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Designing the ideal selective estrogen receptor modulator—an achievable goal?

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Abstract

Selective estrogen receptor modulators (SERMs), which lack the estrogen steroid moiety yet retain the ability to bind the estrogen receptor (ER), are known to confer mixed ER agonist or antagonist effects depending on the target tissue. The tissue-selective effects of SERMs have led to considerations in the clinical profile of an ideal SERM, which would have ER agonist activity in tissues where mimicking the action of estrogens is desirable, and ER neutral or antagonist activity in tissues estrogens have been shown to adversely stimulate. A number of newer SERMs, including bazedoxifene, lasofoxifene, ospemifene, and arzoxifene, are currently in clinical development for the prevention and treatment of postmenopausal osteoporosis and for other indications. Although the possibility of developing a single agent that has all of the desired characteristics of an ideal SERM seems to be unlikely, progress in the clinical development of SERMs targeted to the ER suggests that these newer compounds may have attributes that represent an improvement relative to existing SERMs. Further clinical investigation will help to clarify the relative benefits and risks of novel SERMs in development within specific indications.

Keywords

Selective estrogen receptor modulator (SERM); Postmenopausal; Estrogens; Osteoporosis; Cancer risk

The term selective estrogen receptor modulator (SERM) refers to a structurally diverse group of compounds that bind to the estrogen receptor (ER) despite lacking the estrogen steroid moiety.¹ Whereas estrogens typically exert ER agonist effects, SERMs confer mixed functional ER agonist or antagonist activity depending on the target tissue. The tissue-selective effects of SERMs have led to considerations in the clinical profile of an ideal SERM (Table 1). Conceptually, an ideal SERM would have ER agonist activity in tissues where mimicking the action of estrogens is desirable (eg, skeletal, cardiovascular, and central nervous systems), and ER neutral or antagonist activity in tissues estrogens have been shown to adversely stimulate (eg, breast and endometrium). Whether one SERM would be able to achieve the perfect blend of tissue-selective properties remains unknown.

Despite the lack of an ideal SERM to date, a number of SERMs have demonstrated a favorable benefit–risk balance within specific therapeutic indications and are available for clinical use (Table 2). Newer SERMs are currently undergoing clinical investigation for the management of postmenopausal conditions associated with estrogen deficiency, particularly

osteoporosis. This perspective describes the most recent literature on SERMs to evaluate their strengths and weaknesses in the context of an ideal SERM. It should be noted that the US Food and Drug Administration (FDA) recently replaced the term “SERM” with “estrogen agonist/antagonist drug”; however, for the sake of simplicity, the term “SERM” will be used throughout this article.

THE PROMISE OF SERMs

Like estrogens, SERMs are known to bind to ERs with high affinity and to mediate transcriptional events^{2,3} across a range of tissues.^{4–7} The promise of SERMs lies in their ability to differentially act as ER agonists or antagonists depending on the target tissue.⁸ The exact mechanisms by which SERMs exert their tissue-specific actions are not fully understood, although evidence suggests that the balance of ER coregulators and the cellular microenvironment interact to determine the effect of a SERM on a given cell type.⁹ Microarray gene expression analysis has shown that different sets of genes are regulated through ER- α versus ER- β in response to estradiol and SERMs.² The wide-ranging effects of SERMs seem to be mediated by expression of the ER in different tissues, ER conformation after binding of the ER ligand, and expression and binding of the ER–ligand complex to coregulator proteins.¹

SERMs are characterized by their complex pharmacologic effects on ER-regulated signaling pathways rather than a common chemical structure. As a result, SERMs must be evaluated individually because each SERM has unique pharmacologic properties that determine its clinical potential. An ideal SERM would prevent bone loss and fractures; reduce the risk of breast and endometrial cancer (and limit endometrial proliferation); provide relief of hot flashes and other menopausal symptoms; and not increase the risk of coronary heart disease, stroke, or deep vein thrombosis.^{10,11} It should be noted that the first generation of SERMs was not developed with these targeted goals in mind, but rather from existing compounds.

CHALLENGES WITH CURRENTLY AVAILABLE SERMs

As previously mentioned, a number of SERMs are approved for clinical use (Table 2). The criteria for assessing the benefit–risk balance of a particular SERM may vary depending on the specific therapeutic indication. Tamoxifen, which has antiestrogen activity in the breast and estrogen-like activity in the uterus,^{12,13} is recognized as a highly effective agent for the treatment of ER-positive breast cancer. However, tamoxifen exhibits ER agonist activity in the endometrium, conferring a 2- to 7.5-fold increase in the risk of endometrial cancer.^{12,14–16} Tamoxifen has also been shown to provide skeletal and cardioprotective benefits^{17–19}; however, endometrial safety concerns limit its use to the postmenopausal population with breast cancer. Tamoxifen is associated with an increased incidence of venous thromboembolic events, vasomotor symptoms, and sometimes stroke.^{20–23}

Raloxifene is considered the prototypical second-generation SERM. It is indicated for the prevention and treatment of osteoporosis and for the prevention of breast cancer in postmenopausal women. In postmenopausal women with low or normal bone mineral density (BMD), treatment with raloxifene 60 mg was shown to increase lumbar spine BMD by 2.4% relative to placebo ($P < 0.001$).²⁴ The Multiple Outcomes of Raloxifene Evaluation (MORE) trial found that treatment with raloxifene 60 and 120 mg/day for 3 years significantly reduced vertebral fracture risk by 30% (relative risk, 0.7; 95% CI, 0.5–0.8) and 50% (relative risk, 0.5; 95% CI, 0.4–0.7) compared with placebo, respectively, in postmenopausal women with osteoporosis.²⁵ In the Tamoxifen and Raloxifene trial of more than 19,000 postmenopausal women, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive breast cancer.²⁶

Although raloxifene has demonstrated efficacy in vertebral fracture reduction, it has shown no significant effect on the overall risk of nonvertebral fracture.^{25,27} Post hoc analyses of subgroups of women enrolled in the MORE trial²⁸ and those who entered the Continuing Outcomes Relevant to Evista trial²⁹ have shown a significant reduction in nonvertebral fracture risk at six common sites (clavicle, humerus, wrist, pelvis, hip, and lower leg) in raloxifene-treated women with severe baseline vertebral fractures, although there was no treatment effect on the risk of all nonvertebral fractures.

A small but statistically significant increase in endometrial thickness (+0.01 mm) was seen with raloxifene compared with placebo (−0.27 mm) after 3 years ($P < 0.01$ vs placebo) of therapy in the MORE trial, although there was no increase in the risk of endometrial cancer.³⁰ Venous thromboembolic events occurred in 1.0% of women who received raloxifene, compared with 0.3% of women who received placebo (relative risk, 3.1; 95% CI, 1.5–6.2). Findings from the Raloxifene Use for the Heart trial³¹ showed that the overall incidence of stroke was not different among women treated with raloxifene 60 mg/day or placebo (relative risk, 1.10; 95% CI, 0.92–1.32; $P = 0.30$); however, deaths as the result of stroke occurred more frequently in the raloxifene versus the placebo group (relative risk, 1.49; 95% CI, 1.00–2.24; $P = 0.05$).³¹ Like tamoxifen, raloxifene has been shown to induce or exacerbate vasomotor symptoms in postmenopausal women.^{32–35} An analysis of eight randomized trials showed a statistically significant increase in the incidence of hot flashes ($P < 0.05$) with raloxifene relative to placebo (6.3% increase) or hormone therapy (estrogen therapy or estrogen/progestogen therapy; 20.6% and 23.6% increase, respectively).³⁴

NEW SERMs IN DEVELOPMENT

Several new SERMs have entered clinical development in recent years, but some were discontinued because of unacceptable safety and/or tolerability profiles. For instance, the clinical development of idoxifene and levormeloxifene for postmenopausal osteoporosis was discontinued, in part, because of adverse uterine effects, including increased endometrial thickness.^{36–39} Progress in the clinical development of novel SERMs (Fig. 1) is described in the following sections.

Bazedoxifene

Bazedoxifene is in late-stage clinical development for the prevention and treatment of postmenopausal osteoporosis. Bazedoxifene was developed using stringent preclinical selection criteria, including positive effects on bone and lipid metabolism, with a favorable uterine and breast safety profile.⁴⁰ Relative to other new SERMs, bazedoxifene is furthest along in the drug development pathway, and results from phase 3 trials are becoming available. In phase 2 studies of healthy postmenopausal women, bazedoxifene treatment demonstrated statistically significant reductions in markers of bone remodeling without increasing the incidence of breast pain^{41,42} or evidence of endometrial stimulation.⁴³

Phase 3 trials of bazedoxifene for osteoporosis prevention and treatment have been completed. In a 2-year study of 1,583 postmenopausal women with normal or low BMD, treatment with bazedoxifene was shown to prevent bone loss, whereas placebo-treated women experienced loss of BMD at all skeletal sites.⁴⁴ Relative to placebo, bazedoxifene 10, 20, and 40 mg/day and raloxifene 60 mg/day significantly increased BMD at the lumbar spine (1.1%, 1.4%, 1.5%, and 1.5%, respectively) and total hip (1.3%, 1.8%, 1.6%, and 1.7%, respectively; $P < 0.001$ for all comparisons). Bazedoxifene 10, 20, and 40 mg/day and raloxifene 60 mg/day significantly reduced serum levels of osteocalcin (21%, 22%, 22%, and 27%, respectively) and C-telopeptide (25%, 24%, 22%, and 32%, respectively) from baseline ($P < 0.001$ vs placebo for all comparisons) and had favorable effects on lipid

parameters (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol).

Most recently, a 3-year study of 7,492 postmenopausal women with osteoporosis showed that the risk of new vertebral fracture was significantly reduced by 42% (relative risk, 0.58; 95% CI, 0.38–0.89), 37% (relative risk, 0.63; 95% CI, 0.42–0.96), and 42% (relative risk, 0.58; 95% CI, 0.38–0.89) with bazedoxifene 20 and 40 mg/day and raloxifene 60 mg/day, respectively, relative to placebo ($P < 0.05$ for all comparisons).⁴⁵ There were no differences in the incidence of nonvertebral fractures among groups in the overall population. In a post hoc analysis of a subgroup of women ($n = 1,772$) at higher risk for fracture based on known skeletal risk factors (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or ≥ 2 mild vertebral fractures at baseline), bazedoxifene 20 mg/day showed a statistically significant reduction in the risk of all nonvertebral fractures relative to both placebo (relative risk, 0.50; 95% CI, 0.28–0.90; $P = 0.02$) and raloxifene 60 mg (relative risk, 0.56; 95% CI, 0.31–1.01; $P = 0.05$).⁴⁵ Conversely, there were no between-group differences in the incidence of nonvertebral fractures in the lower-risk subgroup (complement of the higher-risk subgroup; $n = 5,710$).

Bazedoxifene was safe and well tolerated in both phase 3 studies, with overall rates of adverse events not different from those with placebo.^{44,45} In these studies, bazedoxifene and raloxifene showed a similar incidence of hot flashes (prevention study: range, 18.6%–24.1%; treatment study: 12.0%–13.0%) that was higher than that with placebo (prevention study: range, 14.2%; treatment study: 6.3%) and is consistent with previous reports of SERMs. The incidence of deep vein thrombosis was similar with bazedoxifene and raloxifene (range, 0.4%–0.5%) and higher compared with placebo (0.1%) in the osteoporosis treatment study ($P < 0.05$).⁴⁵ Bazedoxifene was associated with a favorable endometrial and breast safety profile similar to that of placebo and raloxifene in both phase 3 studies. Endometrial thickness with bazedoxifene remained stable throughout both studies, with no differences from baseline or placebo.^{46,47} There was no evidence of an increased incidence of endometrial hyperplasia or carcinoma with bazedoxifene treatment, and the rates of breast pain and breast cancer were not different compared with placebo.^{44–47}

Bazedoxifene partnered with conjugated estrogens is also currently under clinical investigation for the treatment of menopausal symptoms (hot flashes and vulvar vaginal atrophy) and osteoporosis prevention.^{48,49} Such a combination has the potential to provide the benefits of hormone therapy without the need for a progestogen in postmenopausal, symptomatic women with a uterus.

Lasofloxifene

Lasofloxifene has been investigated for the prevention and treatment of osteoporosis and for the treatment of vaginal atrophy in postmenopausal women. In a 2-year, randomized, double-blind study of postmenopausal women ($N = 410$), the mean change in lumbar spine BMD relative to placebo was significantly greater ($P \leq 0.05$) with lasofloxifene 0.25 and 1.0 mg/day (3.6% and 3.9%, respectively) compared with raloxifene 60 mg (1.7%), although the responses were comparable for total hip. Both lasofloxifene and raloxifene significantly reduced levels of bone turnover markers and low-density lipoprotein cholesterol compared with placebo.⁵⁰ Preliminary clinical data have also shown that treatment with lasofloxifene improves signs and symptoms of vaginal atrophy, including dyspareunia.^{51–53} Results from a study⁵¹ of 387 postmenopausal women with vaginal atrophy demonstrated that after 12 weeks of treatment, at least 52% of participants receiving lasofloxifene 0.025, 0.25, or 0.5 mg/day reported improved discomfort during sexual intercourse, compared with 21% for placebo.

The safety and tolerability profile of lasofoxifene seems to be similar to that of raloxifene, although discontinuation rates because of adverse events have been shown to be more common with lasofoxifene.⁵⁰ Evidence suggests that lasofoxifene treatment may cause increased endometrial thickness compared with placebo, although there has been no evidence of an increased risk of endometrial hyperplasia or cancer.⁵⁰ The manufacturer of lasofoxifene received a nonapprovable letter from the US FDA in September 2005, which cited the need for additional data on safety and benefits on its use as a preventive therapy for osteoporosis. Moreover, lasofoxifene was not approved by the US FDA for the treatment of vaginal atrophy in January 2006. A 3-year phase 3 trial⁵⁴ evaluating the efficacy and safety of lasofoxifene for the treatment of postmenopausal osteoporosis has recently been completed, along with a 2-year phase 3 study⁵⁵ comparing lasofoxifene versus raloxifene and placebo on BMD response, low-density lipoprotein cholesterol, and vaginal pH and maturation index. Lasofoxifene is also currently under investigation in phase 3 trials for efficacy in preventing breast cancer.

Ospemifene

Ospemifene is currently being evaluated in a placebo-controlled phase 3 study for the treatment of vulvar vaginal atrophy in postmenopausal women.⁵⁶ Clinical data from phase 1 and 2 studies have shown an estrogenic effect on the vaginal epithelium with ospemifene treatment.^{57–59} In a 3-month study of postmenopausal women, ospemifene 30, 60, or 90 mg/day was associated with a significant decrease in the percentage of parabasal cells (from approximately 40% at baseline to <10% after 3 months across groups; $P = 0.022$ vs placebo) and significant increases in intermediate and superficial cells ($P = 0.035$ and $P = 0.054$ vs placebo, respectively).⁵⁹

The effects of ospemifene on biochemical markers of bone turnover in postmenopausal women have also been evaluated. In phase 2 studies, ospemifene had a similar effect on most markers of bone resorption and bone formation compared with raloxifene and significantly greater changes from baseline compared with placebo ($P < 0.05$) at most doses.^{60,61}

A phase 2 study found that ospemifene does not induce vasomotor symptoms in postmenopausal women.⁶¹ However, further studies have shown no significant difference between raloxifene and ospemifene in the incidence of hot flashes.⁵⁷ Evidence suggests that ospemifene may be associated with increased endometrial thickness and uterine volume.⁵⁹

Arzoxifene

Arzoxifene (LY353381) was developed by replacing a carbonyl with an ether and methylating a phenolic hydroxyl group in raloxifene, thereby increasing its potency as an ER antagonist.⁶² Arzoxifene was initially investigated for the treatment and prevention of breast cancer.^{63–67} Promising results were observed in early clinical evaluations, as arzoxifene was shown to decrease proliferation indices in breast carcinoma treated 2 to 6 weeks before resection of the lesion.⁶³ The most common adverse event in these clinical trials was hot flashes.⁶⁴ Despite further positive findings from phase 2 trials in patients with metastatic breast cancer as well as a mixed group of stage IIIB and metastatic breast cancer patients,^{65,67} phase 3 studies comparing arzoxifene with tamoxifen for estrogen or hormone receptor–positive breast cancer were terminated early because of inferior efficacy of arzoxifene during the first interim analysis, including progression-free survival (4.0 mo with arzoxifene vs 7.5 mo with tamoxifen; $P = 0.007$) and time to treatment failure (4.0 mo with arzoxifene vs 6.0 mo with tamoxifen; $P = 0.003$).⁶⁸

Arzoxifene is currently being evaluated in phase 3 studies for the prevention and treatment of postmenopausal osteoporosis, based on phase 1 and 2 clinical data showing that arzoxifene decreases bone turnover.^{64,65,67,69} In a phase 2 study of women with hormone-sensitive advanced or meta-static breast cancer, arzoxifene 20 and 50 mg showed statistically significant reductions from baseline in the levels of serum osteocalcin (median change, -5.4 and -3.5 mg/L, respectively) and type 1 collagen fragment (median change, -1,707.0 and -1,173.5 pmol/L, respectively) in the group of women who were postmenopausal (n = 52); however, there was no placebo control, and no dose-dependent effect was observed.⁶⁵

Other SERMs in development

Numerous other SERMs are currently in development, although only preclinical data are available to date. These include Y134, a chemically modified analog of raloxifene that exhibits a higher binding affinity for ER- α than ER- β and acts as a full ER antagonist in CV-1 cells transfected with either ER isoform.⁷⁰ LSN2120310 and RAD-1901 are novel SERMs that have shown favorable skeletal effects with minimal uterine stimulation in animal models.^{71,72} Both have been shown to dose dependently suppress vasomotor effects in a morphine-dependent ovariectomized rat model.

CONCLUSIONS

Intensive efforts in the development of novel SERMs targeted to the ER in recent years have led to significant progress in the identification of therapeutic agents for the management of postmenopausal conditions related to estrogen deficiency, particularly osteoporosis. The possibility of designing a single molecule that has all of the desired characteristics of an ideal SERM seems to be unlikely. Rather, it may be best to consider the clinical potential of SERMs on an individual basis within specific therapeutic indications. For instance, the benefits of tamoxifen use probably outweigh the associated risks in women who have already been diagnosed with breast cancer. However, endometrial safety concerns may not outweigh the bone protection offered by SERMs in development for postmenopausal osteoporosis.

Raloxifene is currently the only SERM approved for the prevention and treatment of postmenopausal osteoporosis, having demonstrated efficacy in preventing bone loss and fractures, with the added benefit of preventing breast cancer. The clinical data on newer SERMs in development indicate that these compounds may have attributes that represent an improvement relative to currently available SERMs. Bazedoxifene has been shown to maintain or increase BMD, reduce bone turnover, and decrease the risk of new vertebral fracture in postmenopausal women without evidence of endometrial or breast stimulation in large, prospective phase 3 studies. In the global placebo- and active-controlled osteoporosis treatment study, bazedoxifene showed a significant reduction in nonvertebral fracture risk in a subgroup of more than 1,700 women at higher risk for fracture relative to both placebo and raloxifene. Other SERMs have shown promise in treating the symptoms of menopause, such as vaginal atrophy, and are also undergoing investigation as possible agents for the prevention of breast cancer. A common adverse event associated with SERMs to date seems to be an increased incidence of hot flashes and warrants further study to determine clinical relevance. Clarification of other safety concerns (ie, venous thromboembolic events) is needed to appropriately determine the benefit–risk balance of SERMs in development.

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FIG. 1.
Chemical structures of novel selective estrogen receptor modulators.

TABLE 1

FDA-approved SERMs and their indications

SERM	Indication(s)
Tamoxifen	Treatment of metastatic breast cancer; adjuvant treatment of breast cancer; reduction of invasive breast cancer risk in women with DCIS after surgery and radiation; reduction of breast cancer incidence in high-risk women
Toremifene	Treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive or unknown tumors
Raloxifene	Prevention and treatment of osteoporosis and for the prevention of invasive breast cancer in postmenopausal women
Clomiphene	Treatment of ovulatory dysfunction in women desiring pregnancy

FDA, Food and Drug Administration; SERM, selective estrogen receptor modulator; DCIS, ductal carcinoma in situ.

TABLE 2

Clinical profile of the ideal SERM

Site of action	Effect	Clinical outcome
Bone	ER agonist	Prevent osteoporosis Reduce fracture risk
CNS	ER agonist	Reduce hot flushes and other menopausal symptoms
Breast	ER neutral or antagonist	Prevent or no increase in breast cancer (and limit proliferation)
Cardiovascular/lipids	ER agonist	Lower cardiovascular risk Lower levels of circulating cholesterol
Uterus	ER neutral or antagonist	Prevent or no increase in endometrial cancer (and limit proliferation)

SERM, selective estrogen receptor modulator; ER, estrogen receptor; CNS, central nervous system.