Atypical Fractures Rare With Bisphosphonates

BY NASEEM S. MILLER

FROM JAMA

Prolonged use of oral bisphosphonates is associated with an increased risk of subtrochanteric or femoral shaft fractures in older women. However, the absolute risk for these fractures is low, according to a large population-based study.

"There wasn't good research about what the absolute risk of the fractures was. This study adds that piece," lead author Laura Y. Park-Wyllie, Pharm.D., said in an interview.

During the 7-year study period, researchers found that women aged 68 years or older who used bisphosphonates for 5 years or longer were 2.74 times more likely to have subtrochanteric or femoral shaft fractures after minimal trauma, compared with women who took the medications transiently (JAMA 2011;305:783-9).

The study also showed that the absolute risk of such atypical fractures was at 1 in 1,000 women.

"If you combine all the information that we have about osteoporosis and the information we have about the risk versus benefits [of bisphosphonates] they would favor the continuation of treatment," Dr. Park-Wyllie said.

The growing number of reports on the issue and conflicting studies prompted the group to launch the study, said Dr. Park-Wyllie, a research fellow at Li Ka Shing Knowledge Institute of St. Michael's Hospital in Toronto.

The American Society for Bone and Mineral Research recently released a task force report about the issue. 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.

The absolute risk of subtrochanteric or femoral shaft fractures in women with at least 5 years of bisphosphonate therapy was at 1 in 1,000 patients.

The population-based, nested case-control study examined 205,466 women 68 years or older who were treated with bisphosphonates between April 1, 2002, and March 31, 2008. The women were followed until the first fracture, death, or end of the study. Women with a history of conditions that could affect bone integrity were excluded.

In the group, 716 women (0.35%) had subtrochanteric (411) or femoral shaft fractures (305). Each case was matched with up to five controls – 3,580 total – from the cohort not hospitalized for either type of fracture, according to the study.

When compared with women who had used bisphosphonates transiently during the study period (less than 100 days in total), women who used the medication for 5 years or longer had an increased risk of subtrochanteric or femoral shaft fracture, the authors concluded.

To validate their findings, the investigators also conducted a secondary analysis, examining the risk of typical osteoporotic fractures among women who used bisphosphonates for 5 years or more, compared with women who used the medication transiently. Of the cohort, 9,723 women sustained femoral neck or intertrochanteric region fractures. "As expected, we found that extended bisphosphonate use was associated with a reduced risk of fracture compared with transient use," the authors wrote.

The absolute risk was estimated from 52,595 women in the cohort with at least 5 years of bisphosphonate therapy. Seventy-one, or 0.13%, sustained subtrochanteric or femoral shaft fractures during the following year and 117 (0.22%) within 2 years.

The authors noted that during their study period (2002-2008) only a small proportion of the cohort received 5 or more years of bisphosphonate therapy. "It is likely that the prevalence of long-term bisphosphonate exposure will increase over time as more women achieve 5 cumulative years of therapy because these drugs are still relatively new and because sustained adherence to bisphosphonates is actively promoted in the community setting," they wrote.

The study should not deter physicians and patients from the use of bisphosphonates, they said, noting that typical hip fractures were far more common than were subtrochanteric or femoral shaft fractures during the study period (9,723 vs. 716).

One of the coauthors – Muhammad M. Mamdani, Pharm.D. – reported financial relationships with Boehringer Ingelheim, Janssen-Ortho, Novartis, and Pfizer. The study was funded by the Ontario Ministry of Health and Long-Term Care. ■

Denosumab Curbs Fractures Equally at All Risk Levels

BY MIRIAM E. TUCKER

FROM THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM

Denosumab reduced the incidence of new vertebral and hip fractures in postmenopausal women with osteoporosis at both higher and lower risk for fracture, in a post-hoc analysis of data from the FREEDOM trial.

The monoclonal antibody denosumab (Prolia) was approved in June 2010 for treatment of postmenopausal women who have a high risk of osteoporotic fractures. In phase II and III trials, denosumab rapidly decreased bone resorption markers and increased bone mineral density at all skeletal sites, compared with placebo, said Dr. S. Boonen of Leuven (Belgium) University and his associates (J. Clin. Endocrinol. Metab. 2011;96 [doi:10.1210/jc.2010-2784]).

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial enrolled 7,808 postmenopausal women aged 60-80 years with osteoporosis to receive either a subcutaneous injection of denosumab (60 mg) or placebo along with daily calcium and vitamin D supplements every 6 months. All subjects had bone mineral density (BMD) T scores of less than –2.5 but not less than –4.0 at the lumbar spine or total hip. At 36 months, denosumab was associated with reductions of 68% in vertebral fracture and 40% in hip fracture (N. Engl. J. Med. 2009;361:756-65).

The new analysis compared high-risk and low-risk groups within the FREEDOM population. High-risk groups included women with two or more preexisting vertebral fractures of any degree of deformity, or one or more vertebral fractures of moderate or severe deformity, or both; a femoral neck BMD T score of –2.5 or less; or both multiple and/or moderate or severe vertebral deformities and a femoral neck BMD T score of –2.5 or less.

For hip fractures, the higher-risk subgroups included women who were age 75 years or older; had a femoral neck BMD T score of –2.5 or less; or were 75 years or older with a femoral neck BMD T score of –2.5 or less. Women who did not have those specified risk factors were included in the lower-risk subgroups.

Over 3 years, denosumab treatment was equally effective at reducing the risk of new vertebral fractures in women at both higher and lower risk for those types of fractures, similar to the overall FREEDOM population. Compared with placebo, denosumab reduced the incidence of vertebral fracture in the subgroups at higher risk by prevalent vertebral fracture status by 9.2% (16.6% placebo vs. 7.5% denosumab) in those at risk via baseline femoral neck BMD T score of –2.5 by 6.8% (9.9% vs. 3.1%), and in those with both risk factors by 12.3% (20.1% vs. 8.1%), Dr. Boonen and associates said.

The numbers needed to treat to prevent one vertebral fracture in each of these higher-risk subgroups were 11, 15, and 12, respectively.

Similar results were seen for the lower-risk groups, including a 4.4% absolute risk reduction in those without prevalent vertebral fracture, 3.7% for those with BMD T score greater than –2.5, and 4.5% for those with without one or both risk factors. Subgroup results for hip fractures were also consistent with the findings from the overall FREEDOM population, with the same efficacy of denosumab consistent across patients with different levels of risk. Compared with placebo, denosumab treatment significantly reduced the incidence of hip fracture among those aged 75 years or older by 1.4% (2.3% placebo vs. 0.9% denosumab); those with a baseline femoral neck BMD T score of –2.5 or less by 1.4% (2.8% vs. 1.4%); and by 2.4% among those with both risk factors (4.1% vs. 1.7%).

"It is reassuring to see that the effect is similar across a range of fracture risk. ... The FDA-approved indication for denosumab is for 'postmenopausal women at high risk of fracture,' but the FREEDOM trial was not enriched with 'women at high risk,' " noted Dr. Nelson Watts, director of the University of Cincinnati Bone Health and Osteoporosis Center, in an interview. Risk reduction for hip fractures was low in the lower-risk subgroups because the incidence of hip fractures was low, and the difference between the denosumab and placebo groups was therefore not statistically significant. Adverse event incidences were also not statistically different between the treatment groups within any of the higher- and lower-risk subgroups, and were consistent with the adverse event incidences for the overall FREEDOM trial, the investigators said.

Overall mortality was lower – but not significantly so – among all the subgroups with denosumab. However, there was a significantly lower incidence of fatal adverse events with denosumab vs. placebo in the higher-risk group with prevalent vertebral fracture (1.8% vs. 4.9%) and in those with both prevalent vertebral fracture and low femoral neck BMD (1.6% vs. 7.1%). The difference in mortality among the higher-risk subgroups was greater than that of the lower-risk groups, they noted.

The reason for the mortality difference is unclear, Dr. Watts said. "This was not an end point in the main trail and only significant in a small subgroup of high risk patients. It's clear that women who fracture have decreased survival, so it's logical that preventing fracture would reduce mortality."

The study was funded by Amgen Inc., from which Dr. Boonen has received renumeration for research, consulting, and lecturing. Four of the study's coinvestigators are employees of Amgen, and the others disclosed relationships with Amgen and several other pharmaceutical companies.

Dr. Watts is director, cofounder, and owner OsteoDynamics and holds stock and patents. He has received fees and/or honoraria from numerous drug companies including Amgen, Novartis, Warner Chilcott, Johnson & Johnson, Merck, and Takeda, and Vivus. ■