ASK THE EXPERT

PRINCES Network to Target JIA Outcomes

Juvenile idiopathic arthritis, the most common pediatric rheumatologic disease, continues to be associated with significant long-term morbidity and mortality despite recent developments that have improved our understanding of the disease and increased the evidence base for emerging therapies. The blame for failing to achieve better outcomes can be placed squarely on the variability in patient care and the absence of definitive management standards, both of which inhibit research and clinical progress and can compromise patient safety, outcomes, and practice efficiency, according to Dr. Esi Morgan Dewitt.

"Determinants of patient outcomes are not systematically tracked in most pediatric rheumatology centers, and we lack evidence-based treatment guidelines. Valuable information that could improve quality of care is not available," said Dr. DeWitt, a pediatric rheumatologist at the Cincinnati Children's Hospital Medical Center. "In addition, most centers do not collect patient data in a fashion that allows tracking of medication use, safety, or effectiveness."

To minimize variation in care across sites and to improve patient outcomes, Dr. DeWitt and other pediatric rheumatologists from centers nationwide have spearheaded the development of a quality improvement initiative called PRINCES (Pediatric Rheumatology Improvement Network for Continuous Excellence and Safety). The collaborative, user-led innovation network aims to develop a data-collection tool to capture quality measures and variables efficiently and to streamline the transfer of evidence-based treatment into practice.

Toward this end, quality improvement teams comprising a physician champion and practice nurse from participating sites will receive training on evidence-based strategies for chronic disease management. Each team will work over 12- to 18-month periods to achieve measurable improvements in JIA care, said Dr. DeWitt, who discusses the PRINCES mission and goals in this month's column.

Rheumatology News: What specific gaps in JIA care will the PRINCES initiative target?

Dr. DeWitt: Juvenile arthritis frequently requires chronic treatment with immunosuppressive medications including biologics, but treatment is not governed by evidence-based protocols, despite the large number of randomized, controlled trials of therapeutics. By creating a large database of JIA patients, systematically recording and tracking how patients are being treated, and simultaneously studying patient outcomes, participating pediatric rheumatologists will be able to better understand which treatment approaches are optimal. Another facet in the management of JIA that needs to be addressed includes disease- and medication-monitoring guidelines. For example, adherence to published guidelines for uveitis screening is not well documented. Furthermore, guidelines for monitoring medication toxicity were created for adult patients. These may not be relevant in the pediatric population. The proportion of physicians and patients who adhere to these guidelines is unknown. We also don't know whether adherence to prescribed treatment results in better outcomes.

RN: How will the PRINCES initiative address these issues?

Dr. DeWitt: Because only small numbers of patients are seen at each individual center, a multicenter collaborative network is necessary to identify the best practices in care for quality improvement through a population registry. The small numbers of patients and shortage of pediatric rheumatologists require efficiency and leveraging of this population registry to monitor safety and study the efficacy of therapeutics. One overall comprehensive registry will reduce duplication of efforts and provide a uniform data collection system, which in turn will improve the processes of care and patient outcomes over time. Additionally, the collaborative will allow collection of long-term longitudinal data, which will result in better understanding of the long-term impact of NSAIDs, disease-modifying antirheumatic drugs, and biologic therapies initiated in childhood. An added benefit to participation in the network is that evidence of quality improvement work will fulfill the American Board of Pediatrics' require-

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Etanercept Registry Data Suggest Low Cancer Risk in JIA

BY AMY ROTHMAN SCHONFELD

Philadelphia — Results from the largest registry of children with juvenile idiopathic arthritis who are taking etanercept indicate that the number of serious adverse events was low and seems not to increase with prolonged treatment.

Adverse events (including serious infections, malignancies, and deaths) were documented, according to Dr. Gerd Horneff, who presented the latest data from the German etanercept registry for the treatment of JIA at the annual meeting of the American Society of Rheumatology.

The significance of the findings was reflected by the overflow crowd that came to hear Dr. Horneff's presentation. Considerable attention to this issue was raised by a Food and Drug Administration alert issued in August that requires manufacturers of tumor necrosis factor (TNF) blockers to update boxed warnings in prescribing information to notify health care professionals of an increased risk of lymphoma and other malignancies in children and adolescents who are treated with infliximab, etanercept, adalimumab, certolizumab pegol, or golimumab.

The FDA identified 48 cases of malignancies in children and adolescents who were exposed to TNF inhibitors, and 20 malignancies in pediatric rheumatology patients. In all, 14 were in children or adolescents taking etanercept. The malignancy reporting rate for etanercept (2.2 per 10,000 patient-years in aged 17 years or younger) was higher than background rates for lymphomas, but similar to background rates for all malignancies. The FDA concluded that because of the relatively rare occurrence of these cancers and the limited number of pediatric patients treated with TNF blockers, as well as the possible role of other immunosuppressive therapies used along with TNF blockers, it was unable to fully characterize the strength of the association between TNF blockers and development of a malignancy, and that more data were needed from long-term studies.

Dr. Horneff presented the safety results for the largest group of children who had been exposed to etanercept to date (1,139), yielding more than 3,300 patient-years of observation. In comparison, only 69 children taking etanercept have been studied in randomized, controlled trials. The German registry includes 43% of children who are taking etanercept and are enrolled in registries around the world, explained Dr. Horneff of the department of pediatrics at Asklepios Clinic in Sankt Augustin, Germany.

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The registry contained reports of serious adverse events (SAEs) in 9% of children. These included, but were not limited to, 34 infections, 21 autoimmune/uveitis reactions, 11 disease flare-ups, 11 neuropsychiatric reactions, and 11 other types of reactions. Five children had allergic/skin reactions. One child had a fatal macrophage activation syndrome reaction 6 months after etanercept discontinuation.

Four children developed malignancies including thyroid carcinoma (diagnosed during the 10th month of treatment), yolk sac carcinoma (diagnosed after 3 weeks of treatment), non-Hodgkin's lymphoma (in a patient exposed to many biologic and nonbiologic agents), and Hodgkin's lymphoma (diagnosed 19 months after discontinuing etanercept following 1.5 years of treatment). These data are consistent with the observation reported by the FDA, although the risk of malignancy was still quite low, said Dr. Horneff.

The background incidence of malignancy in children with JIA has not been well defined. It remains unclear whether the risk of malignancy is increased in JIA. Long-term inflammation may increase the cancer risk. Numerous different types of cancers have been observed, but lymphoma is the most common, he said.

Infections were the most common serious adverse event in this registry. There were no reports of tuberculosis or opportunistic infections. The 0.01 infectious SAEs per patient-year reported in the German registry are similar to the 0.02 SAEs per patient-year reported in the U.S. registry and the 0.04 rate reported in open-label, long-term extension studies, according to Dr. Horneff. Taking steroids with etanercept tripled the risk of developing a serious infection (odds ratio, 2.9; $P = .007$), but adding methotrexate did not significantly increase the risk of infection ($P = .085$). Autoimmunopathies occurred in 2% of children, the equivalent of 0.007 SAEs per patient-year of observation.

The average age of enrollees in the German registry was 12.5 years, and about 70% were female. The average disease duration was 4.3 years. The primary diagnoses were polyarthritis (42%) and extended oligoarthritis (17%). In all, 11% had systemic JIA.

"Randomized controlled trials showed that polyarticular JIA can successfully be treated with TNF inhibitors etanercept, adalimumab, and infliximab, and open-label extension studies demonstrated long-term efficacy," Dr. Horneff said.

"Although no causative relationship can be concluded between etanercept and malignancies, the use of TNF inhibitors should be limited to those patients with severe polyarticular JIA who do not respond to previous treatment. Furthermore, combination treatment with methotrexate or other immunosuppressants may increase clinical efficacy but may also increase risk, and should, therefore, be indicated with caution.

Nevertheless, the extensive use of immunosuppressants other than methotrexate as alternative treatment or pretreatment before considering TNF-inhibitors may also affect the risk for malignancies and should be avoided."

Dr. Horneff disclosed having financial relationships with a number of companies, including Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Chugai, Lilly, MedImmune, Merck Serono, Novartis, Nycomed, Pfizer, Roche, Sandoz, and Wyeth. ■