Panel Backs Expanding Enbrel to Pediatric Psoriasis

BY BECKY JUNGBAUER
"The Pink Sheet"

A Food and Drug Administration panel has recommended that the agency approve etanercept for moderate to severe plaque psoriasis in pediatric patients; however, some members expressed concern over labeling for moderate psoriasis, preferring that the FDA approve the product for severe cases only.

The Dermatologic and Ophthalmic Drugs Advisory Committee voted 8-5, saying that the drug manufacturer (Amgen Inc.) provided sufficient information to demonstrate the safety and efficacy of etanercept (Enbrel) in the pediatric population with severe psoriasis. But members noted a lack of data on long-term adverse events and maintenance of the treatment effect. The outside medical experts also were divided over whether the tumor necrosis factor blocker's risks outweighed its benefits for patients with moderate psoriasis.

The FDA presented data showing the product's adverse events, including life-threatening infections and malignancies. Amgen's senior vice president for global regulatory affairs and safety, Paul Eisenberg, acknowledged that the benefit and risk have not been established beyond 1 year in the pediatric population.

Nevertheless, the panel moved to give physicians the option of prescribing the product. Consumer representative Mary Majumder said, "Nobody wants this to be used widely, and nobody wants it never to be used."

Enbrel already is used off label for the proposed indication, and Amgen intends to continue gathering clinical data on the indication, which helped sway committee members to vote in its favor.

The company said it will target several thousand pediatric patients, aged 4-17 years, over the next few years in proposed postmarketing studies, including a prospective long-term safety registry with a minimum 5-year follow-up. It also plans to extend its current 3-year open-label extension study to 5 years.

The same committee unanimously voted in favor of approving Centocor Inc.'s ustekinumab recently, also calling for additional long-term studies. ■

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Cancer Link?

TNF Blockers *from page 1*

imumab (Humira), and infliximab (Remicade) "for a possible association between their use and the development of lymphoma and other cancers" in children and young adults who have been treated with these agents for juvenile idiopathic arthritis (JIA) and Crohn's disease, according to the FDA statement.

The fourth TNF blocker, certolizumab pegol (Cimzia), recently was approved for treating adults with moderate to severe Crohn's disease. As part of its postmarketing requirements, the manufacturer of Cimzia, UCB S.A., will start a 10-year study in 2009 that will evaluate the long-term risks of lymphoma and other cancers.

"While the review is ongoing, FDA advises prescribers to weigh the possible association with lymphoma and other cancers against the benefits of treatment when prescribing TNF blockers to children and young adults," the statement said. Still, "at the current time, the FDA believes that the potential benefits of the use of TNF blockers outweigh the potential risks in certain children and young adults having one of the diseases for which the TNF blockers are approved."

The agency is investigating about 30 reports of cancer in children and young adults, who started treatment with a TNF blocker for JIA, Crohn's disease, or other diseases when they were aged 18 years or younger. The other diseases listed included ankylosing spondylitis, psoriatic arthropathy, ulcerative colitis, uveitis, and sarcoidosis; others were listed as unknown, an FDA spokesperson said. The reports were submitted to the FDA's Adverse Event Reporting System over 10 years, starting in 1998, through April 29, 2008, according to the FDA. The children also were taking methotrexate, 6-mercaptopurine, or other immunosuppressive treatments. In about half the cases, the cancers were lymphomas, including non-Hodgkin's and Hodgkin's; others were solid organ cancers, leukemia, and melanoma.

The potential for an increased risk of cancer has been a concern since these TNF blockers were approved because of their mechanism of action, and their prescribing information for each agent already includes warnings about the possible risk of cancer associated with treatment.

In controlled trials of adults, there were more lymphomas in those treated with TNF blockers, and postmarketing studies have been following patients for cancers and other serious adverse events.

The Remicade prescribing information also includes information about the risk of hepatosplenic T-cell lymphoma in children and young adults treated with the biologic and other immunosuppressive drugs for Crohn's disease.

Of the four TNF blockers approved by the FDA, three were approved for pediatric indications: Etanercept in 1999 for the treatment of moderate to severe JIA in children aged 2 years and older; adalimumab in February 2008 for moderate to severe JIA in patients aged 4 years and older; and infliximab for treating children with Crohn's disease. The agency has requested that makers of these products provide it with information about all cases of cancer in children and young adults who were treated with TNF blockers.

Dr. Edward H. Giannini, professor of pediatrics in the division of rheumatology at the Cincinnati Children's Hospital Medical Center said, "Further investigation [of the cancer risks associated with TNF blockers] is necessary and is in the best interest of all concerned." However, there is a background rate of cancer among children. Whether the rates among those treated with TNF blockers are higher than rates among children in the same age group must be studied, he said in an interview.

Controlled data from studies conducted by Dr. Giannini and his associates indicate that cancer rates were not higher than expected among etanercept-treated patients across all indications, including adult indications. In a registry study of 601 JIA patients, aged 2-18 years, treated with methotrexate, etanercept, or both, there were no cases of lymphoma or malignancies over a total of 1,200 patient-years of follow-up, said Dr. Giannini, the study's principal investigator. Dr. Giannini has served as a consultant to Amgen while developing study protocols.

Dr. Lehman is a speaker or consultant for Amgen and Wyeth, which markets etanercept with Amgen; and Humira manufacturer, Abbott Laboratories. ■

Health care professionals and patients can report adverse events associated with the use of Enbrel, Humira, Remicade, and Cimzia to the FDA's MedWatch Adverse Event Reporting System at www.fda.gov/medwatch/report.htm or by calling 800-332-1088.

Low Vitamin D Seen in Young Musculoskeletal Pain Patients

BY JANE SALODOF MACNEIL
Senior Editor

ALBUQUERQUE — A prospective pilot study of 41 children with complaints of nonspecific musculoskeletal pain found their average levels of vitamin D were low even though the youngsters lived in the sunny southwest of the United States.

The mean level of serum 25-hydroxy vitamin D was lower in a group of 35 children with vague pain complaints than in 6 children found to have diagnosable conditions that explained their pain: 28 ng/mL vs. 38 ng/mL. While this difference was statistically significant, average vitamin D levels in both groups of children (aged 2-17 years) met the study's definition of hypovitaminosis D.

Moreover, when eight children were given vitamin D supplements, five had "marked subjective improvement or complete relief" from pain. Those making a recovery included one of two children with documented hip effusion as well as children with back pains and leg pains that had lasted, in some cases, for years.

"I am certainly not saying growing pains are caused by vitamin D deficiency, but it is something we are exploring," Dr. Elizabeth A. Szalay said in an interview after presenting the data at the annual meeting of the Pediatric Orthopaedic Society of North America.

What was, perhaps, most remarkable, was that the children lived in New Mexico—an area not typically used in vitamin D studies because it has abundant sunshine year round. The National Health and Nutrition Examination Survey III suggests that 3% of healthy adolescents at a higher latitude have vitamin D levels below 25 ng/mL during summer, she said. In the New Mexico study, 30% of the youngsters in pain had vitamin D levels below 25 ng/mL.

Dr. Szalay, an orthopedic surgeon at the University of New Mexico and Carrie Tingley Hospital, both in Albuquerque, and her coinvestigator Elyce B. Tryon used a local laboratory's classification of vitamin D levels in their analysis. Ranges were presented as 0-5 ng/mL for deficiency, 5-20 ng/mL for insufficiency, 20-40 ng/mL for hypovitaminosis D, 40-100 ng/mL for sufficiency, and more than 100 ng/mL for toxicity.

The highest level recorded was 47 ng/mL. It was seen in both subgroups: those with vague complaints and those with objective explanations of their pain (Legg-Calvé-Perthes disease, arthrogryposis, and chondrolysis). The lowest level in the majority with vague complaints was less than half that of the children with diagnoses: 12 ng/mL vs. 25 ng/mL.

Dr. Szalay speculated that the low levels of vitamin D could be attributed to a convergence of factors. Sunlight is a prime source of vitamin D and 15 minutes of exposure a day is sufficient, she said, but many children do not play outside. They don't walk to school and may spend as much as 44 hours a week on electronic media such as video games.

Diet by itself is unlikely to provide enough vitamin D, she continued. Milk is fortified with vitamin D, but consumption is down, compared with years past. "In 1970, children drank twice as much milk as soda," she said. "In 2000, children drank twice as much soda as milk."

While children benefit from the calcium in other dairy products, she added, these do not contain vitamin D and are usually not fortified. "Eggs have vitamin D, if they feed it to the chickens and, even then, it is a very small amount," she said. "There are only 25 units in an egg. You've got to eat a lot of eggs to get to 800 to a thousand units."

Children's multivitamins, likewise, do not make up for vitamin D deficiency, according to Dr. Szalay. Some only contain 64 U a day, she said, recommending that children at risk take both a multivitamin and a chewy calcium-plus-D supplement plus two glasses of milk a day. For children without pain, she set the desired daily intake at 800-1,000 U of vitamin D, but added that she recommends 1,000-2,000 U for children with pain.

The investigators have started another study in children without pain complaints, she added. One facet will be to compare those engaged in outdoor sports such as soccer, football, and baseball with those who engage in indoor activities. ■