
Raloxifene FAQs: Perspectives on the First Approved SERM—Where Are We Now? Part 2

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 represent the views of The North American Menopause Society or Menopause Management.

As in Part 1 of this article, the data/studies referred to in this Q&A can be found in the articles in the Suggested Reading list (page 29).

Since its approval for the prevention and, later, treatment of osteoporosis, raloxifene has been the source of much discussion and, indeed, debate. In Part 1 of this article (January/February 2001;10(1):16,19-21,25) Drs. Birge, Cosman and Ettinger answered questions about using raloxifene to treat the skeleton, and about its effects on low-density lipoprotein cholesterol. In Part 2 the Q&A participants address potential problems and unknowns associated with raloxifene, and share their thoughts on the SERM's current and future roles in the treatment of midlife women.

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Dealing With Raloxifene's Potential Problems

What can be done to treat women with vasomotor symptoms related to raloxifene use?

Dr. Birge: Vasomotor symptoms associated with raloxifene can be avoided to a great extent by not initiating the drug within the first 5 years after the menopause. Those who do develop vasomotor symptoms can diminish those symptoms with the concurrent use of an SSRI.

Dr. Cosman: In general, some efficacy has been shown with soy isoflavones, and findings from a trial presented by Dr. Charles Loprinzi at the American Society of Clinical Oncology meeting in New Orleans indicate that the antidepressant zenlafaxine (Effexor) is effective. To my knowledge, however, there are no specific studies of any agents in patients who have hot flashes while on raloxifene.

Dr. Ettinger: We had previously recommended slowly tapering and discontinuing estrogen therapy for a month before starting raloxifene. Unpublished studies of various switching regimens show no difference in the occurrence of hot flashes with an immediate switch from one treatment to the other. I favor using raloxifene every other day at first, especially if some hot flashes occur. If hot flashes remain a problem, adding soy protein isolate could be considered (20-25 g protein per day provide about 60-75 mg of isoflavones).

Is there an increase in body weight associated with raloxifene use?

Dr. Birge: There is no evidence of an increase in body weight with raloxifene.

Dr. Cosman: No.

Dr. Ettinger: In clinical trials of

raloxifene there has been no difference in weight gain between women on raloxifene and those taking placebo.

For how long must raloxifene be interrupted if a patient is having surgery? How long (months or years) should a history of thromboembolic events be considered a contraindication to raloxifene therapy?

Dr. Birge: The risk of thromboembolic disease (approximately a threefold increased risk) is identical to that of estrogen and, therefore, the precautions should be the same for both agents.

Dr. Cosman: Therapy should be discontinued 3 days prior to surgery through at least the third day after surgery, or longer, until the patient has resumed normal ambulation. With respect to the thromboembolic events, it's possible that any history of such events should be considered a contraindication.

Dr. Ettinger: After stopping estrogen, tamoxifen or raloxifene, the coagulation factors probably return to normal within a matter of days. On the other hand, in HERS, Grady et al reported that DVT risk was still elevated a month after estrogen was stopped. The raloxifene package insert suggests discontinuation 3 days prior to immobilization; I currently recommend discontinuation a week prior. With respect to the second question, I would be concerned if a woman ever had idiopathic DVT or DVT after using birth control pills or HRT.

Unknowns

What is the mechanism by which raloxifene diminishes the development of cancer cells?

Dr. Birge: Raloxifene blocks the growth of breast cancer cells by blocking

access of estrogen to the receptor, as well as by receptor-mediated antiestrogenic effects.

Dr. Ettinger: There are many *in vitro* studies showing that raloxifene blocks the estrogen alpha receptors in breast and endometrium. It could also have a moderating effect on cell growth by stimulating estrogen beta receptors.

What kinds of hormonal treatments are reasonable for women at high risk for breast cancer?

Dr. Birge: Paradoxically, women at increased risk for breast cancer by virtue of a family history or other risk factors should initiate estrogen replacement. All studies have come to the same conclusion; namely, that women who have taken estrogen for more than 5 years have a consistent and significant (20-50%) reduction in their risk of dying from breast cancer, including those women with a first-degree relative with breast cancer. Recent studies indicate that the breast cancers that arise in women on estrogen are different from those that occur in nonusers of estrogen, in that estrogen users are more likely to develop lobular or *in situ* cancers and less likely to have metastasis to the regional lymph nodes. These studies also suggest that the actual increase in breast cancer incidence is small, on the order of 2-3% per 5 years of use. This increase is within the error of measurement and is, therefore, not significant. However, the addition of a progestin does significantly increase the incidence of breast cancer, including invasive breast cancers.

What can we expect from antiestrogens, such as tamoxifen and raloxifene? As noted above, the long-term exposure to tamoxifen might actually increase the risk, not only of breast cancer expression but also of the expression of more malignant forms of breast cancer—for example, estrogen-receptor-negative tumors—thereby actually increasing one's risk of

dying from the disease. Regrettably, the breast cancer prevention trials have been limited to less than 5 years of follow-up, denying the opportunity to see the emergence of the estrogen-receptor-negative tumors and increased mortality expected with more than 5 years of exposure.

Thus, those women at increased risk of breast cancer should probably initiate estrogen replacement with minimal exposure to progestin, for example cycling every 3-6 months with a progestin. Those women with a recent breast cancer diagnosis should take tamoxifen for 5 years as currently recommended, but they should not then switch to raloxifene, because its mechanism of action on the breast is essentially identical to that of tamoxifen. Whether that woman would be best served by taking estrogen is under investigation.

Dr. Cosman: Raloxifene or tamoxifen would be reasonable choices in people with relatively normal or low bone mass. In more severe osteoporosis, though, bisphosphonates would probably be preferable for osteoporosis treatment.

Dr. Ettinger: I urge women at high risk not to take estrogen systemically (vaginal is OK). Raloxifene is not currently FDA-approved for prevention of breast cancer, but it is not contraindicated either. The preclinical and clinical trial data are quite strong for a protective effect on breast tissue; however, the reduction in risk is best documented in elderly osteoporotic women who were at relatively low risk for breast cancer. Until the STAR study (double-blind, equivalency study of tamoxifen versus raloxifene) is completed, we will not have proof that raloxifene is effective for younger women at increased risk for breast cancer.

What do we know about the long-term effects of raloxifene?

Dr. Birge: We know very little about the long-term consequences of raloxifene use. Clinical trials with raloxifene have

not gone beyond 4 years of follow-up. There is not much more information that can be inferred from our experience with tamoxifen, because the use of this drug has been limited to 5 years as a result of the one large clinical trial that examined the effect of this antiestrogen on breast cancer and found both increased incidence and mortality with more than 5 years of use.

One concern about the long-term effects of any antiestrogen is the potential for adverse effects on the brain. Both tamoxifen and raloxifene cause hot flashes, suggesting that these drugs may be acting as estrogen antagonists with respect to some functions of the brain. Because estrogens might have an effect on reducing the incidence of Alzheimer's disease some 20 to 30 years after exposure to estrogen, the possibility that raloxifene could increase a woman's risk of expressing Alzheimer's disease must be considered.

Dr. Cosman: To date, we know little about the effects beyond the 4-year point.

Dr. Ettinger: Four-year data have now been presented from the MORE (osteoporosis) study. There have been no surprises; reduction in vertebral fracture and of breast cancer continues at about the same rates as those seen in the initial reports. About half the 7,705 women evaluated in that study are continuing on the double-blind protocol for another 4 years. While the primary outcome is breast cancer, all other outcomes will, of course, be examined.

What are the effects of raloxifene in postmenopausal diabetic women?

Dr. Birge: I don't know of any data that address that question.

Dr. Cosman: Nothing significant appears to have been detected so far.

Dr. Ettinger: There is a very large (10,000 women) primary and secondary

CHD study that will give us solid data on possible protection against myocardial infarction. Included in this study are diabetics, hypertensives and heavy smokers—both those at risk for and those with CHD. Thus far there has been no report of any adverse CHD effect such as was found for HRT in HERS and the WHI.

At what age do you recommend starting raloxifene therapy?

Dr. Birge: If one were to start raloxifene, one would want to do so perhaps 5 or more years after the menopause in order to avoid the hot flashes. I would, however, be reluctant to start raloxifene at any age.

Dr. Cosman: I recommend starting treatment during a woman's mid-50s.

Dr. Ettinger: The optimal age is unknown—one needs to balance cost and benefit. The National Osteoporosis Foundation calculated that if you only had 5 years to treat, starting osteoporosis therapy at age 60–65 years would be best. Ideally, it would be best to initiate therapy a few years before fractures would occur. Given that the average age for the first spine fracture is about 70, I think 65 is a good age.

Does raloxifene have a positive or negative effect in the patient with articular disease?

Dr. Birge: There are insufficient data to answer this question. It is not clear what effect estrogen has on articular disease, despite numerous studies.

Dr. Cosman: This isn't known at this time.

Dr. Ettinger: Estrogen seems to reduce the risk of degenerative joint disease. We have, as yet, no data on raloxifene in this regard.

Does raloxifene show the same beneficial effect as estrogens on blood pressure?

Dr. Birge: Again, there are insufficient data to address this question. We do know that raloxifene does affect endothelial function in a manner similar to estrogen, and we therefore can surmise that its effect might be similar to that of estrogen.

Dr. Cosman: Raloxifene appears to produce a slight reduction in blood pressure, compared with placebo.

Dr. Ettinger: Estrogen lowered blood pressure a few mmHg in clinical trials. I have not seen similar data for raloxifene.

What do we know about the effect of raloxifene versus estrogen on brain metabolism and cognition?

Dr. Birge: Raloxifene has both estrogen agonist and antagonist effects on the brain. Again, we don't know which of the multiple effects of estrogen on the brain results in the apparent reduction in the expression of Alzheimer's disease many years after exposure. Therefore, it will be very difficult to extrapolate from *in vitro* studies and short-term clinical trials with raloxifene as to what the long-term consequences of this SERM will be on brain aging and Alzheimer's disease.

Dr. Cosman: In *in vitro* and *in vivo*, studies the effect of raloxifene was neutral or positive.

Dr. Ettinger: *In vitro* studies indicate that both estrogen and raloxifene have trophic effects on neurons. They both promote enzymes responsible for production of neurotransmitters, enhance nerve growth factor production and stimulate dendritic-type neuron outgrowths. Epidemiologic studies of estrogen suggest that it could reduce the risk of Alzheimer's disease, but a large clinical study of estrogen in patients with

Alzheimer's has shown negative results. However, we should only trust the cognitive function effects of these agents in well-designed clinical trials. Neither estrogen nor raloxifene has shown major CNS improvements in clinical trials involving older women. Data from the MORE (raloxifene) study indicate that women receiving raloxifene, compared to placebo, who were over age 70 years did better on verbal memory testing; there were no tests in which raloxifene users did worse than those receiving placebo.

Are there known effects of raloxifene on the immune system?

Dr. Birge: I am not familiar with this literature.

Dr. Cosman: None that I know of.

Dr. Ettinger: Not that I am aware of.

Can raloxifene be used in patients with migraine?

Dr. Birge: Again, I'm not familiar with the literature on this topic.

Dr. Cosman: Yes. There is no significant increase in migraines with raloxifene, and it might actually reduce headache occurrence overall.

Dr. Ettinger: Headaches were not more frequent in women using raloxifene than those receiving placebo.

What is the longest duration for which raloxifene should be used?

Dr. Birge: This is an important question, because raloxifene is being marketed as an alternative to estrogen replacement for the prevention of osteoporosis and cardiovascular disease, with the implication that it might also prevent breast cancer. Efficacy in the prevention of osteoporosis and cardiovascular disease would require long-term, if not in-

definite, use. However, this SERM's effect on the breast and the cardiovascular system is essentially identical to that of tamoxifen. Like tamoxifen, it lowers LDL but has no effect on HDL cholesterol. A meta-analysis of 55 clinical trials involving 37,000 women demonstrated no effect of tamoxifen on cardiovascular disease.

More relevant to this question is the study that examined the effect of tamoxifen use for less than 5 versus more than 5 years. This study demonstrated that breast cancer incidence and mortality increased with tamoxifen use for more than 5 years. It was for this reason that, in 1996, physicians were advised not to continue this agent for more than 5 years. It, therefore, seems prudent that, until data indicate otherwise, raloxifene not be used for more than 5 years because of its similarity of action to tamoxifen.

Dr. Cosman: Probably 5 years, although this is unknown right now.

Dr. Ettinger: In the MORE study, results for up to 4 years for major endpoints and for safety have been presented. As mentioned above, about half these women will continue for another 4 years in this double-blind study. Thus, patients starting on raloxifene can be reassured that we are collecting long-term follow-up information to allow them to continue long-term (many years) therapy, to reap even greater benefits.

Final Thoughts

When all is said and done, do you feel raloxifene has lived up to its potential, as anticipated when first approved? What is its primary role in the treatment of midlife women today, and do you expect this role to change or evolve?

Dr. Birge: Raloxifene has not lived up to its FDA-approved indication: the pre-

vention of osteoporosis. The major reason for the use of an agent to prevent osteoporosis is to prevent hip fractures. The MORE trial has convincingly demonstrated that raloxifene does not prevent this devastating fracture, which would otherwise justify the cost and known risk of thromboembolic disease, as well as the unknown risk of Alzheimer's disease and increased risk of breast cancer mortality. Furthermore, suggesting that this drug is effective in the prevention of osteoporosis implies to physicians and their patients that it will decrease the risk of hip fracture. In doing so they will be prevented from seeking more effective interventions that have been demonstrated to reduce their risk of hip fracture. In light of what we know about more than 5 years of tamoxifen use increasing the incidence and mortality from breast cancer, it would seem reasonable, until we know otherwise, that raloxifene be used for no more than 5 years. This being the case, this drug cannot be considered an alternative for the long-term prevention of osteoporotic fractures. Like tamoxifen, there is little expectation that raloxifene will prevent cardiovascular disease. Therefore, I see no role for this agent in the treatment of the postmenopausal woman.

Dr. Cosman: Raloxifene's most important role is in the prevention of bone loss and vertebral fractures in women in the middle menopausal years (mid-50s to mid-60s), before hip fracture becomes a large issue (70s and 80s). The "side benefit" with respect to reducing breast cancer risk makes raloxifene a great choice for women who need treatment for osteoporosis but who are concerned about breast cancer or at high risk for the disease. Positive cardiovascular outcomes or positive data showing that raloxifene works against fractures other than the spine will expand the use of this agent.

Dr. Ettinger: When I was enumerating the list of health benefits possible with long-term use of raloxifene to a newspa-

perman, the interviewer remarked, "It seems to do everything but the house-work!" There is a remarkable number of potential health benefits from the use of raloxifene—to reduce the risk of diseases that matter most to women and their healthcare providers. Furthermore, our studies show that women starting therapy are more likely to continue on raloxifene than HRT. I suspect it is the perception of raloxifene's multiple benefits, the "health package" it provides, that determines acceptance and continuation. But raloxifene is not ideal—we hope that in the future we will see a SERM that helps hot flashes, that has positive effects on the urogenital tissues and does not increase the risk of venous thromboembolism. We also need to know much more about raloxifene's long-term benefits on the brain, on vascular disease, on tumor development and on immunity. Raloxifene has captured the imagination of many, because it points out the inadequacies of our current postmenopausal hormone regimens and points the way to future improvements of treatment of postmenopausal women.

Suggested Reading

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