Bisphosphonates May Not Raise Fracture Risk

BY SHARON WORCESTER

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

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 at San Francisco and his colleagues wrote.

The data 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 the FLEX trial, 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.

Since radiographs in those with fractures were generally not available, atypical features could not be assessed; if this information were available, it is likely the femoral fracture rate would be even lower, they said.

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 which attributed that to increased use of alendronate in high-risk patients rather than to use of alendronate.

"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, including 71 vertebral fractures and 29 nonvertebral fractures—including 11 hip fractures. Balanced against the annual rate of 2.3 subtrochanteric and diaphyseal femur fractures seen in the three trials, "the hypothetical risk is quite small," they concluded

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

While 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, 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]).

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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CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Osteoporosis in Postmenopausal Women

BY NEIL S. SKOLNIK, M.D., AND LAUREN E. BAKER, D.O.

Osteoporosis is a leading cause of hip and spine fractures in postmenopausal women. Fifty percent of women with hip fractures have long-term loss of mobility, with about 25% requiring long-term care and 25% mortality within the first year of follow-up. The prevalence of osteoporosis increases from 4% in women aged 50-59 years to 52% in those older than 80 years. The North American Menopause Society (NAMS) recently issued guidelines (Menopause 2010;17:25-54).

Diagnosis

Bone strength depends on many factors, with bone mineral density (BMD) the most commonly measured. Results of BMD testing are reported as either a *z* score or a T score, expressed as standard deviation (SD) units. The T score is calculated by comparing a woman's current BMD with the mean peak BMD of a normal, young adult population of the same gender and is used in postmenopausal women. The *z* score is used in premenopausal women under age 50 years and compares a woman's BMD with the mean BMD of women their own age and ethnicity. A T score less than or equal to –2.5 at the total hip, femoral neck, or lumbar spine (AP, not lateral) defines osteoporosis. The presence of a fragility fracture imparts a clinical diagnosis of osteoporosis with or without low BMD. Osteopenia is defined as a T score between –1.0 and –2.5.

Clinical Risk Factors

Osteoporosis is silent and often only detected after a fracture occurs. Most nonvertebral fractures occur during falls. Vertebral fractures often occur spontaneously, with two-thirds of vertebral fractures occurring without pain. The combination of low BMD and increasing number of clinical risk factors increases the risk of fracture and has been incorporated into the World Health Organization's new FRAX tool to predict the 10-year risk of an osteoporotic fracture.

Evaluation

All postmenopausal women should be assessed for risk factors associated with osteoporosis and fracture. This includes history and physical examination, along with any necessary diagnostic tests.

The physical examination should include an annual measurement of height and weight as well as an assessment for chronic back pain, kyphosis, and clinical risk factors. BMD testing should be based on the woman's risk profile. NAMS recommends dual-energy x-ray absorptiometry (DXA) scans in the following populations:

- ► All women aged 65 years and over.
- ► Postmenopausal women with medical causes of bone loss (steroid use or hyperparathyroidism).
- ► Postmenopausal women who have had a fragility fracture.
- ► Postmenopausal women at least 50 years old with risk factors (fracture after menopause, thinness [less than 127 pounds or BMI less than 21], parental hip fracture, smoking, rheumatoid arthritis, and more than two units of alcohol daily).

Management

To reduce fracture risk, all postmenopausal women should be encouraged to eat a balanced diet, exercise, take adequate calcium (1,200 mg/day) and vitamin D (800-1,000 IU/day), avoid smoking and excessive alcohol, and institute preventive measures for falls. NAMS recommends adding pharmacologic management in the following populations:

- ► All postmenopausal women who have had an osteoporotic vertebral or hip fracture.
- ► All postmenopausal women with BMD values consistent with osteoporosis.
- ► All postmenopausal women who have T scores –1.0 to –2.5 and at least a 20% 10-year risk for major osteoporotic fracture or a 3% risk of hip fracture, based on FRAX assessment.

Treatment options include bisphosphonates, the selective estrogen-receptor modulator (SERM) raloxifene, parathyroid hormone (PTH), estrogens, and calcitonin. Bisphosphonates, considered first-line medications, reduce risk of vertebral fracture by 40%-70% and hip fractures by about 20%-35%. Medications in this class include alendronate, ibandronate, risedronate, and zoledronic acid.

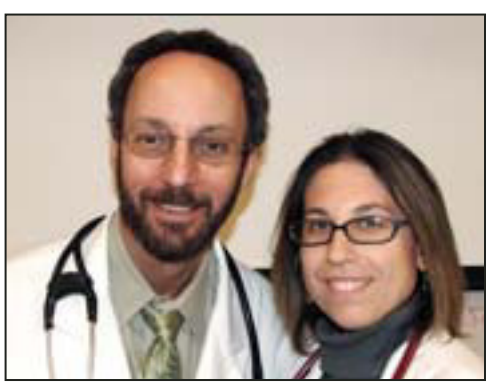
Raloxifene reduces the risk of vertebral fractures by 35%-55%, but its effect on hip and nonvertebral fractures is uncertain. Raloxifene also has been shown to decrease the risk of developing breast cancer and increase the risk of venous thromboembolism.

Teriparatide (PTH 1-34) may be used in postmenopausal women with osteoporosis who are at high risk for fracture. It has been shown to increase BMD and decrease both vertebral and nonvertebral fractures.

Systemic estrogens, with or without progesterone, are primarily used to treat moderate to severe menopausal symptoms and have been shown to increase BMD and decrease fracture risk. Calcitonin is effective at increasing BMD but is not a first-line drug because its bone-strengthening effect is not as good and its BMD effects are less than others.

Bottom Line

Age and risk factors determine which women should receive DXA scans. The FRAX tool combines clinical risk factors and BMD to give a 10-year calculated risk of osteoporotic fractures. Management should focus on lifestyle modifications, along with pharmacologic therapy when appropriate.



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