Premenopausal Night Sweats May Herald Low BMD

Skeletal health should be optimized—further deterioration in BMD is likely after menopause.

BY KATE JOHNSON
Montreal Bureau

New Orleans — Premenopausal vasomotor symptoms, particularly night sweats, are a previously unrecognized risk factor for low bone mineral density and enhanced bone turnover in infertile women—and probably in fertile women as well, although this has not yet been confirmed, according to Dr. Lubna Pal of the Albert Einstein College of Medicine, New York.

Her study won the prize paper award from the Society for Reproductive Endocrinology and Infertility at the annual meeting of the American Society for Reproductive Medicine.

Based on these data, "I would advise providers to specifically ask about vasomotor symptoms in premenopausal women and, for those who are symptomatic, to focus on unmasking additional factors that may enhance their fracture risk, such as low body mass; family or personal history of fractures; or smoking," she said in an interview. "I don't think we are there yet in terms of recommending bone density screening for this population … but these women need to be advised that a further deterioration in their bone density parameters is likely to occur in the postmenopausal period, and measures to optimize skeletal health should be addressed now rather than later."

The cross-sectional study included 86 premenopausal infertile women aged 42 years or younger without premature ovarian failure or oophorectomy. A questionnaire was used to ask about the presence and frequency of vasomotor symptoms, including hot flashes and night sweats. The study also measured subjects' bone mineral density (BMD) and levels of serum N-telopeptide (NTx), a marker of bone turnover.

A total of 12% of respondents reported one or both vasomotor symptoms, and 21% of respondents had evidence of low BMD, Dr. Pal reported at the meeting.

There was a highly significant correlation between vasomotor symptoms and low BMD, with 62.5% of symptomatic women showing evidence of low BMD, compared with 14% of asymptomatic women (odds ratio 10.18). Similarly, 36% of women with low BMD reported vasomotor symptoms, compared with 5% of those with normal BMD.

After controlling for age, body mass index, menstrual regularity, race, and smoking, the study found that vasomotor symptoms (night sweats and/or hot flashes) were independent predictors of low bone density in the study population. The magnitude of this association was most robust for night sweats, with an adjusted odds ratio (AOR) of 52.47, followed by both symptoms combined (AOR 24.10), and then hot flashes alone (AOR 15.10).

The presence of night sweats was also an independent predictor of bone turnover, with higher levels of serum NTx seen in symptomatic compared with asymptomatic women, she said.

And finally, levels of inhibin B, a marker of ovarian reserve, were also significantly lower in women with night sweats compared with asymptomatic women, "suggesting that declining ovarian reserve may be a unifying physiologic mechanism tying vasomotor symptoms to both increased bone turnover and low bone density in this young population," she said.

"I anticipate that the association between vasomotor symptoms and low bone density in the premenopause will hold true for fertile women, but I have not yet studied this population," Dr. Pal said. ■

Once-Yearly Bisphosphonate Infusion Slashes Fracture Rates

BY KERRI WACHTER
Senior Writer

Philadelphia — Once-yearly therapy with zoledronic acid has resulted in impressive reductions in fracture incidence at the three most common fracture sites in postmenopausal women with osteoporosis, according to phase III findings presented at the annual meeting of the American Society for Bone and Mineral Research.

An annual infusion of 5 mg of zoledronic acid (Reclast) reduced clinical vertebral fractures by 75%, hip fractures by 40%, and nonvertebral fractures by 25% at the end of 3 years, said Dennis Black, Ph.D., a professor of epidemiology at the University of California, San Francisco.

Zoledronic acid is currently FDA approved (under the name Zometa) for the treatment of patients with hypercalcemia of malignancy, multiple myeloma, and documented bone metastases from solid tumors. The company is working with the FDA to gain approval for the treatment of osteoporosis.

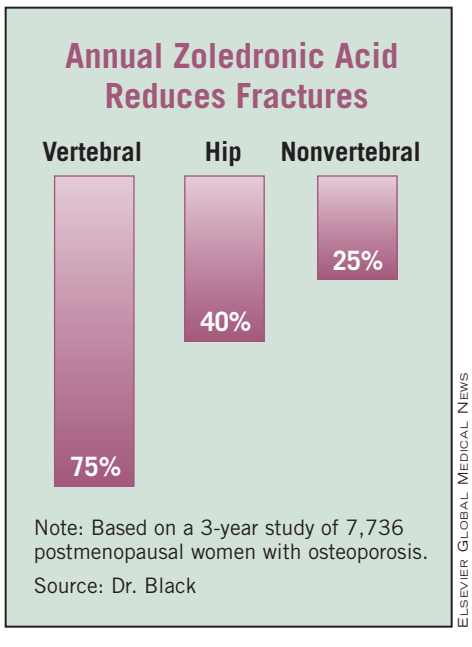
The Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly (Horizon) Pivotal Fracture Trial was a randomized, double-blind, placebo-controlled trial involving 7,736 postmenopausal women with osteoporosis from 27 countries. The trial was funded by Novartis; Dr. Black disclosed a significant financial relationship with Novartis.

In the trial, women randomized to the treatment group received an annual infusion of zoledronic acid (5 mg). All women received calcium (1,000-1,500 mg/day) and vitamin D (400-1,200 IU/day).

Women were included in the trial if they were aged 65-89 years (mean age, 73 years) with either a femoral neck T score of –2.5 or less or prevalent vertebral fracture and a femoral neck T score of –1.5 or less.

Women were recruited into two groups based on their osteoporosis treatment history. A total of 6,084 women were not currently taking an osteoporosis drug and had minimal prior therapy; 1,652 women were currently taking a selective estrogen-receptor modulator, calcitonin, or hormone therapy for osteoporosis at baseline.

Primary end points included new morphologic vertebral fractures in women not currently taking an osteoporosis drug and hip fractures in both those undergoing and those not undergoing treatment at baseline. Secondary end points included nonvertebral fractures, change in bone mineral density (BMD) measured by dual-energy x-ray absorptiometry, changes in biochemical markers of bone metabolism, and changes in bone density and size determined by quantitative CT. Safety end points included evaluation of adverse events, assessment of bone histology by histomorphometry, and postdose monitoring for acute changes in renal laboratory values.



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A total of 3,875 women were randomized to zoledronic acid (3,045 in stratum I and 830 in stratum II), while 3,861 were randomized to placebo (3,039 in stratum I and 822 in stratum II). Dr. Black presented data from the trial start-up to March 31, 2006 (the study was scheduled to end in June 2006). Mean follow-up was 2 years and 8 months. Retention was 84%.

Overall, 3.8% of women receiving treatment had morphometric vertebral fractures at 3 years, compared with 12.8% of women on placebo, representing a 70% reduction. During the first 2 years, there was a 71% reduction, and during the first year, there was a 60% reduction.

"There was a 40% reduction in the risk of hip fractures [at 3 years] that was also highly statistically significant," Dr. Black said. Clinical vertebral fractures were reduced by 75% and nonvertebral fractures were reduced by 25% in treated women, compared with those on placebo. Lumbar spine BMD was increased by 7% and total hip BMD was increased by 6% in treated women, compared with those on placebo.

In addition, bone markers were measured in a subsample of 605 women (300 on zoledronic acid and 305 on placebo). There was a decline in beta C-telopeptide of type 1 collagen (β-CTX), a bone resorption marker, following the first infusion. "The values remain relatively constant over the 36 months of the study," Dr. Black said.

The mean β-CTX values for women on zoledronic acid remained within the premenopausal reference range. There was no progressive decline in β-CTX levels over 3 years.

Additional sampling was performed just after the third infusion at 24 months to determine in more detail how β-CTX levels responded to zoledronic acid infusion. "There is an immediate decline in β-CTX values within 10 days after the infusion. But then the levels begin to increase fairly linearly over the course of that third year," Dr. Black said.

Likewise, there was a decline in bone-specific alkaline phosphatase values following the first infusion of zoledronic acid, but the values remained fairly constant with no progressive decline following subsequent infusions. These values were also within the reference range for premenopausal women.

There were no differences between the treatment and placebo groups in terms of any adverse event, serious adverse events, or discontinuations due to adverse events.

Postdose symptoms were defined as any adverse experience occurring up to 3 days after an infusion. The five most common postdose symptoms were pyrexia, myalgia, flu-like symptoms, headache, and arthralgia. There was "a dramatic decline in the rate of postdose symptoms with the second and third infusions, compared with the first," Dr. Black said.

Short-term renal safety was monitored by measuring serum creatinine levels at days 9-11 in more than 4,000 subjects. There were transient rises in serum creatinine but in only a very small number of patients. All of the rises resolved, and patients were redosed at their next infusion. Based on these results and other measures of renal safety, the researchers concluded that zoledronic acid infusions had no cumulative impact on renal function.

In terms of cardiac safety, atrial fibrillation was more common in the women on zoledronic acid (1.2%) than in the women on placebo (0.4%). In electrocardiogram studies of 559 women at 9-11 days following the third infusion, there were no differences between the two groups.

There were no spontaneous adverse event reports of osteonecrosis of the jaw. The researchers also searched the database for terms related to the condition. Using the definition "exposed bone in the mouth for longer than 6 weeks," three cases were identified—two subjects on placebo and one subject on zoledronic acid. All three healed with antibiotic treatment. ■