CME CREDIT

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Raloxifene: A new choice for treating and preventing osteoporosis

ABSTRACT

Selective estrogen receptor modulators (SERMs) are a new class of drugs that provide a new option for addressing the health challenges of postmenopausal women. This review discusses the proposed mechanism of action of SERMs and describes clinical findings on raloxifene, a SERM now available for treating and preventing osteoporosis.

KEY POINTS

Like estrogen, raloxifene increases bone mineral density, although the magnitude of the effect is not as great. However, raloxifene effectively prevents fractures to as great a degree as has been demonstrated for any other agent.

Raloxifene is free of estrogen's side effects on the breast and endometrium. Both drugs increase the risk of venous thromboembolism. Raloxifene may cause hot flashes in some women.

Raloxifene lowers cholesterol, LDL, and fibrinogen levels but does not affect HDL or triglycerides. Because raloxifene is associated with a decreased incidence of breast cancer in postmenopausal osteoporotic women, some patients may find it more acceptable than estrogen replacement therapy.

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RALOXIFENE (Evista) is one of a new generation of drugs, called selective estrogen receptor modulators (SERMs), with estrogen-like effects on the skeleton and cardiovascular system, but antiestrogen effects on the breast and endometrium. This profile makes it an attractive alternative to estrogen replacement for long-term therapy to treat and prevent osteoporosis in postmenopausal women.

All of the drugs currently available to prevent osteoporosis have unique advantages and disadvantages, both in their clinical action and in terms of patient compliance with therapy.

In this article we first outline the pros and cons of estrogen replacement therapy and bisphosphonates, then discuss tamoxifen, the first SERM, and its analogs. In the final section, we discuss raloxifene, the first in a new class of SERMs (the benzothiophenes), and evaluate its place in the emerging field of postmenopausal women's health.

BENEFITS AND LIMITATIONS OF ESTROGEN REPLACEMENT THERAPY

Estrogen replacement therapy has become the standard of care for perimenopausal and postmenopausal women. It relieves perimenopausal symptoms such as hot flashes and has favorable effects on bone mineral density, bone turnover markers, and cardiovascular risk factors.[1,2]

Estrogen prevents osteoporosis

Estrogen replacement is the most established treatment available for preventing and managing postmenopausal osteoporosis.[3] Used prophylactically, it can maintain bone mass.[4]

In patients with established osteoporosis, it increases bone mineral density in the lumbar spine and various other skeletal sites by 2% to 5%.[5] In the elderly, it can arrest bone loss even many years after menopause.[6] Observational studies suggest that estrogen therapy may reduce the risk of hip and spine fractures, although the benefit is attenuated once therapy is stopped[7,8]; at present, however, data are lacking from prospective, randomized, controlled trials to confirm these findings.

Estrogen's effect on coronary artery disease is unclear

Estrogen replacement affects a variety of risk factors for coronary artery disease, lowering serum levels of cholesterol, low-density lipoprotein (LDL), and fibrinogen and raising high-density lipoprotein (HDL).[9] On the other hand, it raises serum triglyceride levels.[9]

Observational studies suggest that postmenopausal women who receive estrogen replacement have lower rates of coronary artery disease than those who do not.[10,11] Only one prospective, controlled, randomized trial has been performed to determine if estrogen replacement actually prevents coronary events, however, and it had negative results.[12]

The HERS study: No benefit from estrogen in coronary artery disease

This recent trial was called the Heart and Estrogen/progestin Replacement Study (HERS).[12] Participants were postmenopausal women with established coronary artery disease. Treatment consisted of the combination of conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg or placebo. At an average of 4.1 years of follow-up, there was no difference between the groups in the incidence of myocardial infarction, coronary heart disease death, or other cardiovascular outcomes. In fact, there were more events in the estrogen group than in the placebo group in the first year (but fewer events in years 4 and 5).

These findings apply only to the population and drug regimen studied. Studies are underway that may eventually clarify the long-term cardiovascular benefits of hormone replacement therapy in postmenopausal women.

Risks of cancer, thromboembolism: Small but significant

Estrogen replacement therapy carries a small increased risk of serious complications, and the risk increases with duration of therapy.

Endometrial cancer occurs up to four times more frequently in women with a uterus who take unopposed estrogen than in nonusers. The risk may be reduced, but not completely eliminated, by adding a progestin.[13]

Breast cancer risk may increase slightly with hormone replacement. In the Nurses' Health Study,[14] the risk of death from breast cancer was 43% higher in women who had used hormones for more than 10 years than in nonusers. In a reanalysis of data from 51 epidemiological studies involving more than 150,000 breast cancer cases and controls, the relative risk for breast cancer was 1.35 for women who had used hormone replacement therapy for 5 years or more.[15]

Venous thromboembolism is rare but increases with estrogen use. Observational studies report an approximately threefold increase in the incidence of venous thromboembolism in women receiving hormone replacement therapy.[16,17] This finding was confirmed in the HERS clinical trial.[12]

Compliance is low

Uterine bleeding, breast pain, and fear of cancer and thromboembolism probably all contribute to a low rate of compliance with hormone replacement therapy: approximately 70% of women refuse it outright or stop taking it prematurely.[18] This reality diminishes the potential benefit of estrogen therapy in the postmenopausal population.

BISPHOSPHONATES AND OTHER DRUGS

Bisphosphonates

Bisphosphonates (eg, etidronate, alendronate, others) inhibit resorption of bone. In clinical studies in women with osteoporosis, these drugs increased bone mineral density and reduced fractures.[19,20] On the minus side, alendronate can cause esophagitis, and regimens for bisphosphonates in general are complex. These factors may limit long-term compliance.[21] Etidronate is available for osteoporosis treatment in Europe and Canada.[22]

Calcitonin and other drugs

Calcitonin also inhibits bone resorption, may increase bone density, and may prevent fractures in osteoporotic women.[23,24] Other agents for possible use in postmenopausal osteoporosis prevention are also under study.[3] Further discussion of these agents is beyond the scope of this review.

BENEFITS AND LIMITATIONS OF SERMS

An ideal drug for long-term use in postmenopausal women would offer the benefits of estrogen but not its undesirable side effects and associated cancer risks. SERMs are being developed to address this need.[25]

How SERMs work

SERMs are a structurally diverse group of compounds. All of them bind with high affinity to estrogen receptors, and all of them are believed to change the shape of the receptor in a unique way.[26] The ligand-receptor complex combines with specific adapter proteins and interacts with target DNA sequences, either promoting or inhibiting gene transcription.[27]

Depending on the SERM, the tissue in question, and the estrogen-dependent pathway being considered, a SERM may produce either estrogen-like effects or estrogen-blocking effects.[25] Part of the explanation for this may involve the different types of estrogen receptors. There are two different known estrogen receptors: alpha and beta. Different tissues contain different ratios of alpha and beta receptors.[28] SERMs bind to both types, but differential actions through these receptors may contribute to the nature and magnitude of the biological response in a specific tissue to an estrogen or to a particular SERM.

Tamoxifen: The first SERM

Tamoxifen (Novaldex), a triphenylethylene SERM, has estrogen-like effects on the skeleton, lipid levels, and uterus, but antiestrogen effects on the breast.

Tamoxifen has been used for many years to treat breast cancer.[29] In 1998, it was shown to reduce the incidence of breast cancer in healthy women at high risk for developing this disease.[30]

In addition, tamoxifen prevents resorption of bone, increasing lumbar spine bone mineral density in postmenopausal women.[31] It reduces serum levels of cholesterol and LDL, but has little effect on HDL.[32] However, tamoxifen stimulates the endometrium, and users have an increased risk of endometrial cancer[30,33] and thromboembolism.[34]

Tamoxifen analogs and other SERMs

Toremifene (Fareston), droloxifene (not yet available), and idoxifene (not yet available) are analogs of tamoxifen. Like tamoxifen, they appear to be estrogenic in the skeleton and antiestrogenic in breast tissue.[35,36] Toremifene, which is approved for treating advanced breast cancer, also stimulates the endometrium,[37] but an association with endometrial cancer has not been established.[38] Clinical reports on the safety and efficacy of droloxifene and idoxifene in treating breast cancer and postmenopausal osteoporosis are limited, but preliminary findings suggest that they may stimulate the uterus to a lesser degree than does tamoxifen.[39,40] Nonetheless, trials of idoxifene in osteoporosis were stopped because of unacceptable genitourinary side effects.[41]

Newer SERMs include benzothiophenes (such as LY353381), tetrahydronaphthylenes (such as CP-336,156), and benzopyrans (such as EM-800).[42] These compounds are chemically and pharmacologically distinct from the triphenylethylenes, and their clinical efficacy and safety remain to be determined.[43]

Different SERMS have different effects on different organs

RALOXIFENE

Raloxifene belongs to the benzothiophene class of SERMs. It has been investigated more extensively than any other SERM for its skeletal antiresorptive effects, and it appears to have a profile well-suited to the needs of postmenopausal women—ie, it has estrogen-like effects on the skeleton and on blood lipid levels, but estrogen-blocking effects in the breast and uterus.

Studies in animals

In ovariectomized rats, raloxifene preserved bone mass and reduced serum cholesterol levels.[44] In ovariectomized, cholesterol-fed

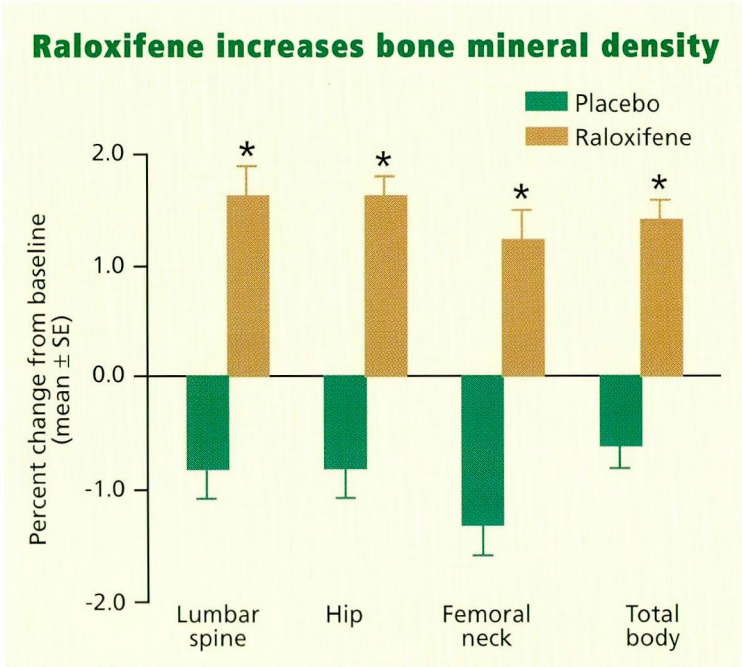

FIGURE 1. Changes in bone mineral density in postmenopausal women treated with placebo or raloxifene 60 mg/day for 2 years. Bone mineral density was measured by dual-energy x-ray absorptiometry and expressed as mean percentage change from baseline ± standard error of the mean (SE). Asterisks denote statistically significant difference from placebo, $P < .05$, using least-squares analysis.

DATA FROM DELMAS ET AL.[55] FIGURE REPRODUCED WITH PERMISSION FROM RESCH H, CIACCIA AV, DRAPER MW. *SELEKTIVE ÖSTROGEN-REZEPTORMODULATOREN (SERMS): NEUE MÖGLICHKEITEN DER AUFRECHTERHALTUNG DER GESUNDHEIT IN DER MENOPAUSE.* J MINERALSTOFFWECHSEL 1999; 6(2):22–28.

rabbits, raloxifene inhibited aortic accumulation of cholesterol.[45] On the other hand, in ovariectomized cynomolgus monkeys raloxifene failed to reduce coronary atherosclerosis significantly when compared with conjugated equine estrogen.[46] However, the monkeys who received estrogen had higher-than-expected blood levels of 17β-estradiol, the coronary plaques varied in size, and the sample number was low, and all of these may have limited the ability of this model to detect an effect of raloxifene.[47] Raloxifene antagonizes the stimulatory effects of estrogen in the mammary gland of mice and prevents mammary tumors induced by carcinogens in rats. In these studies, raloxifene had little or no effect on uterine weight and histology.[48,49]

Effect on osteoporosis in humans

Studies in humans have also shown that raloxifene, like estrogen, protects the skeleton.

In a study of calcium kinetics,[50] both raloxifene and estrogen replacement reduced bone resorption in the first 4 weeks of therapy without significantly altering bone formation. With raloxifene, the rates of resorption and formation did not change significantly between the 4th week and 31st week of therapy, whereas both were lower with estrogen. In other studies, raloxifene exerted a positive effect on several biochemical markers of bone metabolism, similar to estrogen.[51,52] Histomorphometry studies indicate that bone quality is normal in patients receiving raloxifene.[53]

Furthermore, in a study in healthy postmenopausal women,[51] raloxifene 60 mg/day (approved dosage) for 2 years effectively prevented bone loss, significantly increasing the bone mineral density of the lumbar spine, hip, and total body by about 2% relative to placebo (FIGURE 1).[51] This increase was somewhat less than the increases observed in studies of alendronate and hormone replacement therapy.[5,54]

In the Multiple Outcomes of Raloxifene (MORE) trial, a double-blind, placebo-controlled, clinical trial that enrolled 7,705 osteoporotic women, raloxifene treatment for 3 years significantly reduced the risk of new vertebral fractures by 30% to 50%,[55] similar to the results reported in a comparable trial with alendronate.[19,20] This finding suggests that even though raloxifene's effects on bone mineral density are less than those of some other established therapies, it reduces vertebral fracture rates to as great an extent as other therapy.

Effect on cardiovascular risk factors in humans

Raloxifene also has favorable effects on markers of cardiovascular disease. In one study, LDL cholesterol concentrations were significantly decreased by about 10% after 8 weeks of treatment with either raloxifene 200 mg/day or conjugated equine estrogens.[52] Similar changes in serum lipid concentrations were observed in studies in which women in their early years after menopause received raloxifene 60 mg/day for 2 years (FIGURE 2).[51] In contrast to estrogen replacement therapy, raloxifene does not increase HDL cholesterol, nor

does it raise triglycerides.[56] However, in one study, raloxifene decreased fibrinogen levels by 12% to 14%, whereas hormone replacement therapy had no significant effect on this cardiovascular risk factor.[56]

The potential cardioprotective effects of raloxifene are being evaluated in the Raloxifene Use for the Heart (RUTH) trial, which will enroll 10,000 postmenopausal women. The primary endpoint will be the combination of coronary death and nonfatal myocardial infarction.[57]

Little or no effect on endometrium

Unlike estrogen, raloxifene does not stimulate the endometrium.[58,59] Results from the MORE trial suggest that the risk for endometrial cancer is not increased after 3 years of raloxifene treatment.[60] In contrast, in women taking tamoxifen, increases in endometrial cancer incidence have been observed within the first 2 years of therapy.[30] Continued follow-up will be needed to fully evaluate the effect of raloxifene on the endometrium.

May decrease breast cancer

Women receiving raloxifene report no increased incidence of breast pain,[61] a well-known side effect of estrogen replacement therapy.

In addition, in the MORE trial, the incidence of newly diagnosed breast cancer was approximately 75% lower in raloxifene-treated subjects than in the placebo group, through 3 years of treatment.[60] Most tumors diagnosed during the first 3 years of this trial were probably present at a subclinical level at the start of the trial. Thus, the reduction in breast cancer risk currently observed with raloxifene may represent suppression or regression of subclinical cancer.[60]

Long-term trials will be required before a definitive assessment can be made of raloxifene as a chemopreventive agent. In addition, raloxifene has not been adequately studied in women with active breast cancer and is not indicated for the treatment of this disease.

Side effects of raloxifene

In clinical trials in postmenopausal women, raloxifene was well tolerated. Common drug-related adverse events include hot flashes and leg cramps (TABLE 1).

Raloxifene improves cholesterol and LDL but not HDL and does not worsen triglycerides

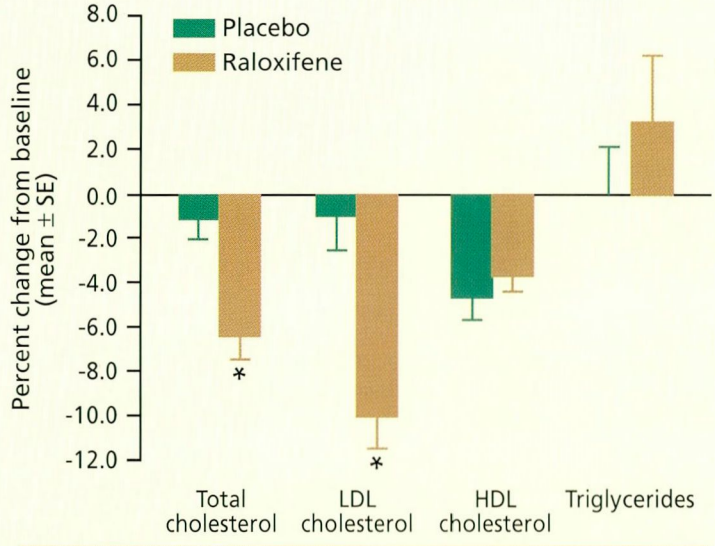

FIGURE 2. Changes in serum lipid concentrations in postmenopausal women treated with placebo or raloxifene, 60 mg/day for 2 years. Serum lipid data are expressed as mean percentage change from baseline ± SE. Asterisks denote statistically significant difference from placebo, $P < .05$, using least-squares analysis.

DATA FROM DELMAS ET AL.[55] FIGURE REPRODUCED WITH PERMISSION FROM RESCH H, CIACCIA AV, DRAPER MW. *SELEKTIVE ÖSTROGEN-REZEPTORMODULATOREN (SERMS): NEUE MÖGLICHKEITEN DER AUFRECHTERHALTUNG DER GESUNDHEIT IN DER MENOPAUSE* J MINERALSTOFFWECHSEL 1999; 6(2):22–28.

Hot flashes early in menopause were more common in women taking raloxifene 60 mg/day than in those taking placebo, but this did not increase the discontinuation rate.[61] The incidence of hot flashes was only statistically significantly higher in the raloxifene group during the first 6 months of therapy. Postmenopausal women are more likely to experience hot flashes on raloxifene therapy if they are younger than 55 years, have had a hysterectomy, or had previously experienced hot flashes.[62]

Leg cramps (mild) were reported by about 5% of raloxifene-treated patients.[61] However, no patients dropped out of raloxifene clinical trials because of this symptom. The reason for these leg cramps remains unknown, but they do not appear to be associated with serious complications.

TABLE 1

Raloxifene at a glance

Brand name
Evista

Therapeutic category
Selective estrogen receptor modulator (SERM)

Use
Treatment and prevention of osteoporosis in postmenopausal women

Contraindications
Male gender, pregnancy, history of thromboembolic events, prolonged immobility

Warnings and precautions
A risk of thromboembolism exists and is greatest in the first 4 months of therapy; discontinue raloxifene at least 72 hours before any prolonged immobilization such as surgical recovery; the safety of raloxifene has not been extensively studied in patients with hepatic failure, premenopausal status, or concomitant use of systemic estrogen replacement therapy

Adverse reactions
Hot flashes, leg cramps (common); thromboembolism (rare)

Drug interactions
Cholestyramine reduces the absorption and metabolism of raloxifene; raloxifene can reduce the prothrombin time when given with warfarin; caution should be observed when raloxifene is given with other highly protein-bound drugs such as clofibrate, indomethacin, naproxen, ibuprofen, diazepam, and diazoxide

Pharmacokinetics and metabolism
Rapidly absorbed after oral administration; highly bound to plasma proteins; undergoes extensive first-pass metabolism in the liver (but not by cytochrome P450 pathways); excreted in the feces

Dosage
60 mg/day; can be given at any time of day without regard to meals

Patient information
Patients should be advised to undertake lifestyle changes to reduce the risk of osteoporosis—ie, maintain an adequate intake of calcium and vitamin D, undertake weight-bearing exercise as tolerated, limit alcohol intake, and stop smoking

Venous thromboembolism (deep vein thrombosis and pulmonary embolism) is more common in raloxifene users than in nonusers, as it is with users of tamoxifen and estrogen replacement therapy. For this reason, raloxifene is contraindicated in women with active venous thromboembolic disease or a significant past history of venous thromboembolic events.[63] The greatest risk for these events occurs during the first 4 months of treatment with raloxifene, and the magnitude of the risk appears to be similar to that with tamoxifen[30] or estrogen replacement therapy.[12]

Who should receive raloxifene?

Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women. TABLE 2 gives the currently accepted definition of osteoporosis and lists important risk factors for this disease.

Why use raloxifene instead of estrogen replacement therapy? One possible reason would be if a woman refuses, stops, or cannot take estrogen owing to:

- Symptomatic problems associated with estrogen replacement therapy (ie, breast tenderness, vaginal bleeding)
- Fear of breast cancer or endometrial cancer
- A family history of breast or endometrial cancer
- History of dysfunctional uterine bleeding.

Why not use a bisphosphonate? Raloxifene may be useful if a woman cannot comply with a complicated bisphosphonate regimen. It also may offer a "two-for-one" benefit if a woman also is at risk for cardiovascular disease, especially if she is diabetic and has elevated triglyceride levels. (This point remains conjectural, however.)

Owing to the risk of thromboembolism, candidates for raloxifene or estrogen replacement therapy should be ambulatory.

CONCLUSIONS

Among more recently developed options, certain SERMs may be unique in that they hold promise for protective effects in the skeleton and the cardiovascular system, while at the same time demonstrating antiproliferative actions in reproductive tissues.

Raloxifene, a new SERM, has undergone extensive clinical investigation. At present it is the only SERM approved for treating and preventing osteoporosis in postmenopausal women, as studies have found that it prevents bone resorption and maintains bone mass in women in early postmenopause, and reduces the risk for osteoporotic vertebral fractures by as much as 50% in women who already have

osteoporosis.

At the same time, raloxifene has few side effects. Because of its estrogen antagonist action in the endometrium and breast, in clinical trials it produced no more vaginal bleeding or breast pain than did placebo.

Although raloxifene is currently indicated only for treating and preventing osteoporosis, it also shows some effects that may eventually make it useful in preventing cardiovascular disease and breast cancer. It changes lipid levels in directions that should reduce cardiovascular risk, and its effect on clinical cardiovascular outcomes is being evaluated. In a trial in osteoporotic, postmenopausal women, raloxifene reduced the incidence of new cases of breast cancer by approximately 75% after 3 years.[60]

Further research is needed to clarify its role in the prevention of cardiovascular disease and breast cancer. These effects may eventually prove to be the desired combination for many postmenopausal women, which could then result in good long-term compliance with this regimen.

TABLE 2

Candidates for raloxifene therapy

Postmenopausal women at risk for osteoporosis, ie, with any of the following:
- Family history of osteoporosis
- Evidence of rapid or extensive bone loss early in menopause
- Caucasian or Asian descent
- Slender body habitus
- Smoking history
- Excessive alcohol consumption
- Low calcium diet
- Sedentary lifestyle

Postmenopausal women with osteoporosis, ie, with one or more of the following:
- Low bone mineral density (T-score ≤ -2.5)
- History or radiographic documentation of osteoporotic fracture
- Physical signs of vertebral crush fractures (eg, height loss, dorsal kyphosis)

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