

FPIN's Clinical Inquiries

Raloxifene for Prevention of Osteoporotic Fractures

Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).

This series of Clinical Inquiries is coordinated for American Family Physician by John Epling, M.D., State University of New York Upstate Medical University, Syracuse, N.Y. The complete database of evidence-based questions and answers is copyrighted by FPIN. If you are interested in submitting questions to be answered or writing answers for this series, go to <http://www.fpin.org> or contact CI2Editor@fpin.org.

Clinical Question

Does raloxifene (Evista) prevent fractures in postmenopausal women with osteoporosis?

Evidence-Based Answer

Raloxifene (60 mg daily for three years) will prevent one vertebral fracture, including asymptomatic fractures, for every 46 postmenopausal women with osteoporosis or presence of previous vertebral fractures. Raloxifene has not been shown to prevent nonvertebral fractures. It is unclear if longer duration of treatment is warranted, or whether this risk reduction is sustained after discontinuation of treatment. [Strength of recommendation: A, based on systematic reviews of randomized controlled trials (RCTs)]

Evidence Summary

Raloxifene is a selective estrogen receptor modulator with tissue-specific estrogen receptor effects. Raloxifene inhibits bone resorption and may decrease breast cancer risk.

A systematic review¹ of osteoporosis therapies summarized the results of two RCTs.^{2,3} The largest of these studies is the Multiple Outcomes of Raloxifene Evaluation (MORE) study, an RCT of 7,705 postmenopausal women who met the World Health Organization criteria for osteoporosis based on low bone mineral density (T-score lower than -2.5)¹ or presence of previous vertebral fracture. The MORE study found a reduction in the risk of vertebral fracture for women with osteoporosis after three years of treatment with 60 mg of raloxifene daily

(number needed to treat [NNT] for three years: 46), as well as in a subgroup of women with osteopenia (bone mineral density T-score lower than -1.5)¹ and pre-existing fractures (NNT: 16). Results with 60 and 120 mg doses of raloxifene were not significantly different. The incident vertebral fractures were radiographically determined at 24- and 36-month visits, or at any time if the women developed symptoms of vertebral fractures. The study did not report whether there was a difference in clinically apparent vertebral fractures. Nonvertebral fractures were determined by interview at six-month intervals.²

A second large RCT⁴ included in the systematic review¹ showed no significant effect of raloxifene; however, because it was designed for breast cancer prevention and measured fracture prevention only as a secondary outcome, the inclusion criteria did not include osteoporosis risk factors and may have led to an uneven distribution in treatment and placebo groups. Asymptomatic vertebral fractures may have been undercounted because fractures were only diagnosed by patient self-report.¹ A 12-month blinded extension of the MORE study showed that raloxifene (60 or 120 mg) continued to decrease the cumulative relative risk of new vertebral fractures in women with osteoporosis through year 4.⁵ A smaller, one-year RCT³ confirmed that raloxifene significantly decreased asymptomatic vertebral fractures when the fractures were diagnosed using strict radiographic criteria. Raloxifene had no significant effect on symptomatic vertebral fractures or on nonvertebral fractures. The ratio of treatment group responders to control group responders was 0.9 (95 percent confidence interval: 0.8 to 1.1). This smaller RCT was limited by sample size and shorter duration of monitoring.

Side effects from raloxifene include venous thromboembolism (number needed to harm [NNH] after three years: 161), hot flashes (NNH: 22), and leg cramps (NNH: 32). Raloxifene may decrease the risk of breast cancer (NNT: 93).^{2,6}

Recommendations from Others

The American College of Obstetricians and Gynecologists and the American Association of Clinical Endocrinologists recommend raloxifene as an acceptable option for the treatment of women with postmenopausal osteoporosis and risk factors for fracture, and for women in whom nonpharmacologic preventive measures have not stopped continued bone loss or low-trauma fractures.^{7,8} Other therapies may be more effective or preferred in a given clinical situation (see Clinical Commentary). Non-pharmaceutical preventive options for osteoporosis include weight-bearing exercise, abstaining from tobacco, intake of calcium and vitamin D, and using safety measures to decrease fractures caused by falls or accidents.⁷

Clinical Commentary

From a clinical standpoint, the more interesting question might be when to use raloxifene as opposed to other medications for the prevention of fractures in postmenopausal women with osteoporosis or pre-existing fractures. While raloxifene, bisphosphonates, calcitonin, and calcium plus vitamin D all significantly reduce vertebral fractures, only the bisphosphonates and calcium plus vitamin D also lower the risk of hip fractures in women with osteoporosis or institutionalized women, respectively.^{9,10} The discontinuation rate for bisphosphonates because of gastrointestinal side effects is significantly higher compared with raloxifene. For those who

have gastrointestinal problems, raloxifene is a good alternative.¹¹ Women with a medical history including venous thromboembolism who are immobilized for prolonged periods, or who receive hormone therapy should not take raloxifene because of an increased risk of venous thromboembolic events. The decision to continue raloxifene treatment beyond three years depends on the patient's experience of side effects and her desire to continue raloxifene for its benefit in reducing breast cancer risk.⁶

The injectable parathyroid hormone teriparatide is expensive and more difficult to administer, but is generally well tolerated and does reduce the risk of both vertebral and nonvertebral fractures in postmenopausal women with prior vertebral fractures.¹² The use of estrogen-only therapy and estrogen-plus-progestin therapy for the prevention of bone loss after menopause have both fallen out of favor since the Women's Health Initiative reported that the overall health risks are equivalent to the benefits for estrogen-only therapy and that the risks exceed the benefits for estrogen-plus-progestin therapy.^{13,14} Although somewhat less effective, calcitonin nasal spray is an alternative for the prevention of vertebral fractures in osteoporotic women who cannot tolerate or do not wish to take estrogen-only therapy, estrogen-plus-progestin therapy, bisphosphonates, or raloxifene.¹⁰

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REFERENCES

1. Nelson HD. Hormone replacement therapy and osteoporosis. Systematic evidence review no. 12. Rockville, Md.: Agency for Healthcare Research and Quality, 2002. Accessed online May 27, 2005, at: <http://www.ahrq.gov/downloads/pub/prevent/pdfser/hrtosteo/hrtostserpdf.zip>.
2. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al, for the Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a

3-year randomized clinical trial [published correction appears in JAMA 1999;282:2124]. JAMA 1999;282:637-45.

3. Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knickerbocker RK, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J Bone Miner Res 1998;13:1747-54.

4. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst 1998;90:1371-88.

5. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al, for the Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized control trial. J Clin Endocrinol Metab 2002;87:3609-17.

6. Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, et al., for the CORE investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004;96:1751-61.

7. Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW, et al., for the AACE Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003 [published correction in Endocr Pract 2004;10:90]. Endocr Pract 2003;9:544-64.

8. Selective estrogen receptor modulators. Washington D.C.: American College of Obstetricians and Gynecologists, 2002. Accessed online May 27, 2005, at: http://www.ngc.gov/summary/summary.aspx?ss=15&doc_id=3987.

9. Häuselmann HJ, Rizzoli R. A comprehensive review of treatments for postmenopausal osteoporosis. Osteoporos Int 2003;14:2-12.

10. Chesnut CH 3d, Silverman S, Andriano K, Genant H, Gimona A, Harris, et al., for the PROOF study group. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. Am J Med 2000;109:267-76.

11. Turbi C, Herrero-Beaumont G, Acebes JC, Torrijos A, Grana J, Miguelez R, et al. Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: an open-label, prospective, nonrandomized, observational study. Clin Ther 2004;26:245-56.

12. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41.

13. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.

14. Anderson GL, Limacher M, Assaf A, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.