Bisphosphonates May Not Increase Fracture Risk

BY SHARON WORCESTER

The risk of subtrochanteric and diaphyseal femur fractures is not significantly increased in women who take bisphosphonates, even among those who are treated for up to 10 years, judging from findings from a secondary analysis of data from three large randomized bisphosphonate trials.

The findings follow several case reports that hinted at an increased risk of these atypical fractures in bisphosphonate users.

However, the current study, which included a review of 283 hip or femur fractures in 14,195 women with 51,287 patient-years of follow-up, showed that only 12 subtrochanteric or diaphyseal femur fractures occurred in 10 women, for a rate of 2.3 per 10,000 patient-years, Dennis M. Black, Ph.D., of the University of California, San Francisco, and his colleagues wrote.

The data that were analyzed in the current study were from the phase III Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial, and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT).

The relative hazard ratios for subtrochanteric and diaphyseal femur fractures were 1.03 for alendronate vs. placebo in FIT, 1.50 for zoledronic acid vs. placebo in HORIZON-PFT, and 1.33 for continued alendronate use vs. placebo in FLEX, the investigators reported (N. Engl. J. Med. 2010 March 24[doi10.1056/NEJMoa1001086]).

Even in the FLEX trial, which included up to 10 years of treatment with alendronate, the risk of femur fracture

and atypical femur fracture was very low, with no significantly increased risk of fracture among those who continued treatment for the full 10 years and those who discontinued treatment, they wrote.

Because radiographs in those with fractures were generally not available, atypical features—such as those associated with cortical thickness and fracture morphology—could not be assessed. If this information had been available, it is likely that the femoral fracture rate would be even lower, noted the investigators. The findings support those from population-based studies, including one that found evidence of an increased incidence of hip and femur fractures with alendronate use, but that attributed that finding to the increased use of alendronate in high-risk patients rather than to the use of alendronate.

More devastating fractures are prevented than are caused by bisphosphonates, but physicians should reevaluate patients on long-term therapy in the context of current guidelines.

"Although we can confidently conclude that absolute rates of such fractures are low, wide confidence intervals (resulting from the very low incidence of events) preclude definitive conclusions regarding the relative risk of treatment," the investigators wrote.

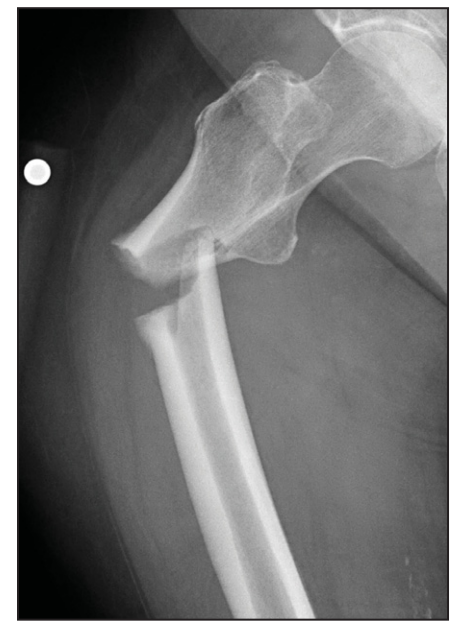
However, based on data they analyzed, the investigators estimated that 3 years of bisphosphonate treatment in 1,000 women with osteoporosis would prevent about 100 fractures, comprising 71 vertebral fractures and 29 nonvertebral fractures (including 11 hip fractures).

Balanced against the annual rate of 2.3 subtrochanteric and diaphyseal femur fractures that were seen in the three trials, "the hypothetical risk is quite small," they concluded

Additional research is needed to more fully address the matter of bisphosphonate use and the risk of subtrochanteric and diaphyseal fractures, Dr. Elizabeth Shane wrote in an accompanying editorial.

The current findings provide assurance that these types of fractures are extremely rare, and that many more common and equally devastating hip fractures are prevented than are caused by bisphosphonates.

That said, physicians should "reevaluate patients who are receiving long-term bisphosphonate therapy in the context of contemporary guidelines for treatment initiation, progress while receiving therapy, current bone mineral density measurement, and risk factors for fracture," wrote Dr. Shane of Columbia University, New York (N. Engl. J. Med. 2010 March 24 [doi:10.1056/NEJMe1003064]).



Courtesy Dr. Melvin Rosenwasser, Columbia University

X-ray shows an atypical fracture in a patient on bisphosphonates for years.

It is reasonable to consider drug holidays, particularly in those with substantially reduced levels of bone turnover markers, but again, the evidence of persistent antifracture efficacy after discontinuation must be balanced with data showing that 10 vs. 5 years of alendronate use is associated with significantly fewer new vertebral and nonvertebral fractures in those with bone mineral density T scores of –2.5 or lower, she wrote. ■

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