Cancer Risk in JIA Is Not a Treatment Effect

VITALS

Major Finding: Patients with JIA had a 2.3-fold increased risk of all types of cancers and a 4.2-fold increased risk of lymphoproliferative cancers, compared with matched children without JIA; both differences were statistically significant.

Data Source: Review of 9,000 children and adolescents with JIA from a national Swedish inpatient registry during 1969-2007, and 45,000 matched children from the general Swedish population.

Disclosures: Dr. Askling said that he had no relevant disclosures. One of his coauthors has been a consultant for Abbott Scandinavia. Dr. Harrison is an employee of Pfizer Inc. Dr. Southwood said that he and two of his coauthors received research funding from Wyeth, which is now part of Pfizer, the company that markets etanercept (Enbrel) with Amgen Inc. In addition, two other coauthors of his study were Wyeth employees when the study was done. Enbrel was marketed by Wyeth when the drug first became available.

BY MITCHEL L. ZOLER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME — Treatment with tumor necrosis factor inhibitor drugs did not appear to substantially boost the risk for cancer in children and adolescents with juvenile idiopathic arthritis, according to results from two separate studies reported at this premier European rheumatology congress.

But the results from one of these studies, as well as from a third analysis reported at the meeting, documented a significantly increased incidence of cancer, particularly lymphoproliferative cancers, among JIA patients, independent of treatment. These findings represent the first compilation of solid evidence on the relative cancer incidence in these patients.

A review of Swedish national inpatient registry data that were collected during 1969-2007, plus specialized outpatient visits during 2001-2007, identified 9,000 children aged 0-18 years who were diagnosed with JIA. Comparison of the overall cancer and lymphoproliferative cancer incidence rates in these patients against 45,000 matched children from the Swedish general population showed no significant differences in cancer rates. However, a subgroup analysis that focused on children who were diagnosed with JIA during 1987-2007 showed a statistically significant 2.3-fold higher incidence rate for all cancers, and a significant 4.2-fold higher rate for lymphoproliferative cancers, compared with matched children without JIA, Dr. Johan Askling said at the meeting.

The increased risk for 1987-2007 might be explained by changes in disease coding, data quality, or the treatment of JIA, or it might be a chance finding, said Dr. Askling, an epidemiologist at the Karolinska Institute in Stockholm.

These data are reassuring, compared with what the FDA released, showing a cancer signal in children.

DR. SOUTHWOOD

Lymphoproliferative cancer is "an uncommon outcome, despite the increased relative risk. The fourfold increased risk results in about one additional case for every 1,000 patients with JIA, Dr. Askling noted.

An initial report from the Food and Drug Administration in June 2008, followed by an announcement in August 2009 of an updated boxed warning for the tumor necrosis factor (TNF) inhibitors on the U.S. market, first called attention to the issues of cancer rates in patients with JIA and of a possible role for TNF inhibitors in boosting the rate. The FDA said last August that it had received reports of 48 cases of malignancies in children and adolescents with JIA or other diseases who received treatment with a TNF inhibitor. The 48 patients included 15 with JIA and 21 children or adolescents with Crohn's disease. The 48 cases of malignancies led with 10 cases of hepatosplenic T-cell lymphoma and 7 cases of non-Hodgkin's lymphoma.

The boxed warning that was mandated by the FDA last August alerted prescribers about an increased risk of lymphoma and other malignancies in children and adolescents who were treated with TNF inhibitors.

The new analysis reported by Dr. Askling and his associates found that although JIA patients had an increased rate for all cancers and lymphoproliferative cancers compared with matched children during 1987-2007, the rate during 1999-2007 was no higher than that of 1987-1998, before TNF inhibitors became available, which suggests that the higher rates did not link with drug use.

A second analysis of cancer rates in JIA patients used data from 3,600 patients (average age, 11 years) who were previously untreated with a biologic agent, compared with nearly 38,000 age-matched children without JIA who were drawn from a U.S. commercial insurance database of more than 60 million beneficiaries.

The risk for all types of cancers in the JIA group exceeded the rate in the controls by 2.8-fold, but the difference was not statistically significant, Dr. Melanie Harrison, a rheumatologist and epidemiologist with Pfizer, reported in a poster at the meeting.

A third report at the meeting examined the incidence of cancers among patients with JIA who received at least one dose of the TNF inhibitor etanercept in three registries, from Germany, the United Kingdom, and the United States. The three combined registries included a total of 1,641 patients with JIA who received at least one dose of etanercept before turning 18 years old. Two patients developed a cancer before reaching 22 years, a rate that was 3.7-fold higher than expected, but the difference was not statistically significant. One of the two cancers developed within 90 days of the first dose of etanercept, timing that suggested the case was not treatment related. After excluding this case, the single remaining case produced a calculated cancer incidence rate two times higher than expected, again not a statistically significant difference, reported Dr. Taunton Southwood, professor of pediatric rheumatology at the University of Birmingham (England).

Lymphoproliferative cancer remains uncommon, despite the increased relative risk in JIA.

DR. ASKLING

"These data are reassuring, compared with the data the FDA released. The FDA looked at all children exposed to any TNF inhibitor, including etanercept, infliximab, and adalimumab. And not just JIA but other diseases associated with an increased risk of cancer, such as inflammatory bowel disease," Dr. Southwood said.

"Any chronic, inflammatory disease is probably linked with cancer because it likely interferes with the normal pathway that detects cancer, he added. ■

Child's 'Hot' Hip: Transient Synovitis or Septic Arthritis?

BY DAN HURLEY

EXPERT ANALYSIS FROM ACEP ADVANCED PEDIATRIC EMERGENCY MEDICINE ASSEMBLY

NEW YORK — Is that 3-year-old child with a limp and a low-grade fever just another case of transient synovitis, or is it a much more serious but far rarer case of septic arthritis?

With published decision rules in conflict on how to distinguish one from the other, physicians need to apply clinical judgment appropriate to their available resources, Dr. Martin G. Hellman said at the meeting sponsored by the American College of Emergency Physicians.

"Even a very experienced clinician is not going to see many cases of septic arthritis on a routine or even a nonroutine basis," said Dr. Hellman, clinical assistant professor of pediatrics at the University of Pittsburgh.

Findings from a study of children presenting to Children's Hospital Boston, between 1979 and 1996, identified four clinical predictors that, taken together, could reliably differentiate between septic arthritis and transient synovitis: history of fever, non-weight-bearing status, erythrocyte sedimentation rate (ESR) of at least 40 mm/hr, and serum white blood cell (WBC) count of more than 12,000 cells/mm^3. The probability of septic arthritis was found to be less than 0.2% when a child had none of the predictors, 3.0% for one predictor, 40.0% for two predictors, 93.1% for three predictors, and 99.6% for four predictors (J. Bone Joint Surg. Am. 1999;81:1662-70).

But researchers at St. Louis Children's Hospital asserted that a better set of variables would be to check for a history of fever, a serum total WBC count of greater than 12,000 cells/mm^3, and a previous health care visit for the same complaint. With those three variables present, the predicted probability of septic arthritis rose to 71% (J. Bone Joint Surg. Am. 2004;86:956-62).

A prospective study from Children's Hospital of Philadelphia described 53 children for whom the suspicion of septic arthritis was so strong that they had undergone hip taps. The researchers concluded that a C-reactive protein (CRP) level greater than 2 mg/dL was a strong risk factor for septic arthritis. Fever above 38.5° C was the most influential risk factor; no patients with transient synovitis had a fever above that temperature (J. Bone Joint Surg. Am. 2006;88:1251-7). "However, temperature less than 38.5° C had a false negative more than 50% of the time. And 12% of the septic arthritis cases had zero or one of the factors. That's a little scary," he said.

Dr. Hellman proposed the following plan for evaluation and consultation of hip pain.

"Begin with a careful physical exam," Dr. Hellman said. "Don't forget the possibility of abdominal problems."

For an afebrile child who looks well aside from limited range of motion in the hip and refusal to bear weight, he recommended that physicians take plain x-rays of the pelvis and frog lateral. The physician could choose to stop testing at that point, or could consider obtaining lab tests for CRP, ESR, and WBC. Assuming all tests come up negative, parents should still be given strict instructions to return for immediate evaluation if symptoms worsen.

On the other hand, with a febrile child who does not look well, lab tests would be strongly advised. ■