Atypical Fracture Risk Low for Bisphosphonates

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FROM THE NEW ENGLAND JOURNAL OF MEDICINE

The magnitude of the absolute risk for atypical fractures of the femoral shaft among women taking bisphosphonates is small, according to a recent report.

The absolute risk remains small even though there is a high prevalence of use of the drugs in patients who develop such fractures. Moreover, that risk is small enough to be easily outweighed by bisphosphonates' benefit in preventing fractures, said Dr. Jörg Schilcher of Linköping (Sweden) University and his associates.

These findings, which come from nationwide population-based analyses of data on all 12,777 women in Sweden who were aged 55 and older and sustained a femoral fracture in 2008, "should be reassuring for bisphosphonate users," they noted.

The American Society for Bone and Mineral Research has formed a task force report about the issue, ant the Food and Drug Administration has announced that it intends to monitor instances of such cases. There have also been several studies on the topic, but the authors of this report say that the studies were too small to establish or negate an association.

Another population-based study in longtime elderly bisphosphonate users in Ontario recently showed that the absolute risk of atypical fractures was 1 in 1,000 women (JAMA 2011;305:783-9).

The investigators first reviewed the radiographs of all femoral subtrochanteric and shaft fractures that were treated throughout Sweden that year. They identified the 1,234 cases among older women that resulted from falls.

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Major Finding: The difference in the absolute risk of atypical femoral fracture between users and nonusers of bisphosphonates was five cases per 10,000 patient-years; the number need to harm was 2,000 for every year of use.

Data Source: A nationwide cohort analysis of data on all 12,777 women aged 55 and older in Sweden who sustained a femoral fracture during 2008, and a population-based, case-control study of a subgroup of 322 of these patients.

Disclosures: This study was funded by the Swedish Research Council. Dr. Schilcher's associate reported ties to Eli Lilly and Amgen, and holds stock in AddBIO, a company that is attempting to commercialize a method for bisphosphonate coating of implants to be inserted in bone and that holds a patent on that method.

The researchers then identified 47 cases of typical stress fractures (transverse on the lateral side without intermediate fragments, plus a thickening of the lateral cortex at the fracture site and no involvement of the trochanteric or condylar areas).

A second group of 12 patients had suspected stress fractures with the same characteristics as the fractures in the first group, but either without a thickening of the lateral cortex or with an intermediate fragment.

In a case-control analysis, Dr. Schilcher and his associates compared the use of bisphosphonates between these 59 women and 263 women who were chosen as control subjects and did not have stress fractures but who did have breaks in similar locations.

The prevalence of bisphosphonate use was much higher among the subjects who had atypical stress fractures (78%) than it was among the control subjects (10%). However, the absolute risk of sustaining an atypical fracture while using bisphosphonates was small: five cases per 10,000 patient-years.

This translates to a number needed to harm of 2,000 for every year of use; that is, 2,000 patients would need to use bisphosphonate for one case of drug-related atypical fracture to occur per year, Dr. Schilcher and his colleagues reported (N. Engl. J. Med. 2011;364:1728-37).

Thus, "the benefits of fracture prevention with bisphosphonate use will greatly outweigh the risk of atypical femoral fracture," they wrote.

The risk of these atypical femoral fractures also appeared to be unrelated to the use of systemic glucocorticoids and other medications that affect bone. "It has been proposed that glucocorticoids and proton pump inhibitors are likely to contribute to the risk of atypical fractures, but our data suggest that this is not the case," they added.

The risk of atypical femoral fracture also was independent of coexisting conditions and of patient age in this study population.

Previous studies that suggested that bisphosphonates raised the absolute risk of atypical femoral fractures to an unacceptable degree "relied on registry data or hospital records," whereas this study relied on direct examination and classification of fractures from radiographs.

"The specific radiographic classification is important, since our analysis shows that the rare atypical femoral fracture will be overshadowed by other types of fractures in registry studies, impeding the detection of their association with bisphosphonates," the investigators noted.

This study was limited in that it did not assess long-term bisphosphonate use or bone density. It also included only women of Northern European ethnicity, so the results may not be generalizable to men and other ethnic groups, they added. ■