Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Selective estrogen receptor modulators in the treatment of osteoporosis: a review of the clinical evidence

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The ideal selective estrogen receptor modulator will protect against fractures, prevent estrogen receptor-positive breast cancer, suppress vasomotor symptoms, offer cardiovascular protection, maintain vaginal and bladder health and prevent endometrial stimulation, with an acceptable safety and tolerability profile. Raloxifene is available in most countries and has been approved for the prevention of vertebral (not nonvertebral fractures) and estrogen receptor-positive breast cancer but do not offer cardiovascular protection. The development of arzoxifene was terminated because superiority compared with raloxifene could not be shown. Bazedoxifene has a profile very similar to raloxifene, but protects against nonvertebral fracture in patients at high risk of fracture and has superior endometrial protection that allows pairing with conjugated estrogen. Bazedoxifene is approved and available in some countries. Lasofoxifene prevents vertebral and nonvertebral fractures and protects against cardiovascular events and stroke without increasing the risk of endometrial cancer. Although it has been approved in the EU, it has not been approved in the USA and is not yet commercially available.

Keywords: bone mineral density • fractures • osteoporosis • postmenopausal • selective estrogen-receptor modular • tissue-selective estrogen complex

Osteoporosis is a systemic skeletal condition characterized by diminished bone strength that increases the risk of fracture when falling from own body height. The most common osteoporosis-related fractures are fractures of the vertebrae, hip, wrist, pelvis, sacrum, ribs, sternum, clavicle and humerus. Osteoporotic fractures are important in terms of disability and pain [1] and can result in significant morbidity and increased mortality [2]. Osteoporosis-related fractures are common and will affect at least a third of women above the age of 50 years. Osteoporosis affects an estimated 75 million people in Europe, USA and Japan but in view of increased life expectancy, it is estimated to increase by 240% by 2050. The prevention and treatment of osteoporosis-related fractures is a health priority and can be attained by a combination of lifestyle modifications and pharmacological intervention [3]. Numerous agents for the prevention and treatment of osteoporosis-related fractures are currently available, including estrogen hormone therapy (EHT), bisphosphonates, parathyroid hormone, calcitonin, strontium ranelate, denosumab (a human monoclonal antibody against receptor activator of NF-κB [4]), and the selective estrogen receptor modulators (SERMs), raloxifene and bazedoxifene [5]. Although existing pharmacologic agents for postmenopausal osteoporosis have been shown to be effective, they may not be appropriate for all women because of safety or tolerability concerns. The search is ongoing for the ideal drug that will be effective in the prevention of all osteoporosis-related fractures (vertebral and nonvertebral including hip); that will have an acceptable safety and tolerability profile and offer extraskeletal benefits that will increase cost–effectiveness.

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This article will focus on the clinical evidence to support the use of SERMs in this context.

Concept of SERM

It has been known for many years that the hormone estrogen can prevent bone loss associated with menopause and that estrogen increases bone mineral density (BMD) in osteoporotic patients [6]. Evidence of the ability of estrogen to prevent all osteoporotic fractures, even in patients at low risk of fracture, was documented in the Women's Health Initiative study [7]. The bone sparing effect of estrogen is attained by activation of estrogen receptors (ERs) in bone. Stimulation of ER in the brain (suppression of vasomotor symptoms) and favorable changes in lipid metabolism are added extraskeletal benefits of EHT therapy. The utility of EHT in osteoporosis treatment and prevention has been limited by unwanted ER activation in the breast and endometrium.

The concept of SERMs aims to confer mixed ER agonist or antagonist activity depending on the target tissue. The ideal SERM will protect against fractures, prevent ER-positive breast cancer, suppress vasomotor symptoms, offer cardiovascular protection, maintain vaginal and bladder health and prevent endometrial stimulation, while maintaining an acceptable safety and tolerability profile. The tissue-specific action of SERMs is the result of the relative level of expression of the co-regulator proteins (co-repressors and co-activators) that are present in different target tissues [8]. When a SERM binds to an ER (α or β), the SERM–ER complex, depending on the tissue, will either be activated or repressed by the specific co-regulator recruited. More than 70 SERM molecules have been identified. Based on pharmacological structure, SERM molecules can be categorized as the triphenylethylenes, the benzothiophenes, the tetrahydronapthalenes, the indoles and the benzopyrans. All SERMs have a different clinical expression. The aim of this article is to evaluate the clinical evidence supporting the use of SERMs in the prevention and treatment of osteoporosis. Only SERMs subjected to Phase III fracture prevention trials will be discussed. The clinical utility of the SERMs will also take into account the extraskeletal effects of the drugs.

Raloxifene

Raloxifene is a benzothiophene derivative and has undergone extensive clinical investigation. Raloxifene is registered and available for the prevention and treatment of osteoporosis in most of the world. The Multiple Outcomes of Raloxifene Evaluation (MORE), a 3-year (with fourth-year extension) randomized controlled trial of 7705 postmenopausal women at risk of fracture, is the pivotal trial of raloxifene. A significant decrease in the rate of vertebral fractures (30–50%) sustained over 4 years in patients with and without previous fractures [9] was documented. There was, however, no difference between raloxifene and placebo groups in the risk of nonvertebral fractures, including hip fractures. However, in a *post hoc* analysis, significant protection against nonvertebral fractures were found in a subgroup of women with severe vertebral fractures at baseline [10]. The fracture protection in MORE was attained despite a very modest increase in BMD as measured at the spine (2.6%) and femoral neck (2.1%). A moderate decrease of 30% in the levels of biochemical markers of bone resorption was recorded. These results were corroborated in a meta-analysis [11] as well as in the Raloxifene Use for the Heart (RUTH) study [12]. A reanalysis of the MORE data further showed that raloxifene was also effective in significantly reducing the risk of vertebral fractures in subjects with osteopenia [13]. A recent reanalysis concluded that there was no significant interaction between efficacy in reducing fracture risk and fracture probability using the FRAX® model of risk assessment [14]. This means that raloxifene reduces vertebral fracture risk to an equal extent in patients at low or high risk of fracture.

Raloxifene reduces the risk of ER-positive breast cancer by approximately 60% as recorded in MORE and the 4-year follow-up CORE study. Raloxifene was as effective as tamoxifene in preventing ER-positive breast cancer in patients at risk of breast cancer in the Study of Tamoxifen and Raloxifene (STAR) study [15].

Expectations were raised that raloxifene would protect against coronary arterial disease (CAD), based on Phase II studies of raloxifene that reported favorable effects on risk factors for CAD such as LDL-cholesterol, C-reactive protein and homocysteine. Unfortunately, no protection against CAD was found in the MORE trial (patients at low risk) or the RUTH trial (patients at high risk). A recent subgroup analysis of RUTH patients by age found a significant reduction in coronary events in patients younger than 60 years [16]. In RUTH, raloxifene was associated with an increased risk of fatal stroke (absolute risk increase 0.7 per 1000 woman-years) but the number of strokes was not different between treatment and placebo arms. Venous thromboembolism was increased (absolute risk increase 1.2 per 1000 woman-years).

No adverse effect on the endometrium was recorded, but patients on raloxifene recorded increased hot flushes, compared with patients on placebo.

Bazedoxifene

Bazedoxifene is an indole-based SERM that has been registered for the treatment and prevention of postmenopausal osteoporosis in 27 countries at a dose of 20 mg/day. Clinical data will be presented to show

that bazedoxifene is effective in preventing bone loss and vertebral osteoporotic fractures in postmenopausal women, without breast or endometrial stimulation [17]. Two large, prospective, international Phase III studies have been completed. In the 2-year prevention study of 1583 postmenopausal women with low or normal BMD, daily therapy with bazedoxifene 10, 20 or 40 mg/day and raloxifene 60 mg/day was shown to prevent bone loss at all skeletal sites compared with placebo [18]. All doses of bazedoxifene and raloxifene 60 mg showed significant reductions in markers of bone turnover (serum osteocalcin and C-telopeptide) compared with placebo.

The pivotal Phase III treatment study evaluated the efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis [19]. Women received bazedoxifene 20 or 40 mg/day, raloxifene 60 mg/day, or placebo for 3 years. In the intent-to-treat population (n = 6847), the incidence of new vertebral fractures at 3 years was significantly reduced with bazedoxifene 20 mg (42%), bazedoxifene 40 mg (37%), and raloxifene 60 mg (42%) compared with placebo. The treatment effect was similar among women with or without prevalent vertebral fracture. No effect was demonstrated on clinical vertebral fractures by any treatment group. This may be explained by a very low incidence of clinical fractures of less than 1% in all groups.

In the overall study population (n = 7492), the incidences of nonvertebral fractures were not significantly different between all groups. However, a *post hoc* analysis of a subgroup of women at higher fracture risk (femoral neck T-score of -3.0 or less, 1 or more moderate to severe vertebral fractures, or multiple mild vertebral fractures; n = 1772) showed that bazedoxifene 20 mg significantly reduced nonvertebral fracture risk by 50% relative to placebo and 44% relative to raloxifene 60 mg. Bazedoxifene 40 mg reduced nonvertebral fracture risk by 30% relative to placebo and 22% relative to raloxifene 60 mg in the higher risk subgroup, but these differences were not statistically significant.

Reanalysis with FRAX found that bazedoxifene (data for 20 and 40 mg combined) was associated with a significant reduction in the risk of morphometric vertebral fractures in women with 10-year fracture probabilities at or above 6.9% [20]. A significant reduction in the risk of all clinical fractures was seen in women with 10-year fracture probabilities at or above 16% and on nonvertebral fracture in women with 10-year fracture probabilities at or above 20%. These results suggest that bazedoxifene is particularly effective in reducing the risk of clinical, vertebral and nonvertebral fractures in women at higher risk of fracture and that the efficacy of bazedoxifene was shown to increase with increasing probability of fracture.

After 5 years, bazedoxifene was associated with an overall favorable safety and tolerability profile, with no evidence of endometrial or breast stimulation [21]. For the 2-year extension study, all patients in the 40 mg bazodoxifene group were switched to 20 mg (40/20 mg group). The incidence of hot flushes and leg cramps was significantly increased with all doses of bazedoxifene compared with placebo. The total number of venous thromboembolic (VTE) events in patients treated with bazedoxifene compared with placebo was increased, but not significantly so. The majority of VTE events occurred during the first 2 years of treatment. The increase in VTE events was accounted for by an increase only in deep vein thrombosis (DVT; no increase in pulmonary embolism, retinal vein thrombosis or superficial thrombophlebitis was found). The increase in DVT episodes was only significant in patients in the 40/20 mg group and not in the 20 mg group. The incidence of cerebrovascular events based on adjudicated data was similar overall among the bazedoxifene and placebo groups over 5 years. Bazedoxifene showed neutral effects on the breast in terms of a wide range of parameters including invasive breast carcinoma, ER-positive breast cancer, mastalgia and benign fibrocystic breast disease. Fewer cases of endometrial carcinoma (overall p = 0.05) were reported with bazedoxifene 20 mg (n = 0) and bazedoxifene 40/20 mg (n = 3) compared with placebo (n = 6). There was no difference in the effect on endometrial thickness between bazedoxifene- and placebo-treated patients.

The strong inhibitory effect of bazedoxifene on the endometrium creates an opportunity to be paired with conjugated estrogens (CEs) to form a tissue selective estrogen complex (TSEC) [22]. Synergy between these two drugs can potentially inhibit the vasomotor symptoms associated with SERMs and the stimulation of the breast and endometrium associated with CE therapy. A Phase III trial employing a combination of various doses of bazedoxifene and CE has been completed [23]. Conjugated equine estrogen (0.625 or 0.45 mg/day) combined with bazedoxifene (20 mg/day) resulted in a significant improvement of BMD at the spine when compared with placebo or raloxifene, and at the hip when compared with placebo. TSEC improved vasomotor symptoms and vaginal health without causing endometrial hyperplasia, increasing breast density or compromising the overall safety profile of the individual drugs [24,25]. TSEC can potentially replace progestins as the endometrial protective agent used in combined hormone therapy. The use of TSEC in osteoporosis will be subject to proving fracture protection. It should also be noted that these results should not be extrapolated to other SERM/estrogens combinations, since they all act differently and it is possible that the other available SERMS may not adequately protect the endometrium.

Lasofoxifene

Lasofoxifene, a third-generation SERM, is a naphthalene derivative. In the Postmenopausal Evaluation and Risk Reduction With Lasofoxifene (PEARL) trial, a randomized controlled trial, 8556 postmenopausal women with osteoporosis received once-daily lasofoxifene at a dose of either 0.25 or 0.5 mg/day or placebo for 5 years [26].

Lasofoxifene at a dose of 0.5 mg per day, as compared with placebo, was associated with significant reduced risks of vertebral fracture (42%), nonvertebral fracture (24%), ER-positive breast cancer (83%), total breast cancer (79%) [27], coronary heart disease events (32%) [28] and stroke (36%). Lasofoxifene improved BMD over 5 years in the lumbar spine by 3.1% at a dose of 0.5 mg/day compared with the placebo group. Lasofoxifene at a dose of 0.25 mg/day, as compared with placebo, was associated with significant reduced risks of vertebral fracture (31%) and stroke (39%). Lasofoxifene increased BMD in the femoral neck by 2.9% and by 2.7% in the total hip. Both the lower and higher doses, as compared with placebo, were associated with an increase in VTE events (2.4 and 1.5 extra cases per 1000 person-years, respectively). Endometrial cancer occurred in three women in the placebo group, two women in the lower-dose lasofoxifene group, and two women in the higher-dose lasofoxifene group. There were more cases of benign endometrial hyperplasia and polyps in the lasofoxifene groups compared with placebo. Rates of death per 1000 person-years were not significantly different between placebo and either of the two treatment groups. There were 5.1 deaths per 1000 person-years in the placebo group, 7.0 in the lower-dose lasofoxifene group ($p = 0.50$), and 5.7 in the higher-dose lasofoxifene group ($p = 0.51$). Although there were more cases of lung cancer in the lower-dose lasofoxifene leg compared with placebo, this was not significant. There is no clear biological reason why the lower dose should be associated with more deaths and this may have been a chance finding. Reports of leg cramps, hot flushes and vaginal candidiasis were significantly more common in women assigned to lasofoxifene than in those assigned to placebo. In March 2009, lasofoxifene 0.5 mg/day was approved by the European Commission for the treatment of osteoporosis-related fractures in postmenopausal women. Lasofoxifene has not yet been approved by the US FDA.

Arzoxifene

Arzoxifene is a nonsteroidal benzothiophene SERM. In preclinical animal studies arzoxifene was shown to be potentially more effective in the prevention of nonvertebral fractures than raloxifene [29]. Arzoxifene was subsequently studied in a multicenter, placebo-controlled, double-blind 5-year randomized trial of 9354 women with osteoporosis (n = 5252) or low bone mass (n = 4102) [30]. Arzoxifene, after 3 years, significantly reduced the risk of vertebral fracture in patients with osteoporosis by 41% but failed to have a significant effect on nonvertebral fractures. Results were similar in participants with low bone mass. In arzoxifene-treated patients BMD improved by 2.6% in the total hip, 2.8% in femoral neck, and 2.9% at lumbar spine. Arzoxifene has been withdrawn from further clinical development, as in the absence of nonvertebral efficacy, arzoxifene offers no improvement on raloxifene.

Clinical perspective

Considering the high prevalence of osteoporosis related fractures, there will always be a need for new therapies to satisfy individual preference. The utility of any drug in osteoporosis will predominantly be determined by efficacy in fracture prevention.

Raloxifene, bazedoxifene and lasofoxifene are as effective as most other bone sparing drugs in the prevention and treatment of vertebral fractures, but of the three SERMs, only lasofoxifene is effective in preventing nonvertebral fractures in the primary analysis. Bazedoxifene was shown to be effective in the prevention of nonvertebral fractures in *post hoc* subgroup analysis of patients at high risk of fracture.

The most attractive extraskeletal effect of SERMs is the prevention of breast cancer. This has been well documented in the case of raloxifene and lasofoxifene. Bazedoxifene, in the 3-year analysis, had a neutral effect on breast cancer. It should be noted that raloxifene in the same study also failed to show protection against breast cancer. This may have been due to the overall low incidence of breast cancer in this particular study.

The promise of protection against cardiovascular events and stroke has only benn realized in the case of lasofoxifene.

No endometrial stimulation was documented with any of the three SERMs. Bazedoxifene seems to offer superior suppression of endometrial stimulation, enabling pairing with estrogens.

All SERMs increase hot flushes, DVT and leg cramps. Raloxifene was documented to cause an increased risk of fatal stroke in patients at high risk of cardiovascular disease.

It is concluded that the three SERMs as discussed, have a significant role to play in the prevention and treatment of osteoporosis, especially so in the case of the patient at risk of fracture and breast cancer.

Future perspective

Considering the high cost of new drug development and Phase III fracture trials, it is unlikely that the development of an entirely new SERM will be commissioned in the near future. Lasofoxifene is the SERM with the most

promise as monotherapy in the osteoporosis arena. It is the opinion of the author that approval of registration by the FDA should be pursued as a matter of high priority. Although bazedoxifene will be used as single therapy in the prevention of osteoporosis-related fractures, its greatest utility would be in combination with CE. The TSEC compound has the potential to replace conventional combined estrogen/progestin menopausal hormone replacement therapy in non-hysterectomized women.

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Executive summary

Epidemiology of osteoporosis

- Osteoporosis is a systemic skeletal condition characterized by diminished bone strength, which increases the risk of fracture when falling from own body height.
- Osteoporotic fractures are important in terms of disability and pain, and can result in significant morbidity and increased mortality.
- Osteoporosis affects an estimated 75 million people in Europe, USA and Japan but in view of increased life expectancy, it is estimated to increase by 240% by 2050.
- The prevention and treatment of osteoporosis-related fractures is a health priority and can be attained by a combination of lifestyle modifications and pharmacological intervention.

Concept of selective estrogen receptor modulators

- The concept of selective estrogen receptor modulators (SERMs) aims to confer mixed estrogen receptor (ER) agonist or antagonist activity depending on the target tissue.
- The ideal SERM will protect against fractures, prevent ER-positive breast cancer, suppress vasomotor symptoms, offer cardiovascular protection, maintain vaginal and bladder health and prevent endometrial stimulation, while maintaining an acceptable safety and tolerability profile.
- The tissue-specific action of SERMs is the result of the relative level of expression of the co-regulator proteins (co-repressors and co-activators) that are present in different target tissues. When a SERM binds to an ER (α or β), the SERM–ER complex, depending on the tissue, will either be activated or repressed by the specific co-regulator recruited. All SERMs have a different clinical expression.

Raloxifene

- Clinical evidence proves that raloxifene prevents vertebral but not nonvertebral fractures and prevents ER-positive breast cancer.
- Raloxifene offers endometrial protection but no cardiovascular protection.
- Raloxifene increases the risk of venous thromboembolic and fatal stroke in patients at high risk of cardiovascular disease.
- Raloxifene is well tolerated but increases the incidence of hot flushes and leg cramps.
- Arzoxifene failed to show superiority when compared to raloxifene.

Bazedoxifene

- Clinical evidence proves that bazedoxifene prevents vertebral and nonvertebral fractures (in patients at high risk of fracture) and has a neutral effect on the breast.
- Bazedoxifene offers superior endometrial protection that allows pairing with conjugated estrogen.
- Bazedoxifene offers no cardiovascular protection and increases the risk of deep vein thrombosis.
- Bazedoxifene is well tolerated but increases the incidence of hot flushes and leg cramps.

Lasofoxifene

- Clinical evidence proves that lasofoxifene prevents vertebral and nonvertebral fractures and prevents ER-positive breast cancer.
- Lasofoxifene causes benign endometrial hypertrophy but not hyperplasia.
- Lasofoxifene protects against cardiovascular disease and stroke but increases the risk of deep vein thrombosis.
- Lasofoxifene is well tolerated but increases the incidence of hot flushes and leg cramps.
- It has not been approved by the US FDA and this may be related to an increased risk of death in the group of patients receiving a lower dose of lasofoxifene.

Conclusion

- SERMs play a useful role in the prevention of osteoporosis-related fractures, especially in the patient at risk of breast cancer.

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