

Does raloxifene reduce risk of vertebral fractures?

Is this another, brighter way to treat osteoporosis?

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Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;282(7):637-45.

Research question

Does raloxifene reduce risk of vertebral fractures in postmenopausal women with osteoporosis?

Type of article and design

Multicentre, randomized, blinded, placebo-controlled trial of therapy.

Relevance to family physicians

Osteoporosis has long been a major public health concern.^{1,2} Health care costs and human costs in reduced quality of life are high. Fractures due to osteoporosis result in physical deformity, acute and chronic symptoms, impaired physical and emotional function, decreased enjoyment of life, and shorter lifespan.³

Estrogen therapy can preserve bone mineral density (BMD) in both younger and older postmenopausal women.⁴ It has, however, undesirable effects on many other organs. Debate continues as to its effect on risk of breast cancer.⁵ To date, no large randomized clinical trials have evaluated its efficacy against fractures.⁶

Raloxifene, a tissue-specific estrogen agonist, has estrogen-like effects on bone and serum lipid levels, but does not affect the endometrium or breast.⁷ It has been associated, however, with a decreased incidence of estrogen-responsive malignancies in the breast and endometrium.⁸ Raloxifene's effects on BMD,

serum cholesterol concentrations, and the uterine endometrium in healthy postmenopausal women⁶ have been reviewed elsewhere.⁹ We now look at whether raloxifene has any efficacy in preventing fractures, especially in postmenopausal women with osteoporosis.

Overview of study and outcomes

This multicentre trial took place in 25 countries. It began in 1994 and had 36 to 40 months of follow up. A total of 7705 postmenopausal women aged 31 to 80 years with osteoporosis were divided into two study groups (group 1 with BMD score < -2.5, group 2 with radiographically apparent fractures) and randomly assigned to placebo or one of two daily doses of raloxifene: 60 mg or 120 mg. Placebo and treatment arms all received supplemental calcium and cholecalciferol. The study's primary end point was radiographically apparent new vertebral fractures and changes in BMD. Another end point was nonvertebral fractures.

Inclusion criteria were postmenopausal for at least 2 years and no severe or long-term disabling conditions except osteoporosis, which was defined as low BMD, radiographically apparent vertebral fractures, or both. Women were excluded if they had a history of bone diseases other than osteoporosis, estrogen-related symptoms or carcinoma, nonskin cancer, thromboembolic disorders, endocrine disorders requiring therapy (except for type 2 diabetes or hypothyroidism), active

renal lithiasis, abnormal hepatic function, untreated malabsorption, any medications that would affect BMD (eg, androgen, calcitonin, or bisphosphonate) within the previous 6 months, or creatinine levels > 225 µmol/L (2.5 mg/dL), or if satisfactory thoracic and lumbar radiographs could not be obtained.

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Results

Of the 7705 women, 6828 (89%) had baseline and follow-up radiographs. After 36 months, 503 (7.4%) women had new vertebral fractures. Women receiving raloxifene had fewer new fractures than those receiving placebo (6.6% in the 60 mg/d group, 5.4% in 120 mg/d group, and 10.1% in the placebo group). Risk of vertebral fractures was lower in the treated groups (60 mg/d group: relative risk [RR] 0.7, 95% confidence interval [CI] 0.5 to 0.8; 120 mg/d group: RR 0.5, 95% CI 0.4 to 0.7). Incidence of vertebral fractures was similar in the two treatment groups, but those taking the higher dose had a lower incidence of fractures overall (10.7% vs 14.7%).

The difference in risk of nonvertebral fractures was not statistically significant between treatment and placebo groups (RR 0.9, 95% CI 0.8 to 1.1). Compared with placebo, 60 mg/d and 120 mg/d of raloxifene increased BMD in the femoral neck 2.1% and 2.4%, respectively, and in the spine 2.6% and 2.7%, respectively.

At 40 months, significantly more venous thromboembolic events had occurred among women taking raloxifene than among those taking placebo (25 women in the 60 mg/d group and 24 in the 120 mg/d group versus eight in the placebo group; RR 3.1, 95% CI 1.5 to 6.2). The most common adverse effects of raloxifene were hot flashes (11% of women), leg cramps (7%), peripheral edema (6%), and influenza syndrome (13.5%).

Hot flashes were the most common reason for withdrawal from the therapy. Incidence of vaginal bleeding and breast pain was similar in control and raloxifene groups. About 23% of the women dropped out of the study: 25% in the placebo group and 22% in the treated groups.

Analysis of methodology

This large, well-designed, randomized placebo-controlled trial had a clearly stated primary end point, and its findings were solid. Unfortunately, like the previous trial,⁷ the study was too short to indicate long-term outcomes, especially for fractures in large bones. The trial was not designed to measure long-term outcomes and adverse effects other than fractures. Findings were also limited because raloxifene was not directly compared with estrogen, the standard therapy for preventing postmenopausal osteoporosis.

Application to clinical practice

This 3-year study shows that raloxifene is effective in reducing vertebral fractures related to osteoporosis in postmenopausal women at high risk of fracture who have either low BMD, previous vertebral fractures, or both. New fracture risk in the control group was 4.5 times higher in women with existing fractures than in

women without previous fractures (21.2% versus 4.5%). This would mean the number needed to treat (NNT) for one woman to be helped was six. Compared with the placebo group, the raloxifene-treated groups had a significantly reduced risk of new vertebral fractures whether or not women had existing fractures. The NNT was smaller among women with previous fractures than among women without them.

To interpret these results, family physicians need to consider the study population. They were aging (average 67 years), white, somewhat overweight (body mass index, 25) women who had been menopausal for 18 to 21 years. Findings might not apply to younger, recently postmenopausal, or normal weight women, or to women of other ethnic groups.

Also, the World Health Organization's definition of osteoporosis was devised for assessment of osteoporosis in postmenopausal women; its application is not clear for men, premenopausal women, or non-white populations.¹ As in the previous trial,⁷ the end points of this study were disease-oriented because they used incidence of radiographically apparent fractures rather than clinically apparent fractures. We assume this overstates the effect.

Neither BMD alone nor spine radiography is sensitive or specific enough to precisely define risk in individual patients.¹ Risk factors for low bone mass are different from those for fracture; they include age >70, positive family history, prior fracture, propensity for falls, reduced BMD, and postural instability.¹

Family physicians know that protecting bone health is multifaceted and requires attention to diet, lifestyle, and education to reduce risk of falling. We cannot conclude that the positive effects on women's spines in this study are from raloxifene alone because women were also getting the beneficial effects of calcium and cholecalciferol, both proven to reduce fracture incidence in older adults and women with osteoporosis.^{10,11} Furthermore, raloxifene has not been proven to prevent nonvertebral fractures more effectively than calcium alone. In fact, there seems to be a higher incidence of hip fracture among the treated women than among control subjects, but this non-significant result might be due to the short follow up. Compared with a 2-year study of raloxifene,⁷ this 1-year-longer study shows the serious adverse effects of raloxifene. Women receiving raloxifene had a threefold risk of venous thromboembolism compared with women receiving placebo.

Bottom line

- Raloxifene therapy reduced risk of vertebral fracture in high-risk postmenopausal women. This trial, like

others in the field, however, bases its findings on examination of radiographs rather than people.

- Raloxifene, a tissue-specific estrogen, was expected to have fewer side effects than estrogen. The drop-out rate, however, was high at 23%. Also, compared with placebo, it increases risk of venous thromboembolism and might decrease breast cancer rates. Whether it actually decreases breast cancer rates or simply delays onset has yet to be fully evaluated.¹²
- Raloxifene does not relieve hot flashes, and its effect on heart disease and fracture prevention still need to be worked out. There is some promise here but until more long-term, definitive comparisons are available, raloxifene should be used only for women who are not candidates for estrogen or bisphosphonate therapy. ❖

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Points saillants

- Une thérapie au raloxifène réduit le risque de fracture vertébrale chez les femmes post-ménopausiques présentant des risques élevés. Cette étude, comme d'autres dans ce domaine, fonde ses conclusions sur un examen des radiographies plutôt que des personnes.
- On s'attendait à ce que le raloxifène, un œstrogène spécifique de tissu, ait moins d'effets secondaires que l'œstrogène. Le taux de cessation était toutefois aussi élevé que 23%. De plus, par rapport au placebo, il accroît le risque de thromboembolie veineuse et pourrait réduire les taux de cancer du sein. Il reste à évaluer plus en profondeur s'il réduit vraiment les taux de cancer du sein ou s'il ne fait que retarder son apparition¹².
- Le raloxifène ne soulage pas les bouffées de chaleur et son effet dans la prévention des cardiopathies et des fractures reste encore à préciser. Il est porteur de promesses éventuelles mais, avant que les résultats de comparaisons définitives à plus long terme soient disponibles, le raloxifène ne devrait être administré qu'aux femmes qui ne sont pas candidates à une thérapie à l'œstrogène ou au bisphosphonate.