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Review

An update on selective estrogen receptor modulators for the prevention and treatment of osteoporosis

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ABSTRACT

Several selective estrogen receptor modulators are in clinical development for postmenopausal osteoporosis. Bazedoxifene has shown significant reductions in vertebral and non-vertebral (in higher-risk women) fracture risk, with no evidence of breast or endometrial stimulation. Lasofoxifene has demonstrated significant reductions in vertebral and non-vertebral fracture risk, but has been associated with endometrial/uterine effects. Both selective estrogen receptor modulators were generally safe and well tolerated but have been associated with some "class effects" (e.g., hot flushes, venous thromboembolic events). A tissue selective estrogen complex partnering bazedoxifene with conjugated estrogens is under clinical investigation for the treatment of menopausal symptoms and osteoporosis prevention. Future directions in selective estrogen receptor modulator research include ospemifene and RAD 1901.

Contents

1. Introduction

Osteoporosis is a skeletal disease affecting an estimated 200 million people globally [1]. Women are at an increased risk for the development of osteoporosis, particularly during and following the menopausal transition, owing to the established link between declining estrogen levels and bone loss [2]. In 2000, there were an estimated 9 million new osteoporotic fractures worldwide, including 1.6 million and 1.4 million hip and clinical vertebral fractures, respectively; Europe and the Americas accounted for approximately half (51%) of these fractures [3]. The economic burden of osteoporosis and osteoporotic fractures is significant. Based on data from 2005, direct health care costs related to osteoporosis were approximately 17 billion dollars in the United States and are expected to increase by almost 50% by 2025 [4]. European estimates suggest that total direct costs related to osteoporosis-related fractures were approximately 31.7 billion Euros in 2000 and are projected to increase to 76.7 billion Euros by 2050 [5].

Numerous pharmacologic therapies are currently approved for the prevention and/or treatment of postmenopausal osteoporosis, such as bisphosphonates (oral or intravenous formulations),

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hormone therapy, strontium ranelate (outside North America), parathyroid hormone, calcitonin, and raloxifene, a selective estrogen receptor modulator (SERM). Although these agents have been proven effective for postmenopausal osteoporosis, each is associated with unique benefit/risk ratios; in order to individualize treatment based on women's needs, the continued development of therapies is desirable to help treat and ultimately prevent osteoporosis and its potentially debilitating consequences (i.e., fractures).

Although SERM chemical structures vary from each other and from estrogen itself, SERMs bind to the estrogen receptor (ER), exhibiting ER agonist or antagonist activity in different tissues [6]. Tissue selectivity of individual SERMs has led investigators to characterize the attributes of an "ideal SERM," which would have ER agonist activity in bone, the cardiovascular system, and the central nervous system, and ER neutral or antagonist activity in breast and endometrial tissue [7]. Much research has focused on the development of next-generation SERMs structurally distinct from their predecessors (i.e., tamoxifen and raloxifene) in an effort to retain the favorable qualities of the drug class (e.g., positive effects on bone), while minimizing some of the unfavorable side effects (e.g., endometrial/breast stimulation). The objective of this article is to review current developments in SERMs for the prevention and treatment of osteoporosis in postmenopausal women.

2. Profiles of SERMs under clinical development

Because each SERM has distinct effects on ER-regulated pathways, their individual blend of pharmacologic properties is unique. Several next-generation SERMs are in various phases of clinical testing for the prevention and treatment of postmenopausal osteoporosis. While the concept of an "ideal SERM" remains a goal and not yet a reality, many of these agents display positive benefit/risk profiles for postmenopausal women with or at risk for developing osteoporosis (Table 1).

2.1. Bazedoxifene

Bazedoxifene (Pfizer Inc and Ligand Pharmaceuticals) has been evaluated in global phase 3 trials for the prevention [8] and treatment [9] of postmenopausal osteoporosis. It was approved in the European Union for the treatment of postmenopausal osteoporosis in women at increased fracture risk in April 2009.

Bazedoxifene was evaluated for osteoporosis prevention in a 2-y phase 3 study of postmenopausal women ($N = 1583$) with low or normal bone mineral density (BMD). Women treated with bazedoxifene 10, 20, or 40 mg or raloxifene 60 mg had significantly higher lumbar spine and total hip BMD vs placebo (1.1%, 1.4%, 1.5%, and 1.5%, respectively; $P < 0.001$ for all) [8]. All doses of bazedoxifene and raloxifene were associated with significant reductions in bone turnover marker levels compared with placebo. Bazedoxifene also demonstrated a positive effect on lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol.

In the 3-y, pivotal, phase 3 treatment study, postmenopausal women with osteoporosis ($N = 7492$) received daily treatment with bazedoxifene 20 or 40 mg, raloxifene 60 mg, or placebo [9]. The incidence of new vertebral fractures (primary endpoint) was significantly reduced by 42% and 37% with bazedoxifene 20 and 40 mg, respectively, and by 42% with raloxifene 60 mg relative to placebo ($P < 0.05$ for all comparisons). Bazedoxifene showed significant improvements in BMD, reduced bone turnover marker levels, and had favorable effects on lipid parameters. For the overall population, the incidence of non-vertebral fractures was not significantly different among groups. However, in a post hoc analysis of a subgroup of women at increased risk for fracture (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or multiple mild vertebral fractures; $n = 1772$), bazedoxifene 20 mg significantly reduced the risk of non-vertebral fracture by 50% compared with placebo ($P = 0.02$) and by 44% compared with raloxifene 60 mg ($P = 0.05$).

Independent re-analyses of data from the overall phase 3 study examined treatment effect as a function of fracture risk, utilizing the World Health Organization Fracture Risk Assessment Tool (FRAX®; http://www.shef.ac.uk/FRAX), a Web-based algorithm designed to calculate 10-y fracture probability in women and men based on easily obtained clinical risk factors (with or without BMD) [10]. The results of these analyses demonstrated a significant reduction in the risk of fractures with bazedoxifene vs placebo at or above a FRAX-determined fracture probability [11]. More specifically, bazedoxifene was associated with a significant reduction in morphometric vertebral fracture risk in women with a 10-y fracture probability at or above 6.9% (44th percentile of risk) and a significant reduction in all clinical fractures in women with a 10-y fracture probability at or above 16% (80th percentile of risk). In a subsequent FRAX analysis [12] using data from the same study, bazedoxifene was associated with a significant reduction in the risk of non-vertebral fracture vs placebo in women with 10-y fracture probabilities at or above 20%. These findings, together with data from the post hoc subgroup analysis [9], demonstrate the efficacy of bazedoxifene in women at higher risk for fracture, with significant reductions in the risk of clinical, vertebral, and non-vertebral fractures vs placebo.

Bazedoxifene was shown to be generally safe and well tolerated in both the prevention and treatment phase 3 trials [8,9,13]. Overall, the rates of adverse events (AEs) and discontinuations due to AEs with bazedoxifene were not different from those with placebo. Although hot flushes were more common with active treatment (bazedoxifene or raloxifene) than with placebo, the majority of cases did not lead to study discontinuation. There were more reports of deep vein thrombosis with bazedoxifene or raloxifene than with placebo, but the frequency of cardiovascular events was generally low and similar among groups [9,13]. Bazedoxifene was not associated with stimulation of the endometrium or breast [13–16].

A 2-y extension of the 3-y treatment study [17,18] further evaluated the longer-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis ($N = 4216$) and demonstrated consistent findings with those observed after 3 y of treatment [9]. The raloxifene arm was discontinued after 3 y, and women previously receiving bazedoxifene 40 mg were transitioned to bazedoxifene 20 mg (bazedoxifene 40/20 mg) after 4 y. Bazedoxifene 20 and 40/20 mg were associated with significant reductions in the risk of vertebral fracture (35% and 40%, respectively) vs placebo ($P < 0.05$) at 5 y. There was a trend toward reduced risk of non-vertebral fracture with bazedoxifene in the higher-risk subgroup [18]. Safety and tolerability results from the 2-y extension study were also consistent with what was observed during the 3-y pivotal study [17].

The treatment study was further extended for an additional 2 y ($N = 1732$), and results after 7 y of treatment [19] with bazedoxifene remained consistent with those at 3 and 5 y [9,17,18]. Combined data for all women who received bazedoxifene during the study showed a 37% reduction in the risk of vertebral fracture at 7 y ($P < 0.001$ vs placebo) [19]; the incidence of non-vertebral fractures was similar among groups in the overall population. Consistent with 3- and 5-y data, the overall incidence of AEs was similar among treatment groups [19], and bazedoxifene was associated with a neutral effect on the breast and favorable endometrial safety profile [20].

Table 1
Relative efficacy and safety of investigational selective estrogen receptor modulators for postmenopausal osteoporosis.

Parameter	Bazedoxifene	Lasofoxifene	Arzoxifene[a]	Ospemifene
Bone effects				
Increased BMD	√ • 1.1–1.5% increase in lumbar spine BMD vs PBO at 2 y ($P<0.001$; phase 3 prevention study) [8] • 1.3–1.5% increase in lumbar spine BMD vs PBO at 3 y ($P<0.001$; phase 3 treatment study) [9]	√ • 2.2–3.0% increase in lumbar spine BMD vs PBO at 2 y ($P\leq0.001$; phase 3 prevention studies) [27] • 3.3% increase in lumbar spine BMD vs PBO at 3 y ($P<0.001$; phase 3 treatment study) [30]	√ • 2.9% increase in lumbar spine BMD vs PBO at 2 y ($P<0.001$; phase 3 prevention study) [33] • 2.9% increase in lumbar spine BMD vs PBO at 3 y ($P<0.001$; phase 3 treatment study) [34]	?
Decreased bone turnover	√ • Reduction of 21–22% (OC), 22–25% (CTx) from baseline at 2 y ($P<0.001$ vs PBO; phase 3 prevention study) [8] • Reduction of 37–39% (OC), 46–49% (CTx) from baseline at 1 y ($P<0.001$ vs PBO; phase 3 treatment study) [9]	√ • Reduction of 9–23% (OC), 38–51% (CTx) from baseline at 6 months ($P\leq0.001$ vs PBO; phase 3 prevention studies) [27] • Significant reduction in OC and CTx from baseline from 1 months to 3 y[b] (phase 3 treatment study) [30]	√ • Reduction of 30% (CTx) from baseline at 2 y ($P<0.001$ vs PBO; phase 3 prevention study) [33] • Reduction of 41% (CTx) from baseline at 1 y ($P<0.001$ vs PBO; phase 3 treatment study) [34]	√ • Reduced bone resorption and bone formation marker levels (dose-dependent effect; phase 2 study) [36]
Decreased vertebral fracture risk	√ • Reduction of 37–42% vs PBO ($P<0.05$) at 3 y [9]; reduction of 35–40% vs PBO ($P<0.05$) at 5 y [18]; reduction of 30–37% vs PBO ($P<0.05$) at 7 y [19]	√ • Reduction of 31–42% vs PBO ($P<0.001$) at 3 y [30]; same at 5 y [29]	√ • Reduction of 41% vs PBO ($P<0.001$) at 3 y [34]	?
Decreased non-vertebral fracture risk	√ • No difference in overall population • Higher-risk subgroup[c]: reduction of 50% vs PBO ($P=0.02$) and 44% vs RLX ($P=0.05$) at 3 y; [9] reduction of 37% vs PBO ($P=0.06$) at 5 y [18]	√ • Reduction of 22% relative to PBO ($P<0.05$) at 3 y [30]; reduction of 24% ($P<0.01$) at 5 y [29]	• No difference in overall population [34]	?
Extraskeletal effects				
Favorable lipid effects	√ • Reduction in total and LDL cholesterol and increase in HDL cholesterol vs PBO ($P<0.05$) [8,13]	√ • Reduction in total and LDL cholesterol vs PBO ($P<0.001$) [28,30]	√ • Reduction in LDL cholesterol vs PBO ($P<0.001$) [34]	• No changes in total and HDL cholesterol levels from baseline at 3 months [39]
Favorable vaginal effects		√ • Significant decrease from baseline in vaginal pH vs PBO ($P<0.001$) and favorable effect on vaginal maturation at 3 y [30]		√ • Improvement from baseline in percentage of superficial and parabasal cells, vaginal maturation index, vaginal pH ($P<0.001$ vs PBO) at 12 weeks [35]
Safety				
Endometrial effects	• No difference in endometrial carcinoma/hyperplasia rates or endometrial thickness vs PBO [14,15,17]	√ • No difference in endometrial carcinoma/hyperplasia rates vs PBO [30,31] • Increased endometrial thickness vs PBO ($P\leq0.001$) and increased incidence of polyps ($P<0.001$), vaginal bleeding ($P<0.05$) vs PBO [31] • Increase in diagnostic uterine procedures [30]	• No difference in endometrial carcinoma/hyperplasia rates vs PBO [33,34] • Increased incidence of uterine polyps, vulvovaginitis, and vaginal discharge vs PBO ($P<0.05$) [34]	√ • No difference in endometrial hyperplasia rate, but increased endometrial thickness vs PBO ($P<0.05$) [38]

Table 1 (*Continued*)

Parameter	Bazedoxifene	Lasofoxifene	Arzoxifene[a]	Ospemifene
Breast effects	• No difference in breast cancer rates or change in breast density vs PBO [13–17]	√ • 81% reduction in ER-positive and 85% reduction in invasive breast cancer risk vs PBO ($P < 0.001$) at 5 y [29] • No difference in incidence of breast pain or change in breast density vs PBO [28,30]	√ • 56% reduction in invasive breast cancer risk vs PBO ($P < 0.001$) at 4 y [34]	?
Increased hot flushes	√ • Significantly higher incidence of hot flushes vs PBO ($P < 0.05$) [8,9,13,17]	√ • Significantly higher incidence of hot flushes vs PBO ($P < 0.001$) [29,30]	√ • Significantly higher incidence of hot flushes vs PBO ($P < 0.001$) [34]	√ • Higher incidence of hot flushes vs PBO [35,38]
Increased VTEs	√ • Significantly higher incidence of DVT vs PBO ($P < 0.05$) [13,17]	√ • Significantly higher incidence of VTEs and PE vs PBO ($P \leq 0.01$ and $P < 0.05$, respectively) [29,30]	√ • Significantly higher incidence of VTEs and DVT vs PBO ($P < 0.001$ and $P < 0.01$, respectively) [34]	?

BMD, bone mineral density; PBO, placebo; OC, osteocalcin; CTx, C-telopeptide; RLX, raloxifene; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ER, estrogen receptor; VTE, venous thromboembolic event; DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] Clinical development was recently discontinued by the manufacturer based on initial results from a large phase 3 trial.

[b] Values not reported.

[c] Defined as femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or ≥ 2 mild vertebral fractures at baseline.

Aside from its clinical development as a monotherapy, bazedoxifene has been paired with conjugated estrogens (CE), and this tissue selective estrogen complex (TSEC) is under investigation for the treatment of menopausal symptoms and osteoporosis prevention in postmenopausal women with a uterus [21]. The purpose of a TSEC is to optimally balance ER agonist and antagonist effects. Phase 3 studies of a TSEC partnering appropriate doses of bazedoxifene with CE have shown that this TSEC significantly increased BMD, relieved of hot flushes, and improved measures of vulvar/vaginal atrophy (VVA), while ensuring endometrial and breast safety in non-hysterectomized postmenopausal women [22–25].

2.2. Lasofoxifene

Lasofoxifene (Pfizer Inc and Ligand Pharmaceuticals) has been investigated for the treatment of vaginal atrophy and for the prevention and treatment of postmenopausal osteoporosis. Lasofoxifene was approved (March 2009) in the European Union for the osteoporosis treatment in postmenopausal women at increased risk of fracture. It did not, however, receive approval for osteoporosis prevention or for vaginal atrophy.

In a phase 2 study in postmenopausal women ($N = 410$), daily treatment with lasofoxifene 0.25 and 1.0 mg for 2 y significantly improved lumbar spine BMD compared with placebo or raloxifene 60 mg [26]. Pooled results from 2 identical phase 3 studies in postmenopausal women with normal or low BMD ($N = 1907$) [27,28] showed that lasofoxifene significantly increased BMD and decreased bone turnover markers relative to placebo, with favorable effects on the lipid profile. In the 5-y phase 3 Postmenopausal Evaluation and Risk-reduction with Lasofoxifene (PEARL) study ($N = 8556$) [29,30], lasofoxifene 0.25 and 0.5 mg significantly reduced the risk of vertebral fracture by 31% and 42% relative to placebo, respectively ($P < 0.001$ for both). The risk of non-vertebral fracture was significantly decreased with lasofoxifene 0.5 mg (24% reduction vs placebo; $P = 0.002$). Lasofoxifene 0.25 and 0.5 mg also significantly reduced the risk of ER-positive breast cancer during the PEARL study (48% [$P = 0.07$] and 81% [$P < 0.001$] reductions vs placebo, respectively) [29].

Consistent with what has been observed with other SERMs, the incidence of hot flushes and venous thromboembolic events (VTEs) was higher with lasofoxifene than with placebo [26,29,30]. Lasofoxifene has been associated with a significant increase in endometrial thickness compared with placebo [26,29–31]. In addition, reports of endometrial polyps, uterine leiomyoma, vaginal bleeding, candidiasis, and discharge were higher in women treated with lasofoxifene compared with placebo in the PEARL study [31]. Lasofoxifene treatment was also associated with more diagnostic uterine procedures compared with placebo in the PEARL study, but the risk of endometrial carcinoma or hyperplasia was not increased [29–31]. There was a significantly higher incidence of surgery due to pelvic organ prolapse and/or urinary incontinence with lasofoxifene 0.25 mg (but not for lasofoxifene 0.5 mg) vs placebo [31].

2.3. Arzoxifene

Arzoxifene (Eli Lilly and Company) has been evaluated for the prevention and treatment of postmenopausal osteoporosis and breast cancer. Results from a 6-month phase 2 trial in 219 postmenopausal women with low bone mass showed that arzoxifene 5, 10, 20, and 40 mg significantly reduced bone turnover and increased lumbar spine BMD compared with placebo, with favorable effects on the lipid profile and an endometrial safety profile similar to raloxifene [32]. In a 2-y phase 3 prevention

study of postmenopausal women with normal to low bone mass ($N = 331$), arzoxifene 20 mg significantly improved lumbar spine and total hip BMD and reduced bone turnover markers compared with placebo [33]. Arzoxifene treatment did not increase endometrial thickness or incidence of endometrial hyperplasia or carcinoma, but there was a higher incidence of vulvovaginal mycotic infection in women treated with arzoxifene vs placebo [33].

In the phase 3 Generations Trial, arzoxifene 20 mg significantly decreased the risk of vertebral fracture by 41% vs placebo ($P < 0.001$) at 3 y in postmenopausal women with osteoporosis [34]. There was no difference in the incidence of non-vertebral fractures between the arzoxifene and placebo groups. Arzoxifene reduced the risk of invasive breast cancer by 56% relative to placebo ($P < 0.001$) at 4 y [34]. However, arzoxifene was associated with a significantly higher incidence of serious AEs, including acute cholecystitis, osteonecrosis, metastases to lung, and chronic obstructive pulmonary disease ($P < 0.05$ vs placebo for all). Hot flushes, muscle cramps, vaginal discharge, vulvovaginitis, cough, upper respiratory infections, and pneumonia were also more frequently reported in women treated with arzoxifene vs placebo [34]. In addition, there was a 2.3-fold increase in the incidence of VTEs with arzoxifene relative to placebo [34]. Based on the phase 3 study results, the clinical development of arzoxifene was recently discontinued by the manufacturer.

2.4. Ospemifene

Ospemifene (QuatRx Pharmaceuticals) has been investigated for the treatment of osteoporosis, but is now in development for the treatment of VVA and dyspareunia. Results from a phase 3 study of ospemifene for the treatment of VVA in postmenopausal women [35] showed that ospemifene 60 mg was associated with significant improvement over placebo in 4 measures of VVA at 12 weeks. In phase 2 trials of healthy postmenopausal women [36,37], ospemifene was shown to be effective in reducing bone turnover, with similar levels of biochemical markers of bone resorption compared with raloxifene. Ospemifene has been associated with increased endometrial thickness and uterine volume [38]. In addition, hot flushes were reported more frequently in women treated with ospemifene vs placebo in the phase 3 study described above [35]. Unlike other SERMs, ospemifene has not shown favorable effects on lipid parameters [39].

2.5. Other SERMs in development

Several other next-generation SERMs are in earlier phases of development for the treatment of postmenopausal osteoporosis and other related conditions. For example, RAD 1901 (Radius Health) has shown favorable skeletal effects with minimal uterine stimulation in preclinical studies [40]. Moreover, RAD 1901 dose-dependently suppressed vasomotor effects in a morphine-dependent ovariectomized rat model [40]. Based on these promising preclinical data, a phase 2 randomized, placebo-controlled study is currently ongoing, evaluating RAD 1901 for the treatment of vasomotor symptoms in postmenopausal women (NCT00875420).

Acolbifene (EM-652, SCH57068; Endorecherche, Inc), described as having pure antiestrogenic activity in the mammary gland and endometrium [41], has shown promise from a preclinical perspective, with favorable effects on bone and lipid parameters in animal models [41,42]. It has also been shown to inhibit the growth of human breast cancer [41] and to block endometrial stimulation [42]. A phase 2 study is currently recruiting patients, with the objective of evaluating acolbifene for the prevention of breast cancer in premenopausal women (NCT00853996). Animal models also suggest potential clinical efficacy of another SERM, LSN2120310, which has been shown to lower cholesterol, maintain BMD, and relieve hot flushes in ovariectomized rats [43]. Ongoing and future studies will provide greater insight into the clinical efficacy and safety of these agents.

3. Conclusion

Osteoporosis is a major public health concern worldwide. As the population ages, it becomes increasingly important that new agents are developed that will more safely and effectively prevent and treat this disease. Several next-generation SERMs are being investigated for the prevention and/or treatment of postmenopausal osteoporosis. Bazedoxifene and lasofoxifene were both recently approved in the European Union for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. In large phase 3, placebo- and active-controlled studies of postmenopausal women, bazedoxifene significantly increased BMD, decreased bone turnover marker levels, decreased new vertebral fracture risk relative to placebo, and significantly decreased non-vertebral fracture risk in a subgroup of women at increased risk of fracture. Bazedoxifene also demonstrated favorable effects on the lipid profile and no stimulatory effects on the breast or endometrium. Results of 2 extension studies further support the long-term efficacy and safety of bazedoxifene over 5 and 7 y of treatment. Likewise, lasofoxifene has demonstrated efficacy in phase 3 trials, significantly increasing BMD, decreasing vertebral and non-vertebral fracture risk, and decreasing bone turnover marker levels vs placebo, with positive effects on the lipid profile. Unlike bazedoxifene, however, lasofoxifene has been associated with an increase in endometrial thickness and an increase in diagnostic uterine procedures compared with placebo. Although initial clinical results with arzoxifene in postmenopausal osteoporosis were promising, its development was recently discontinued based on phase 3 trial results. While this group of next-generation SERMs is generally well tolerated, they are associated with what appear to be common “class effects” of SERMs, including an increased incidence of hot flushes and VTEs relative to placebo. Thus, an “ideal SERM” does not currently exist, but progress is being made toward this goal. Nonetheless, a TSEC may prove to be an alternative for symptomatic women, based on phase 3 studies evaluating bazedoxifene plus CE. This combination provided positive effects on bone and relief of common menopausal symptoms, such as hot flushes and VVA. Future directions in SERM research are also encouraging. Recent phase 3 data support the efficacy and safety of ospemifene for the treatment of symptoms associated with VVA and dyspareunia, and further clinical data are awaited. Moreover, several other SERMs are in preclinical or early clinical stages of testing, as well as other non-SERM alternatives. As more clinical data become available, these next-generation SERMs should be appropriately incorporated into the current treatment paradigm for postmenopausal women with or at risk for developing osteoporosis.

Contributors

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