Extended Raloxifene Use Cuts Risk of Breast Ca

BY BRUCE JANCIN
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SAN ANTONIO — Raloxifene continued to markedly reduce breast cancer incidence in postmenopausal osteoporotic women over the course of 8 years in an extension of the landmark Multiple Outcomes of Raloxifene Evaluation trial, according to Silvana Martino, D.O., of the John Wayne Cancer Institute, Santa Monica, Calif.

An attempt to learn in the extended MORE study whether a single baseline serum estradiol measurement might identify subgroups of osteoporotic women who are particularly likely or unlikely to benefit from long-term raloxifene in terms of breast cancer risk reduction proved largely unsuccessful. The magnitude of reduction in invasive breast cancer with raloxifene turned out to be independent of estradiol level, although the absolute benefit was greater in women with a level of at least 5 pmol/L, Dr. Martino said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

MORE was a 4-year randomized double-blind trial in roughly 7,700 women that led to marketing approval of raloxifene (Evista), which is a selective estrogen-receptor modifier (SERM) for prevention and treatment of postmenopausal osteoporosis. Among the predefined secondary end points in MORE was the incidence of invasive breast cancer, which was 72% less with raloxifene, compared with placebo.

Because breast cancer incidence was a secondary end point in MORE, however, an extension trial—the Continuing Outcomes Relevant to Evista (CORE) study—was undertaken to evaluate the safety and efficacy of an additional 4 years of raloxifene use, this time with invasive breast cancer prevention as the primary outcome measure. A total of 3,510 postmenopausal osteoporotic women randomized to raloxifene in MORE were assigned to an additional 4 years of the SERM at 60 mg per day. In addition, 1,703 women from the MORE placebo arm continued on placebo.

MORE and CORE were sponsored by Eli Lilly & Co. Dr. Martino serves as a consultant to the company.

During the 4 years of the extended trial, the incidence of invasive breast cancer was reduced 59% in the raloxifene group, compared with the placebo group. Estrogen receptor–positive invasive breast cancer was reduced 66% with raloxifene as well. Thus, the magnitude of risk reduction during the second 4 years of raloxifene therapy was similar to that noted during the initial 4 years.

This is significant because raloxifene for osteoporosis is essentially lifelong therapy. Moreover, the maximal recommended duration for the use of tamoxifen to reduce the incidence of breast cancer in high-risk women is 5 years.

During the 8 years of the combined MORE and CORE studies, the incidence of invasive breast cancer was reduced 66% with raloxifene, compared with placebo, while the rate of estrogen receptor–positive invasive breast cancer was 76% less in the raloxifene arm than the placebo arm.

There was no difference between the two study arms in the incidence of estrogen receptor–negative invasive breast cancer or noninvasive breast cancer in CORE, nor in the full 8-year combined experience.

In CORE, the incidence of thromboembolism in raloxifene-treated women was 2.9 events per 1,000 woman-years, two times greater than with placebo. The rates in MORE were similar to those in CORE. No new safety concerns emerged with the use of raloxifene during years 4-8 of treatment.

The baseline serum estradiol data suggested the existence of a threshold effect, with women having an estradiol of at least 5 pmol/L—half of all study participants—deriving greater benefit in terms of reduction in invasive breast cancer. (See chart.)

Audience members noted that CORE didn't address the important issue of whether raloxifene is beneficial for prevention of breast cancer in at-risk women who don't have osteoporosis. That issue is being studied in two randomized clinical trials: the Raloxifene Use for the Heart (RUTH) trial in postmenopausal women at elevated cardiovascular risk, and the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) trial, a head-to-head comparison. ■

Invasive Breast Ca Cases Prevented by 8 Years of Raloxifene Tx

Baseline Serum Estradiol (pmol/L)	NNT*	Cases Prevented**
<5	177	8.6
5-10	47	32.1
>10	43	36.9

*NNT is the number of postmenopausal women with osteoporosis who would need to be treated to prevent one case of invasive breast cancer.
**Per 1,000 women treated.

Source: Dr. Martino

High Prevalence of Fractures, Reduced BMD in Systemic Lupus

BY KATE JOHNSON
Montreal Bureau

Patients with systemic lupus erythematosus who are under the age of 50 have a high rate of fragility fractures, osteoporosis, and poor bone mineral density, according to new research.

And as expected, steroid use was significantly linked to reduced bone mineral density (BMD), reported C-S Yee of the University of Birmingham and colleagues (Ann. Rheum. Dis. 2005;64:111-113).

Although bisphosphonates are the only class of drugs that have shown efficacy in the treatment and prevention of corticosteroid-induced osteoporosis, their use in premenopausal women poses serious risks of birth defects in the event of an unplanned pregnancy, noted the authors.

The study included 242 patients with systemic lupus erythematosus (SLE), 231 of whom were female.

Study participants were asked to complete a questionnaire about risk factors for osteoporosis, including details about previous fractures and family history of fractures. There were also asked about drug use and in particular about the use of glucocorticoids, oral contraceptives, hormone therapy, calcium and vitamin D supplementation, and bisphosphonates.

Among the women, 126 (54%) were premenopausal, 39 (17%) had experienced premature menopause, and 64 (28%) had experienced normal menopause. The menopausal status of two patients was unknown because they did not fully complete the questionnaire.

A total of 123 patients (51%) had reduced BMD (T score less than –1.0), and 25 were in the osteoporotic range (T score less than –2.5).

Ten of the patients with reduced BMD and 3 in the osteoporotic range were taking bisphosphonates at the time of the scan.

There were 22 patients (9%) who had experienced fragility fractures since their diagnosis of SLE, all of whom were female. Of these, 2 (9%) had normal BMD, while the other 20 (91%) had reduced BMD, with 7 of these women were in the osteoporotic range. Most of the patients with fragility fractures (82%) were menopausal, and only 3 were taking bisphosphonates at the time of the scan.

Non–Afro-Caribbean race and exposure to prednisolone (more than 10mg/day) were associated with reduced BMD, while age and menopause were associated with osteoporosis, according to a regression analysis.

Only low BMD and advanced age predicted fractures. Steroid exposure did not predict fracture rates, noted the authors. However, "it is likely that the effect of steroids on fractures is mediated predominantly by reduction in bone density in susceptible individuals," they reported.

Despite a high prevalence of fractures in this cohort, the authors noted a low prevalence among the premenopausal women (3%). ■

Routine Bone Scans Appropriate For Some Premenopausal Women

HARROGATE, ENGLAND — Targeted use of bone densitometry in premenopausal women can identify a significant number of patients who would benefit from bone protection, a study has shown.

Of 301 premenopausal women referred to London's Queen Elizabeth Hospital during a 4-year period for dual energy x-ray absorptiometry (DXA) because of possible increased risk of osteoporosis, 41% had abnormal scans, reported said Elizabeth Koshy, M.D., in a presentation at the annual conference of the National Osteoporosis Society.

Premature menopause accounted for 43 (14%) of the patients referred for DXA. Of these, 37% had abnormal scans.

Steroid use accounted for 19% of the referrals, of which 47% of the scans were abnormal. Of the approximately 14% of referrals based on family history, 27% resulted in abnormal scan. Osteopenia or previous fracture was the primary or coexisting indication for 37 or 12% of the patients, and among these, 54% were abnormal. Amenorrhea was the impetus for 11 (3.7%) of the scans, and 64% of these were abnormal, reported Dr. Koshy of Imperial College London.

The medical conditions associated with the highest proportion of abnormal scans were anorexia nervosa (57%) and inflammatory bowel disease (52%), Dr. Koshy noted.

A logistic regression analysis identified low calcium/vitamin D intake, a body mass index of less than 20 kg/m^2, and amenorrhea as significant risk factors associated with a lower bone mineral density. Such findings, Dr. Koshy said suggest that "focused use of bone densitometry in women younger than 50 with any of these risk factors can help to identify patients with future fracture risk who may merit osteoporosis prevention."

In most premenopausal women, it may be that the best treatment option remains supplementation with calcium and Vitamin D, Dr. Koshy stated. However, "selective DXA does seem to identify a significant number who could benefit from additional intervention."

While much attention in recent years has been focused on the importance of routine bone density testing for postmenopausal women, the findings of this study add weight to the argument that younger women who have significant risk factors should be tested as well, "ideally at peak bone mass [between ages 21 and 35]," said Dr. Koshy.

—Diana Mahoney

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