Fracture Risk Factors Not Predictive for Raloxifene

BY KERRI WACHTER
Senior Writer

WASHINGTON — Risk factors for fracture in women with coronary heart disease or at increased risk for coronary heart disease do not predict the likelihood that treatment with raloxifene (Evista) will reduce the incidence of clinical vertebral or nonvertebral fractures.

The findings are derived from a secondary data analysis of women enrolled in the Raloxifene Use for the Heart (RUTH) study presented at an international symposium sponsored by the National Osteoporosis Foundation.

In the main study, 5,057 postmenopausal women treated with raloxifene (60 mg/day) had a reduced incidence of clinical vertebral fractures, compared with 5,044 women on placebo. The drug had no effect on overall incidence of nonvertebral fractures, said Dr. Jane A. Cauley, vice chair for research and professor of epidemiology at the University of Pittsburgh, who presented the findings on behalf of her colleague Dr. Kristine E. Ensrud of the University of Minnesota, Minneapolis.

The women were selected for the RUTH study because they had established coronary heart disease (CHD) or were at elevated risk for CHD, not because they were at risk for fracture. "We wanted to explore whether the effect of raloxifene in this population differed by risk factors for osteoporosis," said Dr. Cauley, who disclosed that she has significant financial relationships with several pharmaceutical companies, including Eli Lilly & Co., which makes Evista and supported the study.

For the study, the women had to be at least 55 years old and postmenopausal for at least 1 year. The women had either an office visit or a telephone contact biannually. Fracture risk factors were assessed at baseline, but bone mineral density was not measured. Clinical vertebral and nonvertebral fractures were ascertained at each biannual visit or telephone contact and were confirmed by x-ray or medical records. The women were followed for an average of 5.6 years.

Risk factors for fracture included older age, smoking, lack of exercise, prior fractures since the age of 50, family history of hip fracture, diabetes, and certain medications (including hormones, thyroid hormone, and statins). Women were also assessed for body mass index (BMI) and were asked about weight loss in the previous year.

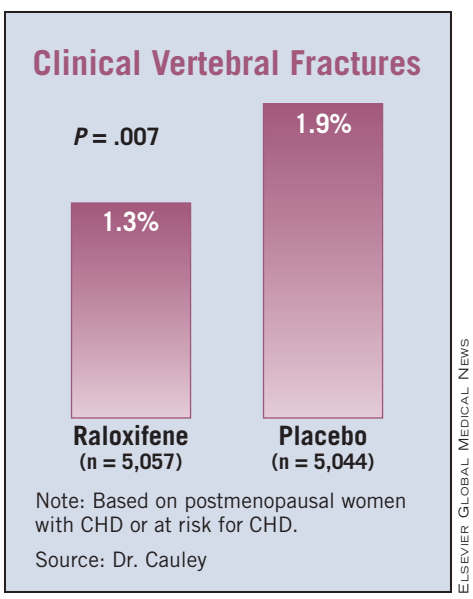
The average age for both the treatment group and the placebo group was 68 years, and women older than 70 years accounted for 39%. The women were predominantly white (84% in both groups). About 6% of women in each group had a history of a fracture, whereas almost 10% in each group had a family history of fracture. About 20% of women in both groups had a history of hormone therapy. Both groups had an average BMI of 29 kg/m^2.

The final regression model for nonvertebral fractures included older age, prior fracture history, and family history of hip fracture. The final regression model for clinical vertebral fractures included age and prior use of hormone therapy.

"There was no difference in the effect of raloxifene on nonvertebral fractures for any of the [individual] risk factors that we examined," Dr. Cauley said. Likewise, whereas there was an overall reduction in clinical vertebral fractures for women on raloxifene, the reduction in treated women was similar regardless of which risk factor was assessed.

In the original study, researchers found no significant difference between the two groups in the primary end point of incidence of death from coronary causes, nonfatal MI, or hospitalization for acute coronary syndrome.

Raloxifene did reduce the incidence of invasive breast cancer (hazard ratio 0.56), primarily because of a reduction in estrogen receptor–positive invasive breast cancer, another primary end point (N. Engl. J. Med. 2006;355:125-37). ■



T Scores Not the Last Word in Osteoporosis

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — A plateau in bone mineral density improvement while on antiresorptive therapy for osteoporosis does not mean the treatment has stopped working, Dr. Steven T. Harris said at a diabetes update sponsored by the University of California, San Francisco.

Explain this to patients at the start of therapy to avoid disappointment or worse when their T scores stop rising, suggested Dr. Harris, of the university.

The most important clinical objective is to prevent fractures, not to produce changes in surrogate markers like bone mineral density or biochemical markers of bone turnover, he emphasized.

The risk of fracture declines significantly despite a slight improvement in T score or even no change in T score in the first year on antiresorptive medication because of improvements in bone quality. The fracture protection continues while the patient is on therapy, despite no further changes in bone mineral density.

Antiresorptive agents such as bisphosphonates, selective estrogen receptor modifiers, calcitonin, and estrogen decrease bone resorption and bone formation. This typically produces an increase in bone mineral density in the first year of therapy and a smaller increase the second year, followed by a plateau. Despite the plateau, fracture protection continues.

"It is the rule, not the exception, that bone density goes up a little, then stabilizes. That is not nonresponse. That does not mean you have to change the therapy. That does not mean your patients are not taking their medications. This is physiology in action," Dr. Harris commented.

Explain this concept early to patients, because many of them logically assume that if a T score of –3.2 won them a diagnosis of osteoporosis, for example, then the goal of therapy is to get the T score back to zero. "As much as we'd all like to have the bone density of the average 19-year-old …it ain't happening, and it doesn't have to happen," he said.

Studies of the bisphosphonates risedronate and alendronate, for example, show that therapy increases spinal bone density 5%-8% and hip bone density by 3%-5% after 3 years in osteoporotic women.

"Not terribly impressive" numbers until you look at the fracture protection, he noted.

The drugs reduced the incidence of vertebral fractures by 40%-65% and the incidence of hip fractures by 40%-60%. "If you had asked me 4 years ago what I thought a 4% increase in bone density could accomplish," these benefits wouldn't have been guessed, Dr. Harris said. ■

IV Bisphosphonate Approved to Treat Paget's Disease of Bone

BY ELIZABETH MECHCATIE
Senior Writer

A 5-mg intravenous formulation of zoledronic acid has been approved by the Food and Drug Administration for treating Paget's disease of bone, based on 6-month studies that found that a single infusion resulted in superior and more sustained responses than did 60 days of daily treatment with an oral bisphosphonate.

The package insert says that treatment is indicated "to induce remission" in patients with elevations in serum alkaline phosphatase (ALP) that are at least two times the upper limit of the age-specific normal reference range, or in patients who are symptomatic or are at risk for complications from the disease. Remission is defined as normalization of serum ALP.

The 5-mg formulation of the potent bisphosphonate, marketed as Reclast by Novartis Pharmaceuticals Corp., is administered as a single intravenous infusion over 15 minutes. Reclast, which is under review at the FDA for approval as a treatment for postmenopausal osteoporosis, is approved for Paget's disease in more than 50 countries, according to Novartis.

In the two 6-month identical studies, published in 2005, of 347 men and women with moderate to severe radiographically confirmed Paget's disease—all of whom had serum ALP levels as stated in the indication—the patients received either a single infusion of Reclast at the start of the study or daily doses of 30 mg of risedronate (Actonel) for 60 days. At 6 months, 96% of those who received Reclast had had a therapeutic response (defined as normalization of the ALP level or a reduction of at least three-fourths of ALP excess), compared with 74% of those on risedronate.

Levels dropped significantly more rapidly among those on Reclast, and ALP levels normalized in nearly 90% of those on Reclast, versus 58% of those on risedronate, also highly significant. The higher response rates associated with Reclast were independent of age, sex, baseline ALP, and the presence or absence of previous therapies for Paget's.

Pain scores improved in both groups, and there were trends toward improved quality of life at 3 and 6 months, as measured with a patient questionnaire, among those on Reclast, with more mixed results among those on risedronate. During a mean 190-day extension of the study in patients who had had a therapeutic response, the therapeutic response was lost in nearly 26% of those on risedronate vs. 0.9% of those on Reclast.

Those who received the infusion had twice as many adverse events in the first 3 days of treatment, primarily influenzalike symptoms that were mild to moderate; most resolved after 4 days. The rates of GI and renal or urinary disorders were similar; one patient in each group had moderate increases in serum creatinine levels, and eight patients on Reclast and one patient on risedronate developed hypocalcemia (N. Engl. J. Med. 2005;353:898-908).

"There is quite a long biochemical and clinical remission when this drug is used," said Dr. Kenneth W. Lyles, professor of medicine at Duke University, Durham, N.C., who was one of the studies' authors. He disclosed that he has received research support from and serves as a consultant to Novartis.

Reclast is contraindicated in hypocalcemia and during pregnancy and lactation, and is not recommended for patients with severe renal impairment, according to the label. ■