Celecoxib for JRA Gets Okay From FDA Panel

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. – The Food and Drug Administration's Arthritis Advisory Committee's nearly unanimous support for approving celecoxib for juvenile rheumatoid arthritis in a vote last month may alleviate some of the need for child-friendly drug formulations and add another JRA treatment option.

"We need the advantages an additional formulation will give," and the advantages of having a different medication which is different from naproxen (Naprosyn) and is a selective cyclooxygenase-2 (COX-2) inhibitor "for at least the potential benefits on bleeding, bruising, and hoped for decrease in GI toxicity," said Dr. Thomas Lehman, chief of pediatric rheumatology at the Hospital for Special Surgery, New York. He pointed out that noncompliance with medication is one of the most difficult issues in pediatric rheumatology.

He added that many children will respond to one NSAID after not responding to another, and that in his own practice, he said it was "very common" to try two or three different NSAIDs, "looking for a good effect and tolerance" before a more potentially toxic drug is considered, unless the child has obvious aggressive disease.

'Switching from drug A to drug B may be the magic bullet,' so having more options makes it possible to try another drug before proceeding to something more toxic.

At the Nov. 29 meeting, the federal advisory panel agreed in a 15-1 vote that the risk-benefit ratio of celecoxib was "adequate" to support its approval for treating JRA.

All panelists agreed that the available data showed the COX-2 selective NSAID was effective for this indication, based on a 3-month randomized, double-blind study comparing naproxen (15 mg/kg daily) with celecoxib (6 mg/kg or 12 mg/kg daily). The study included 242 children and adolescents aged 2-16 years with JRA.

The FDA usually follows the recommendations of its advisory panels.

Celecoxib, marketed as Celebrex by Pfizer, was approved for treating osteoarthritis and RA in adults in 1998. Celecoxib remained available after rofecoxib (Vioxx), which was approved for JRA, was taken off the market in 2004 because of an increased cardiovascular risk seen in a large study. An elevated cardiovascular risk was seen in one of three long-term trials comparing celecoxib with placebo, but it remained on the market with the addition of a boxed warning about the possible increase in serious cardiovascular events.

At the committee meeting for pediatric approval, the panelists' vote on safety was split. All panelists were concerned about the absence of long-term safety data of celecoxib in this population. They strongly recommended that the FDA tie approval to a commitment on the part of Pfizer to use a registry study to follow long-term safety issues, including GI, renal, and cardiovascular safety. They agreed that Pfizer's plan to vigorously investigate spontaneous adverse event reports of celecoxib in children and adolescents was inadequate.

Panelist member Dr. Margaret O'Neil, a pediatric rheumatologist at the University of Oklahoma, Oklahoma City, said that "switching from drug A to drug B may be the magic bullet," so having more options makes it possible to try another drug before proceeding to drugs that are potentially more toxic.

If approved, the oral suspension used in the trial would not be the formulation marketed because of problems producing it on a large scale, so Pfizer has plans to develop a capsule containing a sprinkle formulation that can be added on top of foods such as apple sauce.

The pediatric study of patients with polyarticular and pauciarticular RA was designed to show that celecoxib was not inferior to naproxen. At 12 weeks, both doses of celecoxib studied were considered as effective as naproxen in terms of the ACR Pediatric 30 responses, which ranged from about 70% to 80% in all three treatment groups. Patients on celecoxib had more abdominal pain and headaches, but overall, common adverse events were similar in patients on either drug, and the safety profile was similar to those known for NSAIDs, according to Pfizer.

The efficacy response to celecoxib was sustained throughout the 12-week open-label study of almost 200 of the study participants, including 70 naproxen-treated patients who switched to celecoxib, and no new safety issues were identified.

Speaking for the American College of Rheumatology during the open public hearing, Dr. Balu Athreya, past executive chair of the ACR's pediatric arthritis committee, said that 22 NSAIDs are approved for RA, 5 of which are approved for JRA. Most require dosing 2-4 times a day, he said, noting that pediatric rheumatologists need additional options, with medications that have dosing and safety profiles that are practical for children.

Surveys of pediatric rheumatologists presented at the meeting showed that the available adult formulation of celecoxib is being used off label for JRA. ■

Experts Offer New Definition of 'Improvement' in Juvenile Lupus

BY CHRISTINE KILGORE
Contributing Writer

A new validated definition of response to therapy in juvenile systemic lupus erythematosus may help standardize the conduct and reporting of clinical trials and help physicians decide whether a child has responded adequately to therapy, authors of the definition reported.

The standard for improvement is set high: Juvenile lupus can be considered to have improved only when the symptoms have lessened by at least 50% in three of five specific outcome measures. The definition of improvement culminates a three-stage process undertaken by the Pediatric Rheumatology International Trials Organization (PRINTO) to develop and validate a set of outcome measures and a definition of clinical improvement that can be used to evaluate "global response" to therapy by a child with systemic lupus erythematosus (SLE).

The definition includes a global measure of SLE activity and measurement of 24-hour proteinuria, but it also considers a physician's subjective assessment of the level of disease activity as well as parent-reported outcomes.

"One of the reasons we don't have drugs approved, for instance, is that we haven't had good methods for assessing drugs in clinical trials," said Dr. Edward H. Giannini of Children's Hospital Medical Center in Cincinnati, one of the authors and a facilitator of the consensus conference.

PRINTO worked on the definition in conjunction with the Pediatric Rheumatology Collaborative Study Group. The criteria were approved by the American College of Rheumatology board of directors as "provisional," according to the report (Arthritis Rheum. 2006;55:355-63). "Now the criteria will be used in trials, in larger databases… and we'll look to see whether they continue to be valid," Dr. Giannini said.

The new criteria define "improvement" in children with juvenile SLE as at least 50% improvement from baseline in any two of the five outcomes measures that were earlier developed and validated by PRINTO, with no more than one of the remaining measures worsening by more than 30%.

The outcomes measures include:

- The physician's global assessment of the patient's overall disease activity on a 10-cm visual analog scale.
- Global disease activity as measured using the European Consensus Lupus Activity Measurement (ECLAM) tool, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), or the Systemic Lupus Activity Measure (SLAM).
- Renal involvement as assessed by 24-hour proteinuria.
- The parent's global assessment of the child's overall well-being on a 1-cm visual analog scale.
- A quality of life assessment using the parent's version of the Child Health Questionnaire (physical summary score). ■

Young Athletes More Prone to Apophysitis Than Tendonitis

MIAMI — In young children, think apophysitis instead of tendonitis, Dr. Teri McCambridge said at a meeting on pediatric sports medicine sponsored by the American Academy of Pediatrics.

Dr. McCambridge of Johns Hopkins University, Baltimore, emphasized that excessive participation in a single sport is often a culprit. The American Academy of Pediatrics recommends restricting organized sports participation to children at least 6 years of age, while specialization in one sport should be reserved for adolescents.

The way a young tennis player grips the racket or the placement of cleats on a soccer player's shoes can contribute to an overuse injury such as apophysitis. Dr. McCambridge recommended that physicians look for these fixable causes and consult with a coach or other knowledgeable person if they do not know what to look for in a particular sport.

The last apophyseal centers to close in the lower extremity are those in the hips, and, therefore, physicians should watch for apophysitis of the hip in older athletes.

Calcaneal apophysitis, or Sever's Disease, tends to occur early in the growth spurt. It's most common in sports in which children wear cleats or do not wear shoes. Children with calcaneal apophysitis often complain of ankle pain, although upon closer examination the source turns out to be the heel.

Dr. McCambridge said that x-rays are generally not warranted except in certain instances, such as in children with atypical features or nighttime pain, those on the extremes of the expected age range, and those who do not improve after treatment.

Physicians should be aware of other potential causes of joint pain in children, including tendonitis and, rarely, stress fractures, osteomas, tumors, or rheumatologic conditions. Rest is a critical treatment for apophysitis. Children with calcaneal apophysitis also can use ice and should avoid walking barefoot. Dr. McCambridge suggested that when a child has no pain with daily living, they can return to their sport with modifications.

Another common traction apophysitis is Osgood-Schlatter disease (OSD), which occurs at the tibial tuberosity in children aged 11-15 years. Children often present with pain over the anterior tibia, pain with activity, and pain with full flexion. They also tend to have swelling and palpable tenderness at the tibial tuberosity. Chronic OSD carries the risk of long-term problems due to the formation of painful, nonunited ossicles resulting from fragmentation of the tibial tuberosity.

Because of this risk, Dr. McCambridge tends to radiograph OSD more than any other apophyseal injury.

—Melinda Tanzola