Hylonome

Raloxifene: Results from the MORE study

D. Agnusdei[1], N. Iori[2]

[1]European Medical Coordinator, Skeletal Diseases, Eli Lilly & Co., [2]Clinical Research Physician, Eli Lilly, Italy

Abstract

Raloxifene is the first Selective Estrogen Receptor Modulator (SERM) approved for the prevention and treatment of osteoporosis in postmenopausal women. Acting as an estrogen agonist in the skeleton and on lipid metabolism, raloxifene maintains bone mineral density (BMD) and prevents new vertebral fractures while improving the lipid profile in postmenopausal women. In an osteoporosis prevention study, 601 women without osteoporosis, aged 45 to 60 years, were assigned to receive a placebo or raloxifene 30, 60, or 150 mg/day. All women received calcium (400 to 600 mg/day). Raloxifene 60 mg increased BMD by 2.4% at both the lumbar spine and hip compared with the placebo at 36 months. More importantly, however, raloxifene significantly reduced the risk of new vertebral fractures in Multiple Outcomes of Raloxifene Evaluation (MORE), a placebo-controlled, double-blind randomized trial of 7705 postmenopausal women with osteoporosis. The women, with a mean age of 66.5 years, and with hip or spine T-score <-2.5 and/or prevalent vertebral fractures, were assigned to receive either a placebo or 60 mg or 120 mg of raloxifene. All women were provided supplemental calcium (500 mg/day) and vitamin D (400 IU/day). After 36 months, raloxifene 60 mg/day and 120 mg/day, reduced the risk of new vertebral fractures by 55% (RR 0.45, 95% CI 0.3, 0.7; $p<0.001$), and 40% (RR 0.60, CI 0.4, 0.9) in women without prevalent baseline fractures, respectively; and by 31% (RR 0.7, 95% CI 0.6, 0.9; $p<0.001$), and 49% (RR 0.5, CI 0.4, 0.6) in women with prevalent baseline fractures compared with the placebo. There was no difference in the proportion of women reporting non-traumatic, non-spine fractures among women receiving raloxifene compared to the placebo-treated women. Compared with placebo, BMD increased after 36 months by 2.1 and 2.6% at the femoral neck and spine, respectively, in the 60mg raloxifene group, and by 2.4 and 2.7% at the femoral neck and spine, respectively, in the 120mg raloxifene group. By 40 months of follow-up, there was a higher rate of deep venous thrombosis (38 cases) and pulmonary embolus (17 cases) in the combined raloxifene groups than in the placebo group (5 and 3 cases,), with a relative risk of 3.1, (CI 1.5-6.2). By 40 months, 54 women had a confirmed diagnosis of breast cancer with a relative risk compared to placebo of 0.35, (CI, 0.21-0.58). Raloxifene therapy for 3 years maintains BMD in healthy postmenopausal women and significantly reduces the risk of new vertebral fractures by about half in postmenopausal women with osteoporosis. Raloxifene also reduces the risk of breast cancer by 65% in postmenopausal women with osteoporosis thus providing a new choice for addressing postmenopausal health concerns.

Keywords: Raloxifene, Selective Estrogen Receptor Modulator, Osteoporosis, Fracture Risk

Introduction

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture[1]. This definition of the disease implies a loss of bone mass and a deterioration in bone quality. When these two processes exceed a critical level, fractures occur spontaneously or with minimal trauma. This syndrome may arise as a result of a decrease in bone formation or an increase in bone resorption, or a combina-

tion of both phenomena. Histomorphometric studies suggest both increased bone resorption and decreased bone formation in osteoporotic bone. For a curative treatment of osteoporosis a drug should reverse at least to some extent the decrease in bone mass and the deterioration of bone quality, and induce as a result a decrease, ideally a stop, in the occurrence of fractures. Theoretically, this can be obtained through a decrease in bone resorption not accompanied by a decrease in bone formation of similar magnitude, or by an increase in formation without a similar increase in resorption. Despite the advances which have been made in the prevention of osteoporosis, treatment of the established disease remains a major challenge for the physician, both now and in the future. Drug therapy for osteoporosis can be divided operationally into two main

categories; those which inhibit bone resorption, and thus reduce bone turnover, and those which stimulate bone formation, exerting an anabolic effect.

During the past decade, osteoporosis has been increasingly perceived as a seriously disabling disease, warranting substantial involvement on the part of investigators, governmental agencies, and the pharmaceutical industry in the development and assessment of treatments. Such an involvement is appropriate and is resulting in an increasing number of treatment options. Among the newer treatments for osteoporosis, selective estrogen receptor modulators (SERMs) seem to play a significant role as an excellent therapeutic option for a global approach to the postmenopausal-related changes.

Selective Estrogen Receptor Modulators represent a new therapeutic class of medications that have been developed in an attempt to address the unmet medical needs not realised by the currently available therapeutic options. These compounds selectively modulate estrogen receptors to act as either an estrogen agonist or antagonist depending on the target tissue and hormonal milieu present[2,3]. Among this class of compounds, raloxifene is the most studied and is currently available for clinical use in several countries for the prevention and treatment of osteoporosis in post-menopausal women.

Raloxifene is a non-steroidal benzotiophene derivative acting upon the estrogen receptors. Therefore, it is not a hormone. It does, however, act on cell surface estrogen receptors. Raloxifene selectively activates the estrogen receptor on the skeleton and cardiovascular system, and blocks estrogen receptor activity in the uterus and the breast. A raloxifene response element has been identified which has been shown to elaborate, among others, TGF-β3, an important regulator of bone remodelling[4].

At the skeletal level raloxifene has been shown to prevent bone loss at axial and appendicular sites and reduce serum cholesterol, like estrogen, in oophorectomized rats. Unlike estrogen, raloxifene does not stimulate breast or uterine tissues, and in fact inhibits the progression of estrogen-dependent breast tumours in animal models. Raloxifene has minimal effects on uterine epithelia and antagonises either estrogen or tamoxifen stimulation of the endometrium. These appealing attributes make raloxifene a potential treatment for osteoporosis and other menopause-related risks in middle-aged and elderly women[5].

In an osteoporosis prevention study, 601 postmenopausal women without osteoporosis, aged 45 to 60 years, from 2 up to 8 years after menopause, were assigned to receive either a placebo or raloxifene of 30, 60, or 150 mg/day. All the women received a daily calcium supplement of 500 mg/day. Treatment with raloxifene of 60 mg/day increased bone mineral density (BMD), measured by DEXA, by 2.4% at both the lumbar spine and hip compared with the placebo[6]. Biochemical markers of bone turnover, measured every 3 months in a large subset of the study population showed a significant reduction after 3 months of treatment in the raloxifene treated-group, and at the end of the study period,

the circulating levels of these markers were comparable with those seen in pre-menopausal women[6].

The MORE Study

The MORE (Multiple Outcomes of Raloxifene Evaluation) Study was undertaken in 1994 primarily to examine the effects of raloxifene treatment on bone mass and fracture risk in post-menopausal women with osteoporosis.

Study subjects

Seven thousand seven hundred and five women aged 31 to 80 years (a mean age of 67 years), who were at least 2 years postmenopausal and had no severe or chronically disabling conditions but who had osteoporosis, defined by low bone mineral density or X ray evidence of vertebral fractures, were studied. The women were divided into two groups, those whose femoral neck or lumbar spine bone mineral density was more than 2.5 standard deviations below peak bone density (Study I) and those with ≥1 moderate or ≥2 mild vertebral fractures in the presence of low bone mineral density (as specified for Study I), or ≥2 moderate fractures, regardless of bone mineral density (Study II).

The standard inclusion and exclusion criteria were applied as with other studies dealing with antiresorptive agents performed previously. The women were enrolled at 180 centers in 25 countries. The protocol was approved by the human studies review board at each center and all women gave written informed consent to participate in the study in accordance with the ethical principles stated in the Declaration of Helsinki.

Treatment

Within each sub study, women were randomly assigned to treatment with a placebo or 60 mg or 120 mg per day of raloxifene. All women were asked to take 500 mg of calcium and 400 to 600 IU of vitamin D per day, beginning at entry.

Fracture assessment

Vertebral radiographs were obtained at baseline, 24, and 36 months, when symptoms of vertebral fracture occurred, and, when possible, upon early termination from the study. All vertebral radiographs were assessed at a central site by radiologists unaware of the treatment group assignment. The baseline radiographs were scored using a semi quantitative scale (SQ)[7] for each vertebra (T4 through L4) to establish eligibility for Study II. The grading included 0 (no fracture), 1.0 (mild), 2.0 (moderate), or 3.0 (severe). An incident fracture was defined as a grade change of ≥1.

If no fractures were detected after the review of baseline and endpoint radiographs, the analysis stopped for that patient. If a fracture was observed at baseline or endpoint, a second radiologist determined whether a fracture was

present or absent for each vertebra and performed quantitative morphometry (with a fracture defined as a decrease in anterior, mid, or posterior vertebral height of at least 20 percent and at least 4 mm). A vertebral fracture was scored if confirmed by at least two of the three types of determinations (two independent semi quantitative readings and one quantitative assessment).

Measurements of bone mineral density

Spine and femoral neck bone mineral density were measured annually by DEXA. A central reading facility provided correction factors to adjust for inter-site differences and changes in the performance of the densitometers over time. A stopping rule required that study participation be discontinued to permit conventional therapy if a patient's lumbar spine bone mineral density decreased ≥7 percent or the femoral neck bone mineral density decreased ≥10 percent at 1 year, or if the patient had >2 incident vertebral fractures.

Assessment of adverse effects

Mammograms were obtained at baseline, annually where acceptable, and biannually in all women. All women were questioned about the adverse effects of treatment at each visit; all reported effects were analysed regardless of the investigators' assessments of causality. Adverse effects that resulted in death, hospitalisation, cancer, permanent disability, or threat to life were classified as 'serious'.

Biochemical tests for safety and bone turnover

Hematologic, renal, and hepatic function tests were done periodically during the study. Markers of bone turnover, including serum osteocalcin (ELSA-OSTEO™, CIS-Biointernational, Gif-sur-Yvette, France) and the urinary type I collagen C-telopeptide excretion, corrected for urinary creatinine excretion (CrossLaps™, Osteometer A/S., Herlev, Denmark) were measured in 2,523 women who were enrolled at some sites in North America, Europe, and South America.

Statistical analyses

The primary endpoints in each sub study were the effects of raloxifene on incident vertebral fractures and bone mineral density; secondary endpoints were non-vertebral fractures and vertebral and non-vertebral fractures combined. We included only women who had fractures in vertebrae that were not fractured at baseline. The occurrence of non-vertebral fractures was compared between the raloxifene and placebo groups using proportional hazards analysis. Adverse effects were analysed using chi-square tests. All analyses were performed as an intention to treat (i.e., participants were classified according to their sub study group and treatment assignment regardless of compliance). Missing post-baseline data were imputed by carrying forward the last observation. All comparisons were two-sided and were performed at a 0.05 level of significance. No adjustments were made for multiple comparisons.

Results

There were no differences in baseline characteristics between the groups (Table 1). Compared with the women in Study I, women in Study II were older and had lower bone mineral density at baseline.

Vertebral fractures

Baseline and follow-up radiographs were available for 6,828 women (89%). Of these women, 88% had radiography performed at the 36-month visit, for the others the last post-baseline radiograph was used. There were no differences in baseline characteristics between these women and the 970 women who discontinued treatment and had no follow-up radiographs. After 36 months, 503 of the 6,828 women (7.4%) had 1 or more new vertebral fractures. The women in the raloxifene groups had both overall and in each study fewer new vertebral fractures, regardless of whether the women had prevalent fractures at baseline (Fig. 1).

There were no differences in the risk of any non-vertebral fracture (wrist, hip, or total) after 36 months (RR, 0.9; 95% CI, 0.8-1.1). Among all 12 categories of non-vertebral fractures, only the ankle fracture risk reduction was statistically significant.

Bone mineral density and bone turnover

Compared with the placebo, bone mineral density increased after 36 months by 2.1 and 2.6% at the femoral neck and spine, respectively, in the 60mg raloxifene group, and by 2.4 and 2.7% at the femoral neck and spine,
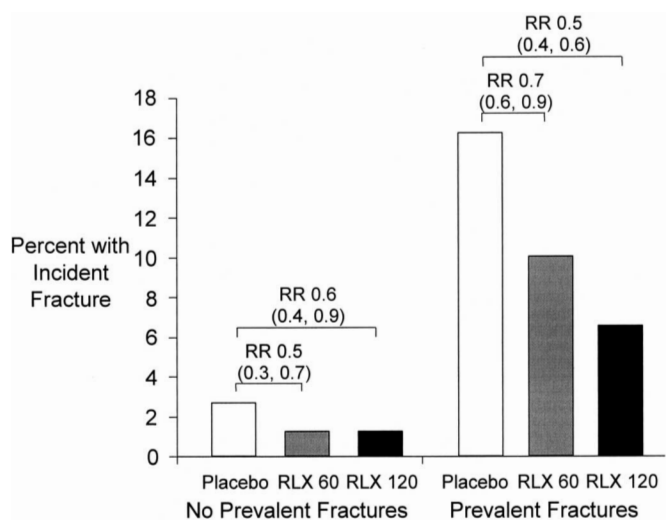

Figure 1. Percentage of Women with Incident Vertebral Fractures, in Women with and without Prevalent Fractures.

Characteristic	Study I Placebo	Raloxifene	Study II Placebo	Raloxifene
Number	1506	2959	757	1513
	M e a n ± S D			
Age (years)	66 ± 7	65 ± 7	69 ± 6	68 ± 6
Years since menopause	18 ± 8	17 ± 8	21 ± 8	21 ± 8
Body mass index (kg/m^2)	25.0 ± 3.9	25.0 ± 3.9	25.7 ± 3.9	25.7 ± 4.2
Fem. neck BMD (g/cm^2)				
Hologic* (n=4286)	0.584 ± 0.060	0.585 ± 0.059	0.565 ± 0.074	0.569± 0.072
Lunar* (n=1945)	0.719 ± 0.069	0.720 ± 0.073	0.707 ± 0.088	0.702 ± 0.084
Norland* (n=466)	0.665 ± 0.056	0.663 ± 0.061	0.647 ± 0.091	0.612 ± 0.088
Lumb. spine BMD (g/cm^2)				
Hologic* (n=4287)	0.769 ± 0.114	0.774 ± 0.111	0.749 ± 0.141	0.747 ± 0.126
Lunar* (n=1956)	0.886 ± 0.144	0.882 ± 0.135	0.845 ± 0.147	0.842 ± 0.142
Norland* (n=467)	0.756 ± 0.130	0.768 ± 0.126	0.749 ± 0.139	0.736 ± 0.140
Prevalent vertebral fractures (%)				
0	90.7	88.7	11.6	10.2
1	7.6	9.4	40.8	40.6
≥2	1.7	1.9	47.6	49.2
Prior HRT (%)	29.5	29.6	27.1	26.4
Prior hysterectomy (%)	20.8	22.6	23.8	21.4
Current smokers (%)	15.3	15.5	16.0	16.4

Approximately 10 percent of the women in each study had a subsequent change in prevalent vertebral fracture status after the more stringent radiographic assessment protocol was followed.

*Type of densitometer.

Table 1. Baseline Characteristics of the 6,828 Postmenopausal Woman with Follow-up Radiographs.

respectively, in the 120mg raloxifene group (P < 0.001, all comparisons).

The median baseline serum osteocalcin concentration and urinary excretion of C-telopeptide were 24.1 μg/L and 248 μg/mmol creatinine, respectively. After 36 months, the mean serum osteocalcin concentrations decreased by 8.6, 26.3, and 31.1%, and urinary C-telopeptide excretion decreased by 8.1, 34, and 31.5% in the placebo, 60mg raloxifene, and 120mg raloxifene groups, respectively (P < 0.001 for each raloxifene dose versus placebo).

Adverse effects

After 36 months, 24.2% of the women had serious adverse effects, with no overall difference among treatment groups. Venous thromboembolic events, including deep vein thrombosis and pulmonary embolism, were the only serious adverse effects believed to be causally related to raloxifene treatment. By 40 months of follow-up, there was a higher rate of deep venous thrombosis (38 cases, 0.7%) and pulmonary embolus (17 cases, 0.3%) in the combined raloxifene groups than in the placebo group (5 cases, 0.2%; 3 cases, 0,1%, respectively). One case of venous thrombo-embolism occurred per 155 women treated with raloxifene for 3 years. The risk of venous thromboembolic events was 3.1 times higher (95% CI, 1.5-6.2) in women assigned to the raloxifene group than to the placebo group[8].

Breast cancer was less frequent in the women receiving raloxifene. By 40 months, 54 women had a confirmed diagnosis of breast cancer (relative risk 0.35, 95% CI, 0.21-0.58). Ten women had endo-metrial cancers, 4 in the placebo group and 6 in the raloxifene group[8].

The most common single adverse effect prompting withdrawal was hot flushes. Thirty-three women (0.6%) assigned to the raloxifene group and 2 (0.1%) assigned to the placebo group discontinued treatment due to hot flushes (p<0.001)[9]. There were no clinically important changes in laboratory values.

Discussion

Treatment with raloxifene for 36 months decreased the risk of radiographic-ally and clinically apparent vertebral fractures by about half. The effect was significant in women with and without vertebral fractures at baseline and was marginally greater in women in the 120mg raloxifene group as compared with the 60mg raloxifene group. These effects on vertebral fracture are comparable with those found in prospective trials of other antiresorptive drugs, including alendronate[10,11], and a small trial with transdermal estrogen[12], and are important, given the morbidity associated with vertebral fractures[13]. A recent trial of another selective estrogen receptor modulator, tamoxifen, suggested a decrease in the risk of clinical osteoporotic fractures of 19 percent[14].

Similar to previous studies of raloxifene in early post-menopausal women without osteoporosis[6], in the MORE study there has been an increase of about two to three percent in spine and hip bone mineral density at 3 years in the raloxifene groups compared with the placebo, and reductions in biochemical markers of bone turnover that were moderate but sufficient to return the median levels to approximately the means seen in pre-menopausal women[15].

Thus, while the effects on bone density and biochemical markers are smaller than those in women treated with alendronate, the reduction in vertebral fracture risk is similar. This supports previous observations that the effect of anti-resorptive drugs on bone mineral density measured by dual-energy X ray absorptiometry is too small to account for their concomitant reduction in vertebral fractures[16],

suggesting that other factors also contribute to the prevention of fractures. Indeed, lower bone turnover is associated with lower hip fracture risk in elderly women independently of bone density[15].

Raloxifene had no effect on non-vertebral fractures. Similarly, approximately 3 years of treatment with alendronate did not decrease the risk of all non-vertebral fractures in women with vertebral fractures, but did decrease the risk of hip and wrist fractures[10]. Our study had limited power to detect effects on specific non-vertebral fractures, such as hip and wrist fractures, because of the low overall rate of hip fractures. Notably, the rate of hip fracture in women in the placebo group was less than half that in the alendronate trial, possibly because the mean age of the women was nearly 5 years less in this study. The calcium and vitamin D supplementation may have also reduced the risk of non-vertebral fractures in this study[17], making any effect of raloxifene more difficult to detect.

The women receiving raloxifene had an increased incidence of venous thromboembolic events as compared with the women receiving the placebo. Overall, the relative risk for venous thromboembolic events was approximately 3, which is comparable to that reported for postmenopausal women receiving estrogen therapy in observational studies[18,19], for those in a prospective trial of estrogen therapy[20], and for those receiving tamoxifen for prevention of breast cancer[14]. Breast cancer was significantly less frequent in the women receiving raloxifene, an effect similar to that reported for tamoxifen in the Breast Cancer Prevention Trial[14].

There were few cases of endometrial cancer in this study overall, with no significant difference in the proportions of women given this diagnosis of endometrial cancer among the treatment groups. Thus, raloxifene-associated endometrial fluid accumulation appears to be clinically unimportant. The adverse effects of leg cramps were also reported more frequently in the women given raloxifene; this symptom has also been reported in women given estrogen replacement therapy[21].

In conclusion, results from the MORE study indicate that 3 years of treatment with raloxifene have a significant beneficial effect on bone metabolism, by reducing the vertebral fracture risk, by increasing BMD at all skeletal sites and by maintaining normal bone quality in postmenopausal women with osteoporosis.

References

1. Consensus Development Statement. Who are candidates for prevention and treatment for Osteoporosis? Osteoporosis Int 1997; 7:1-6.
2. Mitlak B, Cohen FJ. In search of optimal long-term female hormone replacement: the potential of selective estrogen receptor modulators. Horm Res 1997; 48:155-163.
3. Kauffman RF, Bryant HU. Selective estrogen receptor modulators. Drug News Perspect 1995; 8:531-539.
4. Kauffman RF, Bryant HU, Yang N, Harper KD, Huster WJ, Walls EL, et al. Preventing post-menopausal osteoporosis: an update on raloxifene. Drug News Perspect 1999; 12:223-233.
5. Bryant HU, Dere WH. Selective estrogen receptor modulators: an alternative to hormone replacement therapy. Proc Soc Exp Biol Med 1998; 217:45-52.
6. Delmas PD, Bjarnason NH, Mitlak B, Ravoux AC, Shah AS, Huster WJ, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in post-menopausal women. N Engl J Med 1997; 337:1641-1647.
7. Black DM, Palermo L, Nevitt MC, Genant HK, Epstein RS, San Valentin R, et al. Comparison of methods for defining prevalent vertebral deformities: the study of osteoporotic fractures. J Bone Miner Res 1995; 10:890-902.
8. Cummings SR, Eckert S, Krueger K, Grady D, Powles T, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in post-menopausal women. JAMA 1999; 281:2189-2197.
9. Davies GC, Huster WJLY, Plouffe LJ, Lakshmanan M. Adverse events reported by post-menopausal women in controlled trials with raloxifene. Obstet Gynecol 1999; 93:558-565.
10. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348:1535-1541.
11. Liberman U, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in post-menopausal osteoporosis. N Engl J Med 1995; 333:1437-1443.
12. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, et al. Treatment of post-menopausal osteoporosis with transdermal estrogen. Ann Int Med 1992; 117:1-9.
13. Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998; 128:793-800.
14. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report from the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998; 90:1371-1388.
15. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Granjean H, Muller C, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. J Bone Miner Res 1996; 11:1531-1538.
16. Melton LJ, III, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. J Bone Miner Res 1997; 12:1083-1091.
17. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age and older. N Engl J Med 1997; 337:670-676.

18. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. Lancet 1996; 348:977-980.

19. Jick H, Derby LE, Myers MW, vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of post-menopausal oestrogens. Lancet 1996; 348:981-983.

20. Hulley SB, Grady D, Bush TL, Furberg C, Herrington D, Riggs BL, et al. Randomised trial of estrogen plus progestin for secondary prevention of coronary heart disease in post-menopausal women. JAMA 1998; 280:605-613.

21. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. Clin Obstet Gynecol 1997; 4:31-47.