Fracture Risk Assessment Must Be Multifaceted

BY NANCY WALSH
New York Bureau

NEW YORK — Overtreatment for low bone mass has been all too common in women aged 50-60 years since the introduction of the bisphosphonate drugs and the widespread use of bone scans, according to Dr. Stephen Honig.

Routine bone scanning at menopause—very common in this country—creates difficulties in treatment decisions for clinicians, because when low bone density is uncovered in the early postmenopausal years it generally is in the range of osteopenia, not osteoporosis.

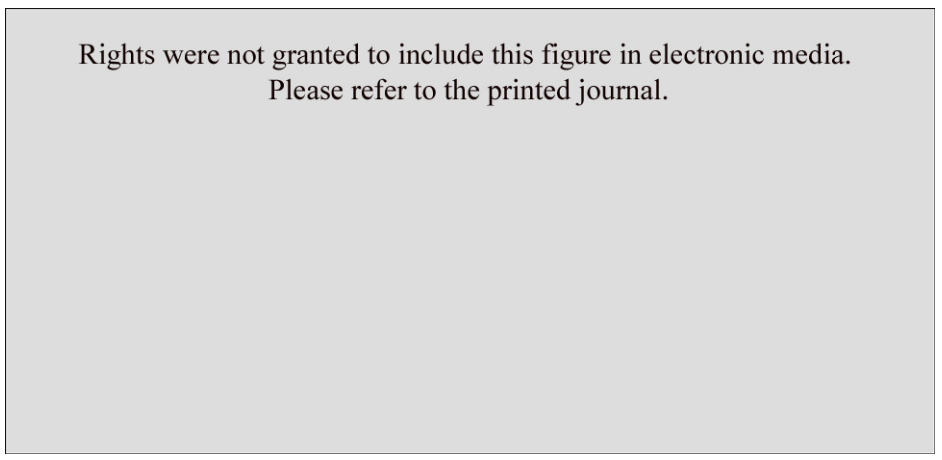
"A common scenario has been a 50-year-old woman who has her last period, goes for a bone scan, and has a spinal T score of –2.2. She's given a prescription for Fosamax, and 10 years later she's still on the drug," Dr. Honig said at a rheumatology meeting sponsored by New York University.

It's important to recognize that for women in the early years after menopause, a bone mineral density measurement does not provide the clinician with enough information to make appropriate treatment decisions.

What is needed is an understanding of an individual woman's risk of fracture in the short and intermediate term, balanced against the consequences of adverse events and the possibility of subtrochanteric fractures associated with excessive suppression of bone turnover.

"We want to avoid overtreating—too much drug, too soon, for too long—and of course we also want to avoid undertreating," he said, adding that many women in their 60s and most women in their 70s can benefit from bone-strengthening therapy.

"For women in their 50s, however, what we really need to know is who is at risk for fracture, not just who has osteopenia," said Dr. Honig of New York University, New York.



Subtrochanteric fracture is seen in a patient who had been on bisphosphonate therapy. BMD measurement alone may not accurately predict fracture risk.

Fractures in women of this age are not simply a result of bone loss. Fractures occur when mechanical forces overcome the bone's capacity for resistance. This bone strength is dependent on structural and material properties of the bone, including size, shape, trabecular architecture, and mineral-to-matrix ratio.

Clearly, other factors also contribute. In the National Osteoporosis Risk Assessment (NORA), which included 200,160 women aged 50 years and older, factors significantly associated with fractures included low bone mineral density, poor health status, personal or family history of fracture, maternal history of osteoporosis, no current hormone replacement therapy, menopause before age 40, corticosteroid use, and current smoking.

Analysis of the NORA data also found that the most important determinants of 3-year fracture risk in women aged 50-64 years were prior fracture, T score at or below –1.1, and self-reported fair/poor health status, with fracture risks of 7.2%, 3.1%, and 2.4%, respectively (Osteoporos. Int. 2007;18:1287-96).

A further difference in fracture risk between women in the early postmenopausal years and those who are older is that the fracture of primary concern is not the hip, but the wrist/forearm. In the Danish Osteoporosis Prevention Study, 872 women whose mean age was 51 years were followed for 10 years.

During that time, 80 fractures occurred in 78 women. There were a total of 64 in the forearm, 8 in the spine, 7 in the proximal humerus, and only 1 in the hip (J. Bone Miner. Res. 2006;21:796-800).

Studies have shown that at menopause, the rate of falls among women begins to increase dramatically. In a study from the United Kingdom that analyzed 90,061 accidents, 38,737 were classified as "underfoot" (events such as slipping or tripping). Among women overall, 51% of accidents were underfoot, as were 32% of accidents in men, but after the age of 50 these numbers increased to 64% in women and 43% in men (Q. J. Med. 2001;94:699-707).

It turns out estrogen has a critical role in postural stability, Dr. Honig said. Declining estradiol levels are associated with decreasing ability to maintain balance, slower reaction and movement times, and lower muscle strength—all of which contribute to falling and injury.

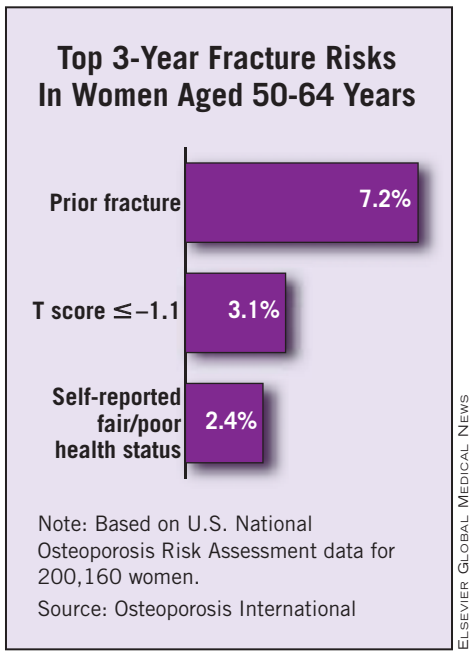
"Most clinicians never give a second thought to the issue of balance in a 50-year-old woman," Dr. Honig said.

Having a fall-related fracture also is a risk factor for an additional fracture. Longer-term follow-up of the NORA cohort found that over 3 years, a prior wrist fracture increased the risk of a future wrist fracture about threefold and doubled the risk of any osteoporotic fracture (Osteoporos. Int. 2008;19:607-13).

In conclusion, healthy young postmenopausal women with low bone mass and no recent fracture history have a low 1- to 3-year risk of fracturing, Dr. Honig said. For these patients, according to new 2008 guidelines from the National Osteoporosis Foundation, treatment should be initiated only if their 10-year hip fracture probability is 3% or greater or their 10-year all-fracture probability is 20% or greater, based on the U.S.-adapted World Health Organization absolute fracture risk model.

The guidelines are available on the Web site of the National Osteoporosis Foundation, at www.nof.org, and a tool for calculating 10-year risk can be found at www.shef.ac.uk/FRAX.

Dr. Honig serves on the speakers bureau of Novartis Pharmaceuticals Corp. ■



Study: Bazedoxifene Prevents Postmenopausal Osteoporosis

BY GREG MUIRHEAD
Contributing Writer

HONOLULU — Bazedoxifene is effective in preventing osteoporosis in postmenopausal women, according to the results of a 2-year, phase III, placebo-controlled trial presented at the annual meeting of the American Society for Bone and Mineral Research.

"In relatively young, healthy, postmenopausal women with normal or low bone mineral density, bazedoxifene treatment prevented bone loss, reduced bone turnover, was generally well tolerated, had a neutral effect on endometrial tissue, and, for the primary end point, had similar BMD efficacy as raloxifene, " said Dr. Paul D. Miller, of the University of Colorado Medical Center, Denver. In addition, "bazedoxifene had a favorable risk-benefit profile, supporting its use for the prevention of postmenopausal early bone loss."

A novel selective estrogen receptor modulator, bazedoxifene has been under development as monotherapy for the prevention and treatment of postmenopausal osteoporosis. In late April 2007, the Food and Drug Administration issued an approvable letter for bazedoxifene for the prevention of postmenopausal osteoporosis; this study was designed to assess the efficacy and safety of the drug for this purpose.

Study participants were healthy postmenopausal women aged 45 years, whose femoral neck bone or lumbar spine T scores were not less than –2.5. Women with vasomotor symptoms that required treatment, as well as those with bone diseases, previous vertebral fractures, or endometrial hyperplasia, were excluded.

In the trial, a total of 1,583 postmenopausal women were randomized to daily bazedoxifene regimens of 10 mg, 20 mg, or 40 mg, or to raloxifene (60 mg), or to placebo. In addition, all women received a daily calcium supplement of 600 mg.

Of 1,583 women enrolled, 1,113 (70%) completed the 2-year study. More than 90% of women in each treatment group were white. Mean body mass index (kg/m^2) in the different treatment groups ranged from 25.3 to 25.9, and the mean number of years since menopause ranged from 10.7 to 11.3 (mean age 57.6 years).

The primary outcome was the percent change in the BMD of the lumbar spine after 24 months of treatment. BMD at other skeletal sites was a secondary outcome.

By month 24 of treatment, BMD loss was prevented in all treatment groups with the exception of women using placebo, who experienced a significant decline in BMD. More specifically, the percent change in lumbar spine BMD from baseline—relative to placebo—was 1.1%, 1.4%, and 1.5%, for bazedoxifene 10 mg, 20 mg, and 40 mg, respectively; it was 1.5% for raloxifene 60 mg (*P* less than .001). Similar dose-response results were found at other skeletal sites for women using bazedoxifene.

Adverse event rates were similar among treatment groups, as were serious adverse event rates and adverse event-caused discontinuations.

Vasodilation was found more often in patients using bazedoxifene 20 mg (20%) and 40 mg (23%) and raloxifene 60 mg (18%), compared with those using placebo (13%). Other cardiovascular adverse event rates were similarly low in all treatment groups. All treatment groups had a similar incidence of leg cramps, ranging from 9% to nearly 12%. All treatment groups had a low incidence of venous thrombotic adverse events, including fewer than 1% of patients using bazedoxifene at any dosage.

The study was supported by Wyeth Research and Wyeth Pharmaceuticals. Dr. Miller also disclosed various financial relationships to a number of research companies, including Wyeth. ■