Novel SERM Cut Postmenopausal Fractures

Lasofoxifene also reduced cancer and heart risks, but one expert says it's no better than existing agents.

BY MARY ANN MOON

VITALS

Major Finding: After 5 years, lasofoxifene reduced the risk of vertebral and nonvertebral fractures by 9.3 cases per 1,000 person-years (HR 0.58) and 5.8 cases per 1,000 person-years (HR 0.76), respectively, compared with placebo.

Data Source: The PEARL study, which randomized 8,556 postmenopausal women with osteoporosis to receive lasofoxifene or placebo for 5 years.

Disclosures: Dr. Cummings has received 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.

The investigational drug lasofoxifene decreased the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis in a large, randomized, placebo-controlled trial.

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, lasofoxifene raises the risk of venous thromboembolism and increases the rate of hot flushes 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 Lasofoxifene (PEARL) study.

Taken together, these findings seem to indicate that lasofoxifene 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 lasofoxifene 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, lasofoxifene seems to offer little, if any, advantage over raloxifene as an agent against osteoporosis," she said (N. Engl. J. Med. 2010;362;752-4).

Lasofoxifene 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.

Lasofoxifene 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 lasofoxifene raised the risk of venous thromboembolism to a similar degree as do raloxifene, tamoxifen, and oral estrogen therapies. Like these agents, lasofoxifene also significantly increased the rate of hot flushes 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, lasofoxifene 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.

The PEARL study was funded by Pfizer, manufacturer of lasofoxifene. 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.

Dr. Becker's financial disclosures are available with the text of the article at www.NEJM.org. ■

Gynecologists Are Not Routinely Assessing Bone Health

BY MARY ELLEN SCHNEIDER

Middle-aged women aren't being routinely assessed for osteoporosis during their ob.gyn. visits, despite this group's increased awareness of the condition, survey results released by the North American Menopause Society showed.

In a poll of 881 women, most of whom were either perimenopausal or postmenopausal, nearly all (98%) said they considered bone strength to be an important health concern. But 45% reported that osteoporosis was not addressed during their last routine ob.gyn. visit, and 26% said they had never discussed osteoporosis with their gynecologist.

Dr. Wulf H. Utian, the honorary founding president and executive director emeritus of the North American Menopause Society (NAMS), said that the survey shows there is more work to be done in raising awareness among ob.gyns. but that the results aren't a cause for concern. "Some important issues don't get attention during the consultation, and that may be a reflection of modern medicine and the limited time that's available," he said in an interview.

In fact, Dr. Utian said both the public and health care providers have significantly greater awareness of osteoporosis and bone health than they did only a decade ago.

But there are barriers to making bone health a regular part of ob.gyn. care, he said. One issue is a lack of reimbursement for performing bone density testing. In some instances, physicians may not be recommending bone density testing because they think it won't be reimbursed, and they believe they can get an adequate risk assessment without the test.

In other cases, physicians are recommending bone density testing, but patients are rejecting it because they will have to pay out of pocket, Dr. Utian said. In fact, the survey found that even though nearly 63% of women reported that their ob.gyn. had recommended a bone scan, 27% of women surveyed had never had one.

Barriers include reimbursement issues, confusion about who should be tested, a lack of communication regarding risk factors, and failure to take adequate patient histories.

Another barrier is the confusion among physicians about who should get a bone density test. There has been a good deal of variation among the recommendations coming out of various medical organizations, Dr. Utian said, creating a sense of uncertainty. In an effort to spell out more clearly the appropriate diagnosis, prevention, and treatment for postmenopausal osteoporosis, NAMS recently issued a new position statement on osteoporosis in midlife (February 2010, p. 1.).

In the position statement, NAMS recommends the use of the World Health Organization's FRAX (Fracture Risk Assessment) tool as well as increased vitamin D_3 intake. NAMS plans to take the scientific paper, which was issued last month, and translate it into a series of consumer education pieces, he said.

The NAMS survey also points to a possible communication gap between women and their ob.gyns. about the risk factors for osteoporosis. For example, among the women surveyed, 45 women said they had a broken bone in the past 5 years that occurred in a site associated with osteoporosis such as the hip, spine, wrist, collarbone, arm, leg, or pelvis. However, 35 of those women said their ob.gyn. was not aware of the break.

Additionally, while most women surveyed said that their ob.gyns. had told them that broken bones could be a sign of osteoporosis, the women were not as well informed about other possible consequences, including loss of height, dowager's hump, and disability or immobility.

The survey results could indicate that physicians are failing to take an adequate history during routine exams, Dr. Utian said. It also could mean that patients are failing to understand the association between bone fracture and menopause. "In other words, the woman doesn't tie the fact that she's had a fracture with anything that's to do with her visit to the gynecologist," he said.

Dr. Utian said that all gynecologists who see women in their middle years should routinely ask about risk factors for bone loss and fracture. ■