
Raloxifene FAQs: Perspectives on the First Approved SERM—Where Are We Now? Part 1

A *Menopause Management* Q & A with Stanley J. Birge, MD; Felicia Cosman, MD; Bruce Ettinger, MD

Editor's note: The opinions expressed in this article are those of the contributing clinicians and do not necessarily express the views of The North American Menopause Society or Menopause Management. The data/studies referred to can be found in the articles in the Suggested Reading list on page 25.

Raloxifene, the first selective estrogen receptor modulator (SERM) used for prevention and treatment of osteoporosis, was marketed in 1995 for the prevention of osteoporosis. Three years later, after results of a large-scale clinical trial, the SERM was approved for osteoporosis treatment. Also in 1998, the scientific world first heard of the significant reduction in risk of breast cancer among elderly women who received raloxifene in this same osteoporosis trial. Positive effects on coronary heart disease (CHD) risk factors have been shown with the SERM, both among early postmenopausal and elderly women. Most recently, raloxifene's benefits on cognitive function among elderly women have been reported. Despite these clinical trial data, there remain uncertainties about raloxifene's risks and benefits, and about which patients are appropriate candidates for treatment with the drug.

In an attempt to address some of these issues, *Menopause Management* asked three clinicians to respond to a range of frequently asked questions about raloxifene. The intention was to get the opinions of practitioners who are likely to have very different opinions about raloxifene and its potential role in the treatment of mid-life women.

Stanley J. Birge, MD, is Associate Professor of Medicine and Director, Older Adult Health Center, Washington University School of Medicine, St. Louis, Missouri. Dr. Birge serves on the speakers' bureaus for Parke-Davis, Pfizer, Inc., and Wyeth-Ayerst Pharmaceuticals. **Felicia Cosman, MD**, is an osteoporosis specialist/endocrinologist at Helen Hayes Hospital and Associate Professor of Clinical Medicine, Columbia University, New York. Dr. Cosman is a member of the speakers' bureaus for Eli Lilly & Company, Merck & Co., Inc., and Procter and Gamble and has a research grant from Wyeth-Ayerst Pharmaceuticals. **Bruce Ettinger, MD**, is Senior Investigator, Division of Research, Kaiser Permanente Medical Care Program, Oakland, California, and Clinical Professor of Medicine and Radiology, University of California at San Francisco. Dr. Ettinger receives grant support from, and serves as a consultant for, Eli Lilly & Company, Berlex, Novogen and Procter & Gamble.

Using Raloxifene to Treat the Skeleton

Is raloxifene as effective as estrogens for treating osteoporosis?

Dr. Birge: Based on the change in bone density, raloxifene has approximately one-half to one-third the efficacy of estrogen replacement therapy (ERT). Whereas about 80-90% of women demonstrate an increase in bone density with estrogen, about 50% increase their bone density in response to raloxifene.

Dr. Cosman: In direct head-to-head comparative studies, raloxifene does not produce as great an effect on bone mineral density (BMD) or bone turnover as does estrogen. There are, however, no direct comparisons of raloxifene and estrogen with respect to fracture occurrence. The MORE trial, with more than 7,700 women with osteoporosis, showed a reduction in vertebral fracture occurrence of 30-50% with raloxifene. The only clinical trial evaluating fracture outcome with estrogen in women with osteoporosis was a study of only 100 individuals. The data indicated a significant effect of estrogen of similar magnitude against vertebral fracture occurrence, but with respect to nonvertebral fractures in treating osteoporosis, there are no comparative data.

Dr. Ettinger: Although there are many observational studies of estrogen and fracture, there has never been an adequately designed clinical trial testing the efficacy of estrogen in treating osteoporosis. I would expect, however, based on effects on bone turnover and bone density, that estrogen's skeletal effects would be similar to those of raloxifene. Although there have been no head-to-head studies of bisphosphonates (alendronate and risedronate) versus raloxifene, I believe the bisphosphonates provide greater fracture risk reduction, particularly against nonspine fractures.

What is the expected benefit of raloxifene for the patient with spinal and nonspinal fractures?

Dr. Birge: Although raloxifene reduces vertebral fractures, nonvertebral fractures were reduced by only 8%—a decrease that was not significant. Of some concern was the observation that hip fractures were actually increased by 14% although, again, this did not reach statistical significance. Because hip fracture is the fracture that osteoporosis prevention strategies are intended to prevent, it is difficult to justify the cost and the potential risk of thromboembolic disease associated with raloxifene.

Dr. Cosman: There is a 30% reduction in vertebral fractures in patients with prevalent fractures of the spine treated with raloxifene, and a 55% reduction in patients without such fractures. One would expect raloxifene to confer a benefit against vertebral fractures similar to the latter figure in women with prevalent nonspine fractures. Importantly, though, there are no data indicating that raloxifene will reduce nonspine fractures in either group of women.

Dr. Ettinger: Raloxifene has only a small (and not statistically significant) ef-

fect on peripheral fractures—less than 10% better than placebo, even after 4 years. If a “quick fix” is needed for someone who has had a hip fracture, I would use a bisphosphonate first, and then, after a few years, I'd consider switching to maintenance therapy with raloxifene. In the future we will probably use parathyroid hormone injections for such patients, since that agent provides even greater fracture risk reductions than do the bisphosphonates.

Is there a reduction in painful (clinical) vertebral fractures associated with raloxifene use?

Dr. Birge: Raloxifene decreases clinical vertebral fracture by about 60%, comparable to the 40% reduction observed with radiologically detected vertebral deformation. These changes are comparable to the reduction in vertebral fractures observed with alendronate.

Dr. Cosman: Yes there is, just as there is a reduction in asymptomatic morphometric fractures. Clinical vertebral fractures were reduced by about 60%.

Dr. Ettinger: Clinical vertebral fractures are those diagnosed by a painful episode prompting a radiograph showing a new fracture (about one in three radiographically demonstrated fractures in most clinical trials are such events). In general, osteoporosis treatments have about the same effect on clinical fractures as those found on routine radiographs. Painful spine fractures are reduced by about two-thirds in the first year of treatment with either of the bisphosphonates and with raloxifene.

Is it possible to use raloxifene and estrogen therapy together?

Dr. Birge: It would be possible, although the rationale for doing so cannot be supported.

Dr. Cosman: There are no data in this area, but combining raloxifene and estrogen is unlikely to be helpful; the effects of each agent might essentially cancel each other out. Furthermore, the safety of combining the two therapies is unknown, especially with respect to thromboembolism.

Dr. Ettinger: I would not use these two agents together because we do not know the safety or efficacy of doing so. The risks of venous thromboembolism might be additive. Raloxifene is not strong enough to block estrogen's stimulation of the endometrium.

What happens if raloxifene and alendronate are used in combination, and when would this be done? What is the role for sequential treatment (e.g., two drugs followed by raloxifene)?

Dr. Birge: There is a synergistic interaction between estrogen and alendronate; therefore, it could be argued that a similar interaction would be seen with raloxifene. This combination would be used in women fearful of breast cancer and in those in whom lowering low-density lipoprotein (LDL) cholesterol is also desired.

Dr. Cosman: Sequential treatment is more likely to be of general applicability, since we don't know about the long-term safety (more than 5-10 years) of any drug—except, perhaps, ERT. The only study of raloxifene and alendronate (abstract presented at the 1999 ASBMR meeting) showed that alendronate was more potent than raloxifene, but the two drugs have additive effects on bone turnover and bone mass. Fracture outcome of combination therapy is unknown at this point. I believe combination therapy should be reserved for women who experience either fractures or active signifi-

cant bone loss on a single drug, and for women who want to stay on the first drug for other reasons, such as beneficial lipid effects. One other category of patient who might benefit from combination therapy is a group of women with extremely low BMD: *T*-scores of -5, for example. There are concerns related to oversuppression of bone remodeling with combination antiresorptive therapy. If bone is not renewed at all, it could accumulate microfractures or other micro-damage, and become subject to fracturing.

Dr. Ettinger: Adding raloxifene to alendronate adds little to the bone turnover or bone density. Those who are considering using antiresorptive drugs together should consider the following: The cost is twice as high; the gains in bone density are quite small; and no fracture effects of combined therapies have been demonstrated. Most importantly, oversuppression of bone turnover increases accumulation of microdamage because bone cannot normally repair itself—and this excessive microdamage will ultimately make bone more likely to fracture. Anyone who considers combination therapy must carefully monitor bone turnover markers and adjust dosages to prevent them from dropping too low.

In all of the raloxifene studies the outcomes have been nearly identical using 60- and 120-mg doses. Are there some cases in which you would treat with 120 mg?

Dr. Birge: Although the effects of the two doses of raloxifene on BMD and vertebral deformation were comparable, there was a greater increase in hot flashes at the 120-mg dose than at 60 mg. There seems to be little justification for use of the higher dose. The risk of venous thrombosis or pulmonary embolism was 3.1 times higher with raloxifene than with

placebo; no significant difference in this rate existed between the 60- and 120-mg groups.

Dr. Cosman: The 120-mg dose is more effective in protecting against vertebral fracture in women with prevalent vertebral fracture, without any published increase in toxicity at the higher dose. Even so, I am not using double-dose raloxifene at this point. I would rather substitute a different drug in a case in which I thought the patient was at high enough risk that the expected reduction in vertebral fractures using the 60-mg dose (30%) was not sufficient.

Dr. Ettinger: I do not recommend the use of a 120-mg dosing regimen, since it costs twice as much and certainly does not add much for the added cost.

Why does the increased BMD effect achieved in the first 12 months of raloxifene therapy not continue afterwards? (There even seems to be a small decrease between 24 and 36 months.) Do antiresorptives (estrogens, alendronate, raloxifene) really increase BMD, or do they just halt bone destruction progression?

Dr. Birge: Antiresorptive agents, such as estrogen and alendronate, do increase bone density, and this increase is sustained for many years or until the bone reaches a point at which there is no further stimulation of bone formation. Weaker antiresorptive agents, such as calcitonin and raloxifene, do not demonstrate a sustained increase and tend to plateau or decline after 1-2 years. The reasons for this difference are a matter of speculation.

Dr. Cosman: Most antiresorptive drugs (raloxifene, estrogens) increase bone mass transiently by closing the remodeling space. Alendronate has a more pro-

longed bone mass effect on bone formation, perhaps related to a relative stimulation of bone formation (or less inhibition of bone formation compared to the inhibition of bone resorption). An alternative explanation is hypermineralization caused by a decreased turnover rate, increased bone formation and increased time for mineral accumulation.

Dr. Ettinger: All antiresorptive drugs produce a transient increase in bone density because of the imbalance between resorption and formation. The increase typically occurs in the first year or two, after which there is a plateau during years 3 to 4. Later on, we usually see a slow decline in bone density—about half the usual rate of loss.

Should bone density be monitored in women on raloxifene and, if so, after how long can an increase in bone density be measured?

Dr. Birge: Bone mineral density should be monitored in any patient undergoing treatment for osteoporosis, just as we monitor blood pressure in patients being treated for hypertension. Because of the modest increase in bone density anticipated, the interval between measurements should be no less than 1 year.

Dr. Cosman: Unfortunately, no perfect monitoring tool exists. BMD changes are, on average, modest in women on raloxifene. Testing can be repeated at 1-2 years, but the treatment shouldn't be changed unless BMD loss exceeds the expected error with this measurement tool *in vivo* (i.e., 3-4% at the spine or >5-7% at the hip).

Dr. Ettinger: First, the FDA approved osteoporosis drugs we have today work well in about 80-90% of cases. Second, fracture protection is only weakly linked to bone density changes. Finally, in indi-

vidual patients, it is very difficult to measure small bone density changes. The error in the density machines is 1-2%; therefore, changes on the order of 3% are required to be sure that bone loss has not occurred. Because of these factors I generally do not use bone density to monitor treatment—although it is fine for deciding on the need for treatment. If you are monitoring treatment with bone density and there is an absence of change, do not conclude that the treatment is not working; instead, be skeptical of the test results.

Are there women who do not respond to raloxifene therapy with a decrease in bone remodeling (as there are with estrogen)?

Dr. Birge: There are women who do not respond to raloxifene. This is one of the reasons their response should be measured.

Dr. Cosman: Yes. Raloxifene is not as potent as ERT with respect to bone remodeling, and some women won't show a significant change, which exceeds the expected error for these tests.

Dr. Ettinger: Approximately 85-90% of women receiving raloxifene "respond," as defined by either increasing or not decreasing bone density over 3 years. Thus, doing bone density testing to monitor effect of treatment is a little bit like looking for a needle in a haystack. Furthermore, Cummings showed that when bone density decreases in women on good treatment, such as raloxifene or alendronate, the bone density test is most likely in error. So, we should be very skeptical of results that do not fit with a good response, and we should not jump to the conclusion that the treatment is not working.

Which patients do you consider for raloxifene therapy without bone density testing?

Dr. Birge: Postmenopausal women who elect to initiate ERT at the time of the menopause for the prevention of cardiovascular disease and osteoporosis, and who are not at increased risk of osteoporosis, do not need to have their bone density monitored. The rationale for this position is that estrogen is considered the optimal intervention for both the treatment and prevention of osteoporosis. This is not the case with raloxifene, since about half of these patients will not respond to the drug and more effective alternatives are readily available.

Dr. Cosman: None. I think bone density should always be tested before initiating therapeutic or preventive therapies for osteoporosis.

Dr. Ettinger: In our health plan about 70% of women are started on raloxifene without bone density testing; some of these patients really should have this testing. Generally, *T*-scores of -3.0 or lower indicate the need for osteoporosis drug therapy; however, an older woman with a history of fractures or with multiple risk factors is so likely to have low bone density that it is not necessary to measure it.

What is the best bone marker with which to measure the skeletal effects of raloxifene?

Dr. Birge: Because of the modest effects of raloxifene on bone turnover, none of the biomarkers of bone remodeling are reliable indicators of long-term effects on bone density or vertebral fractures.

Dr. Cosman: This is unclear. In general, it is possible that resorption markers have the best predictive value for hip

fracture risk; bone formation markers might be slightly better for monitoring. Because of cost, we certainly couldn't recommend doing multiple markers in all patients. Furthermore, there are differences within the groups of resorption markers and bone formation markers. I currently use the urinary N-telopeptide study more than others for monitoring purposes.

Dr. Ettinger: Both osteocalcin and urinary collagen cross-links (NTX, CTx) are good markers. Soon to be available clinically is a much improved serum cross-link test with better sensitivity and precision. Bone markers typically decrease 35-40% with raloxifene treatment; these same markers decrease 50-55% with bisphosphonate therapy.

Nonbone Effects

Does the reduction in LDL cholesterol seen with raloxifene persist over time?

Dr. Birge: The reduction in LDL seems to persist for up to 3 years.

Dr. Cosman: Yes.

Dr. Ettinger: Yes, the same reductions seen after 6 months are observed after 3 years of treatment.

Why does raloxifene, an antiestrogen, reduce LDL?

Dr. Birge: As a SERM, raloxifene could act as an estrogen agonist or antagonist at different tissues. Thus, at the breast, raloxifene acts as an estrogen antagonist, whereas at the bone, it acts as an estrogen receptor agonist. At the liver, raloxifene also acts as an estrogen receptor agonist, as evidenced by its decrease in LDL cholesterol synthesis. But raloxifene

Continued on page 25

is not a complete estrogen receptor agonist, in that it does not increase the synthesis of high-density lipoprotein (HDL) cholesterol.

Dr. Cosman: This is due to raloxifene's tissue-specific effects, which are estrogen-like in the liver but not identical to the effects of estrogen. For example, estrogen increases HDL, whereas raloxifene does not, but estrogen increases triglycerides while raloxifene does not.

Dr. Ettinger: The LDL-lowering effect is probably due to raloxifene's agonistic effects on the Apo-B receptor in the liver.

Do patients starting raloxifene require gynecologic evaluation?

Dr. Birge: Patients initiating raloxifene do not require a gynecologic examination beyond the routine pelvic examination prudent for good health care. Preliminary data suggest that endometrial stimulation and the risk of endometrial cancer will be considerably less than that observed with tamoxifen and, certainly, estrogen. It should, however, be noted that although raloxifene does not increase endometrial thickness, it does stimulate the endometrial endothelium. The long-term consequences of this effect on endometrial cancer risk remain to be determined.

Dr. Cosman: They should follow regular guidelines for gynecologic care, with specific attention paid to vaginal health, since raloxifene does not have the same trophic or salutary effects on vaginal or vulvar tissue as does estrogen.

Dr. Ettinger: Nothing beyond the usual preventive gynecologic exams.

Part 2 of this article will address raloxifene's "potential problems" and "unknowns."

Suggested Reading

- Bergkvist L, Adami HO, Persson I, et al. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progesterone replacement therapy. *Am J Epidemiol* 1989;130(2):221-8.
- Birge SJ. Soy phytoestrogens: An adjunct to hormone replacement therapy? *Menopause* 2000;7(4):209-12.
- Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group (see comments). *Lancet* 1996;348(9041):1535-41.
- Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial (see comments). *JAMA* 1998;280(24):2077-82.
- Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. *JAMA* 1999;281:2189-97.
- Delmas P. Clinical use of selective estrogen receptor modulators. *Bone* 1999;25:115-18.
- Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of Raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337:1641-7.
- Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: An overview of the randomised trials (see comments). *Lancet* 1998;351(9114):1451-67.
- Ettinger B, Black DM, Mitlak BH, 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;282:637-45.
- Goldstein SR. Selective estrogen receptor modulators: A new category of therapeutic agents for extending the health of postmenopausal women. *Am J Obstet Gynecol* 1998;179:1484.
- Grossman LD. Raloxifene: A review. *J Soc Obstet Gynaecol (Canada)* 2000;22:3-10.
- Jordan VC. Antiestrogenic action of raloxifene and tamoxifen: Today and tomorrow. *J Natl Cancer Inst* 1998;90:967-71.
- Lando JF, Heck KE, Brett KM. Hormone replacement therapy and breast cancer risk in a nationally representative cohort. *Am J Prev Med* 1999;17(3):176-80.
- Li CI, Weiss NS, Stanford JL, et al. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. *Cancer* 2000;88(11):2570-7.
- Neilsen J, Mor G, Naftolin F. Raloxifene induces neurite outgrowth in estrogen receptor positive PC12 cells. *Menopause* 1998;5:211-16.
- Prestwood KM, Gunnes M, Muchmore DB, et al. Comparison of the effects of raloxifene and estrogen on bone in postmenopausal women. *J Clin Endocrinol Metab* 2000;85:2197-202.
- Ross RK, Paganini-Hill A, Wan PC, et al. Effect of hormone replacement therapy on breast cancer risk: Estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000;92(4):328-32.
- Sato M, Rippey MK, Bryant HU. Raloxifene, tamoxifen, nafoxidine, and estrogen effects on reproductive and nonreproductive tissues in ovariectomized rats. *FASEB J* 1996;10:905-12.
- Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk (see comments). *JAMA* 2000;283(4):485-91.
- Sellers TA, Mink PJ, Cerhan JR, et al. The role of hormone replacement therapy in the risk of breast cancer and total mortality in women with a family history of breast cancer (see comments). *Ann Intern Med* 1997;127(11):973-80.
- Vardy MD, Cosman F, Heller D, et al. Short-term endometrial effects of raloxifene, tamoxifen and Premarin. *Fertil Steril* 1998;70(Suppl 1):S186-7.
- Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998;279:1445-51.
- Walsh BW, Paul S, Wild RA, et al. The effects of hormone replacement therapy and raloxifene on c-reactive protein and homocysteine in healthy postmenopausal women: A randomized, controlled trial. *J Clin Endocrinol Metab* 2000;85:214-18.
- Willis DB, Calle EE, Miracle-McMahill HL, et al. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes Control (England)* 1996;7(7):449-57.

Coming Soon in

MENOPAUSE MANAGEMENT

Women's Health Through Midlife & Beyond

- Depressive Disorders During the Menopause
- Premature Ovarian Failure: Addressing Patients' Needs
- Biologic and Clinical Effects of Progestins
- Calcium Supplements: Separating Fact From Fiction
- Uses and Limitations of Bone Mass Measurements