Atypical Fractures Rise With Bisphosphonate Use

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH

TORONTO – Patients with osteoporosis who are on bisphosphonate therapy clearly face an increased treatment-linked risk for atypical femur fractures, but at a low rate that is dwarfed by the number of typical hip fractures the drugs prevent.

The risk for atypical fracture appears to rise substantially as time on the drug increases, but an atypical fracture can occur at any time, prompting experts to stress that a bisphosphonate should be given only to a patient who needs the treatment. And the prodromal thigh or groin pain that precedes a majority of atypical fractures should alert physicians to stop bisphosphonate treatment, although stopping the drug is no guarantee against a subsequent atypical fracture.

Above all, experts agreed, atypical fracture risk is no reason to deny bisphosphonate treatment to patients who need it, because these drugs improve bone mineral density and prevent typical hip fractures, and because in appropriate patients this benefit far exceeds the atypical fracture risk.

This consensus on how to view bisphosphonates and their risk for causing atypical fractures pervaded the meeting. One multispeaker session during the meeting reviewed the data compiled by and the recommendations from an American Society for Bone and Mineral Research (ASBMR) task force that were published online late last year, while several other speakers reported some of the incidence data that task force members considered when writing their recommendations (J. Bone Miner. Res. 2010 [doi: 10.1002/jbmr.253]).

"The message is that for patients with osteoporosis at high risk of having a fracture, treatment with a bisphosphonate will benefit far more than risk for an atypical fracture," said Dr. Elizabeth Shane, a professor of medicine at Columbia University in New York, and cochair of the task force.

The largest and most comprehensive look at atypical fracture rates came from data compiled from the 2.6 million beneficiaries older than 45 years enrolled in Kaiser California. During January 2007 through December 2009, 15,819 people had femur fractures, excluding those from major trauma, those secondary to Paget's disease or metastatic lesions, or periprosthetic fractures. The researchers reviewed the radiographs for 1,448 of these fractures located in the diaphyseal region.

Of the reviewed fractures, the researchers identified 135 as atypical, based on their location in the diaphyseal portion of the femur, either in the shaft or subtrochanteric region, as well as other features: a transverse fracture, usually with lateral cortical thickening especially at the fracture site, and flaring of the lateral cortex, Dr. Susan Ott of the University of Washington, Seattle, reported at the meeting.

The 135 patients with atypical fractures were 98% women, with an average age of 71 years and an average body mass index of 26.6 kg/m^2. The fracture patients had a modest, 2% mortality rate during the year following the event. In atypical fracture patients who had bone density information available, the T scores averaged –2.2.

All but 4% of the atypical fracture patients received a bisphosphonate at the time of fracture, and were on their regimen for an average of 6 years. Two-thirds had prodromal thigh pain, and 26% had bilateral atypical fractures. In all, 60% of the fractures occurred in the femur shaft, and 40% were in the subtrochanteric region.

The most common age at fracture was 65-69 years, with a majority of atypical fracture patients aged 65 or older. The fracture rate rose steadily with increasing years of bisphosphonate use, with most fractures occurring in patients who had used the drugs for at least 5 years, even though these long-term users represented a small minority of all Kaiser patients who used a bisphosphonate during the 3 years studied. The number of fractures per 100,000 people exposed rose steadily with increasing years of use, reaching 50 per 100,000 when bisphosphonate use continued for 5 years and 100 fractures per 100,000 patients in those using the drug for 6 years, and then continuing to rise steadily with added years of use, reaching a high of nearly 250 fractures for every 100,000 patients exposed to a bisphosphonate for 12 years.

"These data do not suggest you should stop using bisphosphonates, especially in women with osteoporosis. Bisphosphonates look pretty safe for the first few years," Dr. Ott said. But, she added, "the data argue that if a patient does not have osteoporosis, then bisphosphonates are not the appropriate drug."

The ASBMR task force reviewed Dr. Ott's data before issuing its recommendations in October 2010. The data "were very informative for establishing incidence rates for these fractures," Dr. Shane said in an interview.

Another talk at the meeting presented additional data documenting the relative risks of atypical and typical fractures with bisphosphonate treatment.

Patients taking a bisphosphonate face a risk of about 1 additional subtrochanteric hip fracture for every 100 typical hip fractures prevented, according to an analysis of national data during 1996-2007.

The new data present no direct evidence for a role of bisphosphonate use in causing subtrochanteric hip fractures, which along with femoral shaft fractures constitute the "atypical" category. But the temporal link between the steady increase in bisphosphonate use among elderly American women during 1996-2007 and the concurrent rise in subtrochanteric fractures also in elderly American women strongly suggests that a causal link exists, John Wang, Ph.D., a statistician at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, said.

He analyzed data on U.S. subtrochanteric fracture rates from the Nationwide Inpatient Sample during 1996-2007, along with data on U.S. bisphosphonate use from the Medical Expenditure Panel Survey. The analysis showed that the start of widespread bisphosphonate use in 1996, quickly followed by even broader use over the following years, had a temporal relationship with subtrochanteric fractures, which began rising in 2000. ■

VITALS

Major Finding: The rate of atypical femur fractures in patients with osteoporosis who were treated with a bisphosphonate rose with increased duration of use. On average, 50 atypical fractures occurred for every 100,000 patients treated for 5 years, 100 atypical fractures occurred per 100,000 patients treated for 6 years, and almost 250 atypical fractures occurred per 100,000 patients treated for 12 years.

Data Source: Review of radiographs from 1,448 Kaiser California patients with a diaphyseal femur fracture during January 2007 through December 2009, including 135 that met the atypical criteria.

Disclosures: Dr. Ott and Dr. Wang had no disclosures. Dr. Shane has been a consultant to Amgen and has received research support from Merck, Novartis, and Eli Lilly.

Recommended Steps to Reduce Risk

Despite substantial evidence linking long-term bisphosphonate use and an increased rate of atypical femur fractures, bisphosphonates remain an effective and attractive drug class for treating osteoporosis, experts said at the meeting.

The task force assembled by the ASBMR recommended several steps for physicians to take when they prescribe a bisphosphonate to reduce the atypical fracture risk faced by patients.

Patients with a low absolute fracture risk should not receive a bisphosphonate, said Dr. Peter R. Ebeling, a task force member, summarizing the group's recommendations at the ASBMR's annual meeting.

Another step is minimizing the duration of bisphosphonate treatment. This means realizing that patients with secondary causes of rapid bone loss may not need long-term bisphosphonate treatment. Continued use of the drugs beyond 5 years should be evaluated annually, said Dr. Ebeling, professor and chairman of medicine at the University of Melbourne.

Patients without a recent fracture and with a femoral neck T score of more than –2.5 after 5 years of continuous bisphosphonate treatment should receive consideration for a drug holiday. Patients who are taken off bisphosphonate treatment should undergo an annual assessment of their clinical status, markers of bone turnover, bone density, and fracture risk.

Because a majority of patients who developed an atypical fracture on bisphosphonate treatment had prodromal pain in their thigh or groin, physicians should alert patients to watch for and promptly report such pain. During regular examinations of patients on a bisphosphonate or another potent antiresorptive drug, physicians should ask if prodromal pain exists. When suspicious pain occurs, the patient needs "urgent" radiographic assessment of both femora, even for unilateral pain, Dr. Ebeling said. If the radiographs appear normal, perform a follow-up examination by MRI or radionuclide scintigraphy scanning. Physicians should be aware that bilateral, atypical femur fractures can occur; patients with an atypical fracture of one femur face a fracture risk in their contralateral femur.

If a patient has a fracture while on a bisphosphonate, treatment with the bisphosphonate or any other potent antiresorptive drug should stop. At that time, assess the patient's calcium and vitamin D status and prescribe adequate supplementation if needed. The physician should consider prescribing teriparatide to improve fracture healing, particularly if it appears that the fracture has not healed by 4-6 weeks following surgical repair. In patients who should not receive teriparatide, such as those with a history of breast cancer or skeletal irradiation, consider another option such as treatment with raloxifene.

When an atypical fracture occurs, the physician "should look at the other leg. It's an opportunity to prevent more fractures by paying attention to a patient's symptoms and acting on them," said Dr. Elizabeth Shane. Reduced weight bearing can reduce fracture risk in patients who develop prodromal pain or a unilateral, atypical fracture, she said in an interview. Another option is prophylactic rod placement on their intact femur to reduce future fracture risk.

Dr. Ebeling said that he has served as a speaker for Merck, Eli Lilly, Novartis, and Sanofi-Aventis; that he has been on advisory boards for Merck, Amgen, and Novartis; has received educational grants from Amgen, Eli Lilly, and Sanofi-Aventis; and has received research grants from Merck, Novartis, and Amgen.