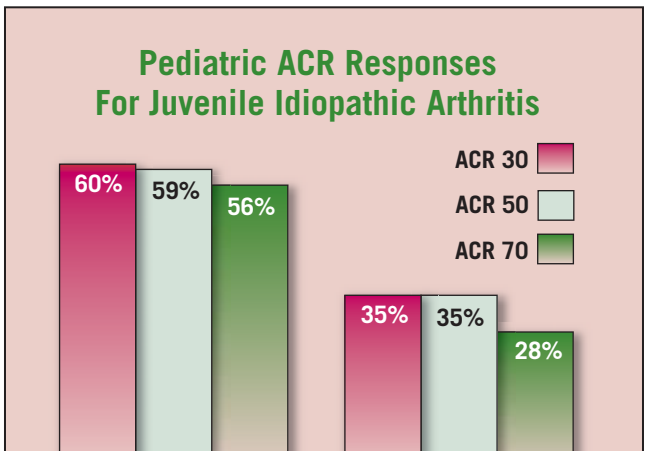
The ACR pediatric responses represent a comprehensive picture of disease activity and impact, Dr. Lovell said in a press conference at the meeting. For an ACR pediatric 30 response, a 30% improvement must be seen in three of six core disease parameters such as physician and parent global assessment and number of joints with active arthritis, and there can be a worsening of no more than 30% in one component.

"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," he said.

Decisions on approval for the two drugs are expected in the first quarter of 2008. Dr. Lovell disclosed that he has received consulting fees from Bristol-Myers Squibb Co. and Abbott Laboratories. ■



Note: Based on a randomized study of 122 patients followed up to 6 months.
Source: Dr. Lovell



Note: Based on a randomized 48-week study of 144 children.
Source: Dr. Lovell

Changes in Synovial Volume Could Predict Progression of Osteoarthritis

BY DAMIAN McNAMARA
Miami Bureau

FORT LAUDERDALE, FLA. — Early screening of synovial fluid volume changes using magnetic resonance imaging could identify patients at risk for progressive knee osteoarthritis, according to interim findings of an ongoing study.

Synovial fluid volume decrease on MRI correlated with both osteophyte formation and joint space narrowing, whereas loss of cartilage volume did not predict progressive disease, Dr. Svetlana Krasnokutsky said during her presentation at the World Congress on Osteoarthritis.

Dr. Krasnokutsky and her associates are conducting a 2-year longitudinal biomarker study of 58 patients with knee osteoarthritis. She presented interim cross-sectional findings at the meeting, which was sponsored by the Osteoarthritis Research Society International.

At baseline, participants' mean age was 62 years, mean body mass index was 28 kg/m^2, and 67% of the participants were women. The National Institute of Arthritis and Musculoskeletal and Skin Diseases sponsored the study.

Semiflexed, anterior-posterior radiographs of the knees at baseline will be repeated at 24 months. Also, 3T MRI with gadolinium will be performed at baseline and 24 months to measure cartilage, synovium, and bone marrow volumes. "X-rays are insensitive to a substantial portion of cartilage loss that can be seen on MRI," said Dr. Krasnokutsky of New York University, New York.

The interim analysis indicates that total cartilage volume does not correlate with the Kellgren-Lawrence (KL) score. "We expected to see a decrease in cartilage volumes in the femur and tibia as the KL score increased, but we did not." In addition, total cartilage volume did not correlate with KL score, joint space width, or osteophyte score.

In contrast, increasing synovial volume correlated with severity of knee osteoarthritis by KL score. "Synovitis is a biomarker of advancing disease and is a parallel feature of the failing joint," Dr. Krasnokutsky said. Synovial volume correlated modestly with bone marrow lesion volume. However, it did not correlate to the Western Ontario and McMaster Universities osteoarthritis index pain score. ■

Life Expectancy No Better in RA Patients, Despite New Therapies

Rheumatoid arthritis patients have not experienced a decline in mortality, despite dramatically increased life expectancy in the general population and newer, more aggressive arthritis treatments.

This stagnation is contributing to a widening mortality gap between patients with rheumatoid arthritis (RA) and their unaffected counterparts in the general population, whose mortality has significantly decreased since the 1950s.

In a population-based incidence cohort study, Dr. Hilal Maradit Kremers and colleagues at the Mayo Clinic, Rochester, Minn., looked at a total of 822 RA patients—all of whom were adult residents of Rochester in whom RA was first diagnosed between 1955 and 1995 and all adult residents of Olmsted County in whom RA was diagnosed between 1995 and 2000.

The patients were followed up through medical records until their death or Jan. 1, 2007. The mean age at incidence at 58 years, and nearly three-quarters of the patients were women. The median length of follow-up was 11.7 years (Arthritis Rheum. 2007;56:3583-7).

RA patients' mortality was unchanged in each of the five periods looked at in the study: from 1955 to 1964, 1965 to 1974, 1975 to 1984, 1985 to 1994, and 1995 to 2000. Female mortality hovered around 2.4 per 100 person-years for each period, and the male mortality was constant at about 2.5 per 100 person-years.

In sharp contrast, mortality in women in the Minnesota general population declined from 1.0 per 100 person-years in 1965 to 0.2 per 100 person-years in 2000.

For men, the rate went from 1.2 to 0.3 per 100 person-years over the same time period.

Dr. Kremers reported no conflicts of interest in relation to this study.

—Denise Napoli

Pages 40a—40b