

Lasofloxifene Cuts Fractures After Menopause

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BY MARY ANN MOON

The investigational drug lasofloxifene decreases the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis, according to a report.

The nonsteroidal selective estrogen-receptor modulator (SERM) also reduces the risk of ER-positive breast cancer, major coronary heart disease events, and stroke without raising the risk of endometrial cancer or hyperplasia.

Like other SERMs, lasofloxifene raises the risk of venous thromboembolism and increases the rate of hot flashes and leg cramps, wrote Dr. Steven R. Cummings of California Pacific Medical Center Research Institute, San Francisco, and his associates in the Postmenopausal Evaluation and Risk-Reduction with Lasofloxifene (PEARL) study.

Taken together, these findings seem to indicate that lasofloxifene performs somewhat better than do other SERMs such as raloxifene, and also has advantages over hormone therapy, tamoxifen, and tibolone.

However, in an editorial accompanying this report, Dr. Carolyn Becker of the division of endocrinology, diabetes, and hypertension at Brigham and Women's Hospital, Boston, argued that the drug "offers no major clinically important

benefits over raloxifene for the skeleton, breast, heart, or reproductive tract.

"Given the plethora of drugs currently available for osteoporosis, studies of new agents should show clear benefits over existing agents," she wrote. Results of the PEARL study do not do so, Dr. Becker added.

Dr. Cummings and his colleagues performed the international, randomized, placebo-controlled PEARL study in 8,556 women aged 59-80 years who had a bone mineral density T score of -2.5 or less at the lumbar spine or femoral neck. A total of 28% already had at least one vertebral fracture at baseline.

After 5 years of follow-up, women who received 0.5 mg per day of lasofloxifene showed a 42% reduction in relative risk for vertebral fractures and a 24% reduction in relative risk for nonvertebral fractures, compared with those who received placebo.

Bone density at the lumbar spine, femoral neck, and total hip improved by about 3% with the active drug, the investigators said (N. Engl. J. Med. 2010;362:686-96).

This decrease in risk of vertebral fractures is comparable with that reported in women taking raloxifene, estrogen therapy, oral bisphosphonates, and tibolone.

The decrease in risk of nonvertebral

fractures also is similar to that observed in women taking other antiresorptive therapies, and it stands in contrast to raloxifene's inability to reduce this risk, they said.

However, Dr. Becker noted in her editorial that nearly all the reduction in risk for nonvertebral fractures could be attributed to forearm and wrist fractures. "A significant effect in the overall group was not evident until 5 years, and absolute risk reductions were very small.

"On balance, lasofloxifene seems to offer little, if any, advantage over raloxifene as an agent against osteoporosis," she said (N. Engl. J. Med. 2010;362:752-4).

Lasofloxifene also reduced the risk of ER-positive breast cancer by 85%, compared with placebo. Although this finding is "impressive," it is similar to the risk reduction reported for raloxifene, Dr. Becker added.

Lasofloxifene was associated with a 32% reduction in relative risk of coronary heart disease events (5.1 cases per 1,000 person-years) and a 36% reduction in relative risk of stroke (2.5 cases per 1,000 person-years), compared with placebo (7.5 and 3.9 cases per 1,000 person-years, respectively), Dr. Cummings and his associates said.

However, Dr. Becker noted that the number of these events was quite small, and there were no differences in rates of fatal stroke. "Although the cardiovascular benefits reported in the PEARL trial seem impressive, one would need to

treat 492 patients for 1 year to prevent a single major coronary event," she said.

The PEARL investigators said that lasofloxifene raised the risk of venous thromboembolism to a similar degree as do raloxifene, tamoxifen, and oral estrogen therapies. Like these agents, lasofloxifene also significantly increased the rate of hot flashes and leg cramps. It did not raise the risk of endometrial cancer or endometrial hyperplasia.

Dr. Becker countered that although the increase in absolute risk of venous thromboembolism was small, lasofloxifene more than doubled the relative risk.

In addition, rates of uterine polyps, endometrial hypertrophy, and vaginal candidiasis all were significantly higher than with placebo, she said.

Pfizer submitted a new drug application to the Food and Drug Administration in 2007, and in 2008 an advisory panel voted 9-3 that the benefits of the SERM outweighed this risk in postmenopausal women with osteoporosis. The FDA has not yet issued a decision. ■

Disclosures: The PEARL study was funded by Pfizer, manufacturer of lasofloxifene. Dr. Cummings reported receiving consulting fees from Amgen, Eli Lilly, GlaxoSmithKline, and Organon, lecture fees from Eli Lilly and Novartis, and grant support from Amgen, Pfizer, and Eli Lilly. Dr. Becker's financial disclosures are available with the text of the article at NEJM.org.

Role of Bisphosphonates in Atypical Fracture Downplayed

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 the FIT trial, 1.50 for zoledronic acid vs. placebo in the HORIZON-PFT trial, and 1.33 for continued alendronate use vs. placebo in the FLEX trial, the investigators reported (N. Engl. J. Med. 2010 March 24 [doi:10.1056/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, they wrote.

Since 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 were available, it is likely the femoral fracture rate would be even lower, they said.

The findings support those from population base studied, including one that found evidence of an increased incidence of hip and femur fractures with alendronate use, but which attributed that to the increased use of alendronate in high-risk patients rather than to the 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 the matter of 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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