

## ASK THE EXPERT

## Osteoporosis in Pediatric Rheumatic Disease

**C**hronic inflammatory diseases in children and adolescents can have a detrimental effect on bone mass, compromising bone growth and development during prime bone-building years. Therefore, the increased risk of osteoporosis and fragility fractures among pediatric patients with conditions such as juvenile arthritis, systemic lupus erythematosus (SLE), and dermatomyositis must be addressed early to prevent long-term pain and disability, according to pediatric rheumatologist Philip J. Hashkes of Shaare Zedek Medical Center in Jerusalem.

Although the guidelines for the treatment of osteoporosis in adults are widely accepted, management in the pediatric population is not as well defined because of the relative lack of substantive data on children and adolescents with osteoporosis, he said.

In this month's column, Dr. Hashkes discusses the underlying mechanisms for osteoporosis in juvenile patients with rheumatic disease, as well as optimal management strategies.

**RHEUMATOLOGY NEWS:** Glucocorticoid use is widely recognized as a risk factor for osteoporosis in children with rheumatic diseases, but multiple studies have observed that the increased risk of compromised bone development can precede the onset of steroid therapy in these patients. What are the presumed mechanisms for this increased risk?

**Dr. Hashkes:** Besides steroid therapy, there are several other mechanisms that may promote osteoporosis, like the disease process itself—specifically cytokines like interleukin-6 that promote osteoclast

activation. Inactivity or immobilization, especially lack of weight bearing as a result of arthritis or myositis, is a major contributor to osteoporosis. Poor intake of foods containing calcium and vitamin D due to anorexia related to inflammation or temporomandibular joint arthritis is another contributor. Patients with inflammatory diseases that affect absorption (dermatomyositis) or renal function (SLE) may have impaired bone metabolism. Another treatment-related factor with the potential to cause vitamin D deficiency is sun protection or a lack of sun exposure, which is recommended for patients with SLE and dermatomyositis.

**RN:** What are some challenges that clinicians face in diagnosing osteoporosis in this population?

**Dr. Hashkes:** The first is realizing that osteoporosis not only is a disease of older people but also can occur in certain childhood conditions. The gold standard for diagnosis is dual-emission x-ray absorptiometry. But the problem with pediatric DXA studies is the overdiagnosis of osteoporosis due to misinterpretation of data based on adult references. Bone density varies greatly with age, so densitometry z scores based on pediatric reference curves are used in the pediatric population, not the T score usually used in adults. Also the definition of osteoporosis is different in children than in adults.

**RN:** Is there a routine osteoporosis screening protocol for children who are newly diagnosed with any of these rheumatic diseases?

**Dr. Hashkes:** In general, children who need steroid therapy for at least 3 months

should undergo baseline DXA, as well as periodic DXA depending on the dose of steroids and other factors. There are no evidence-based guidelines regarding whether children with rheumatic diseases not treated with steroids need to undergo routine DXA. The issue of vitamin D screening has also not been resolved.

**RN:** What are the recommended prevention interventions for children diagnosed with juvenile arthritis or another rheumatic condition without evidence of osteoporosis?

**Dr. Hashkes:** Physicians should ensure that these children have an adequate intake of calcium (500 mg/day for 1- to 3-year-olds, 800 mg/day for 4- to 8-year-olds, and 1,300 mg/day for 9- to 18-year-olds) and vitamin D (at least 400 U/day). The composition of the diet may be important for calcium utilization, with improved absorption in patients consuming a Mediterranean-type diet.

**RN:** What are the current treatment options for osteoporosis in this population, and what are some of the important considerations for initiating and managing treatment over time?

**Dr. Hashkes:** In addition to being used for the dietary issues I mentioned, bisphosphonates can be used in children who have suffered fractures or have extreme osteopenia on DXA. However, for primary prevention, using bisphosphonates in children who take corticosteroids is still not recommended. The safety profile of bisphosphonates in children has been good with minimal effects on growth and on development of normal bone. Additional caution must be

given to children needing dental work, including orthodontics, regarding the potential development of jaw osteonecrosis—although this has not yet been reported in children—and to adolescent females with the potential for childbearing. Bisphosphonates have an extremely long bone half-life, and the effect on the fetus is still not clear. There may be a difference between various agents in the bone half-life that may impact the decision on which agent to use.

**RN:** Children with rheumatoid disease may be treated by adult vs. pediatric rheumatologists. In assessing and managing osteoporosis in children vs. adults, what advice can you provide?

**Dr. Hashkes:** The main issue is awareness. Osteoporosis can occur in children with chronic inflammatory conditions whether they are treated with steroids or not. Adult rheumatologists need to be aware of correct pediatric interpretations of DXA scans, and to ensure the machine they use has pediatric software. They also need to be aware of the increased dietary requirements of calcium and vitamin D in growing children. Recombinant human parathyroid hormone should not be used in children because of potential safety issues, including the potential for the development of bone tumors, which has been observed in growing rats receiving parathyroid hormone therapy.

—Diana Mahoney

*Dr. HASHKES is the head of the pediatric rheumatology unit at Shaare Zedek Medical Center in Jerusalem. He reported no conflicts of interest.*

## Global Data: Cancer Very Rare in Children on Etanercept

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

**ROME** — Global data are quite reassuring that the risk of cancer in children taking etanercept is elevated very little if at all, judging from data from two studies.

In all, 18 malignancies in etanercept-treated pediatric and young adult patients were reported worldwide in clinical trials, registries, postmarketing surveillance studies, and published case reports during the 11-year period of 1998-2009. The youths were placed on the tumor necrosis factor inhibitor mainly for juvenile idiopathic arthritis (JIA) or psoriasis.

This translates to a cancer incidence rate of 1.5 cases per 10,000 patient-years of exposure to etanercept (Enbrel). That's essentially the same as

the projected background rate of 1.47 cases per 10,000 patient-years in normal 4- to 17-year-olds in the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) database, Dr. Peter McCroskery reported.

Moreover, the figure of 1.5 cancers per 10,000 patient-years probably overestimates the true incidence of malignancies in etanercept-treated youths. For one thing, 4 of the 18 cases could not be confirmed. And three of four leukemias included in the series were diagnosed less than 4 months after initiation of etanercept, in one case after only 29 days on the biologic; the timing of these three cases suggests they may very well have involved early musculoskeletal

symptoms of leukemia being initially mistaken for juvenile idiopathic arthritis, noted Dr. McCroskery of Amgen Inc.

Of the 18 patients, 15 were also receiving immunosuppressive agents linked to cancer. These included cyclophosphamide, methotrexate, cyclosporine, and azathioprine. Three patients had also received other biologic agents.

These caveats, confounding because of concomitant immunosuppressive medications and the rarity of pediatric cancers, underscore the difficulty in attempting to assess the true risk of cancer associated with the

use of etanercept in children and adolescents, the physician said.

"Concerns have been raised recently about a potential link between the use of TNF inhibitors and the development of malignancies in adults and children. This study was an attempt to be completely and totally transparent and let the data speak for themselves," he said in an interview.

The Amgen-sponsored study yielded no signal of an increased risk of cancer overall in association with etanercept. There was a slight signal for lymphoma, with an incidence of 1 case per 10,000 person-years of treatment in 4- to 17-year-olds, compared with a background rate of 0.26 per 10,000 person-years based upon SEER data.

However, as Dr. McCroskery noted, another study presented at the European congress con-

cluded that the risk of cancer is already increased in JIA patients who've never been on a biologic therapy.

Dr. Melanie J. Harrison presented a retrospective cohort study involving 3,605 biologics-naïve JIA patients and 37,689 matched controls without JIA. The data were extracted from a claims database including more than 60 million commercially insured Americans. The risk of cancer in the biologics-naïve JIA group was elevated 2.8-fold.

"These findings suggest that the underlying risk of cancer in JIA is elevated, and any risk associated with the use of biologics should be interpreted in this context," according to Dr. Harrison of Pfizer Inc. ■

**Disclosures:** Dr. McCroskery is an employee of Amgen, which makes Enbrel. Dr. Harrison's employer, Pfizer, is a partner of Amgen.

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