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New Selective Estrogen Receptor Modulators (SERMs) in Development

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Abstract Selective estrogen receptor modulators (SERMs) or estrogen agonists/antagonists have shown promise in osteoporosis in that they have the potential to reduce the risk of fracture, and also reduce the risk of breast cancer. SERMs maybe classified according to their core structure, which is typically a variation of the 17 beta-estradiol template and subclassified according to the side chain at the helix 12 affector region. The best known are the triphenylethylenes such as tamoxifen, used in the management of breast cancer. However, the clinical application of this class of SERMs has been limited due to endometrial stimulation. A second class is the benzothiophenes such as raloxifene and arzoxifene, which have skeletal benefit with little, if any, uterine stimulation. Indole-based SERMs such as bazedoxifene have a 2-phenyl ring system that serves as a core binding unit. Other classes include benzopyrans and naphthalenes (eg, lasofoxifene). In this review article, I will discuss raloxifene and three new SERMs—arzoxifene, bazedoxifene, and lasofoxifene—that have been recently studied. I will discuss their effect on bone, breast, and the cardiovascular system, as well as on safety.

Keywords SERMs · Osteoporosis · Arzoxifene · Bazedoxifene · Lasofoxifene

Clinical Trial Acronyms

GENERATIONS	Global Investigation to Determine Efficacy of Arzoxifene on At-risk Postmenopasal Patients
MORE	Multiple Outcomes of Raloxifene Evaluation
PEARL	Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene

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Introduction

We now have a diverse menu of osteoporosis therapies including both antiresorptive and anabolic therapies. Antiresorptive therapies include bisphosphonates, calcitonin, and selective estrogen receptor modulators (SERMs), also called estrogen agonists/antagonists. The first SERM, raloxifene, was shown to reduce risk of vertebral fracture but not nonvertebral fracture with an important extraskeletal effect of reducing invasive breast cancer [1]. The potential to reduce fracture risk and breast cancer risk has led to further development of new SERMs with the hope that a SERM would also reduce nonvertebral fracture risk. In this article, I will discuss newer SERMS in late development: arzoxifene, lasofoxifene, and bazedoxifene.

Effect on Bone

Raloxifene

The MORE trial was an international, randomized, placebo-controlled 3-year trial of the safety and efficacy of raloxifene in 7,705 postmenopausal women who met the World Health Organization criteria for having osteoporosis [1]. Women were randomized to 60 or 120 mg of raloxifene or placebo. Raloxifene reduced the risk of vertebral fracture compared with placebo (hazard

ratio [HR], 0.7; 95% CI, 0.5–0.8). Raloxifene did not reduce the risk of nonvertebral fracture. Raloxifene reduced markers of bone turnover by 26% to 31% for osteocalcin and by 32% to 34% for CTX-I. Raloxifene increased bone mineral density (BMD) by 2.6% to 2.7% at the lumbar spine and 2.1% to 2.4% at the femoral neck.

Lasofoxifene

The PEARL trial was an international, randomized, placebo-controlled 5-year trial of the safety and efficacy of lasofoxifene [2••] in which 8,556 postmenopausal women with osteoporosis in the femoral neck or spine were randomized to a placebo, low-dose (0.25 mg) or high-dose lasofoxifene (0.5 mg). Lasofoxifene at a dose of 0.5 mg/d compared with placebo was associated with reduced risk of vertebral fracture (HR, 0.58; 95% CI, 0.47–0.70). Lasofoxifene was associated with reduced risk of nonvertebral fracture (HR, 0.76; 95% CI, 0.64–0.91). Lasofoxifene improved BMD over 5 years in the lumbar spine by 3.1% at a dose of 0.5 mg compared with the placebo group. Lasofoxifene increased BMD in the femoral neck by 2.9% and by 2.7% in the total hip.

Bazedoxifene

The bazedoxifene study was a 5-year international, double-blind, randomized, placebo- and active-controlled trial of 7,492 women at 206 sites [3••]. Results of the first 3 years have been published and will be discussed here. The results of the 5 years have been presented but not published. Treatments included 20 or 40 mg of bazedoxifene, 60 mg of raloxifene, or placebo taken once daily. Inclusion criteria included women 55 to 85 years of age with osteoporosis as defined by a BMD of −2.5 to −4.0 or at least one radiographic-confirmed vertebral fracture with a BMD greater than −4.0. Bazedoxifene reduced the risk of new vertebral fractures at both doses: 20 mg (HR, 0.58; 95% CI, 0.38–0.89), and 40 mg (HR, 0.63; 95% CI, 0.42–0.96); compared with raloxifene, 60 mg (HR, 0.58; 95% CI, 0.38–0.89), compared with placebo. For nonvertebral fracture, no significant differences in nonvertebral fracture rate were seen in the general study population. However, in a post hoc analysis of 1,772 women who were at higher risk for fracture (eg, a femoral neck T-score<−3.0 and/or had at least one moderate or severe vertebral fracture or more than one mild vertebral fracture at baseline), bazedoxifene at 20 mg reduced the nonvertebral risk by 50% versus placebo (P=0.02). In addition, the risk of nonvertebral fracture risk was 44% lower than with raloxifene in the same group (P=0.05).

Arzoxifene

Arzoxifene was studied in the GENERATIONS, a multicenter, placebo-controlled, double-blind 5-year randomized trial of 9,354 women with osteoporosis (n=5,252) or low bone mass (n=4,102) [4]. Arzoxifene reduced the risk of vertebral fracture up to 3 years in patients with osteoporosis (HR, 0.59; 95% CI, 0.45–0.77; P<0.01) but not nonvertebral fracture (HR, 0.92; 95% CI, 0.71–1.19; P=0.071). Results were similar in participants with low bone mass. At 12 months, in participants with low bone mass, arzoxifene reduced bone markers such as CTX by 32%, was associated with a 42.1% reduction in CTX, and 33.5% reduction in P1NP in 12 months, with 3-year increases in BMD of 2.6% in the total hip, 2.8% in femoral neck, and 2.9% at lumbar spine. In the absence of nonvertebral efficacy, arzoxifene has been withdrawn from further clinical development.

Relationship of SERMs Efficacy to Fracture Risk

One of the questions asked of all agents is the relationship of fracture risk to efficacy. The assumption has been made that patients with higher fracture risk would have greater efficacy with an osteoporosis agent. The effects of the SERMs have not been consistent. Raloxifene, as reported by McCloskey et al. [5], which had significantly decreased risk of all clinical fractures and morphometric fractures in the MORE trial, had no significant interaction of efficacy with 10-year fracture risk assessment tool (FRAX) probability. In the case of morphometric vertebral fractures, efficacy decreased with increasing age. At the 90th percentile of age, vertebral fracture risk was reduced by 31% independent of FRAX probabilities. In contrast, at younger ages, efficacy was higher and increased further still with decreasing fracture probability. In contrast, the same investigators found that reductions in fracture risk with bazedoxifene were greater as the probability of fracture risk increased [6].

Cardiovascular Effects

Selective estrogen receptor modulators offer the promise of reducing the burden of coronary artery disease (CAD) based on the promise of lipids and markers of inflammation being reduced.

Raloxifene failed to lower the risk of CAD in postmenopausal osteoporotic women but doubled the risk of venous thromboembolism. The risk of CAD was lowered in a subgroup of patients at high risk. In a large, randomized, controlled trial with CAD as the primary end point, raloxifene failed to significantly reduce CAD while

significantly increasing the fatal stroke of venous thromboembolism [7].

In the primary trial, bazedoxifene also increased the risk of venous thromboembolism [3••]. In the PEARL trial, lasofoxifene reduced the risk of heart disease events, as well as the risk of stroke, whereas the risk of deep vein thrombosis remained in line with other SERMs [2••].

Reports of the effect of arzoxifene on cardiovascular events have not been published.

Effects on Breast Cancer

Raloxifene has been noted to reduce the risk of invasive breast cancer [8]. In the GENERATIONS trial, arzoxifene reduced the risk of invasive breast cancer by 56% after 4 years of treatment (P=0.002). Lasofoxifene reduced the risk of estrogen receptor–positive breast cancer, 0.3 versus 1.7 cases per 1,000 person-years (HR, 0.19; 95% CI, 0.07–0.56).

Effects on Uterus

Of the newer SERMs in development, lasofoxifene has been shown to reduce fractures and decrease the risk of breast cancer but has been associated with increased incidence of vaginal bleeding and endometrial thickening and endometrial polyps [9]. However, lasofoxifene has also shown beneficial effects in the vaginal epithelium [9]. Bazedoxifene has had no adverse effects on endometrium or breast [10].

Conclusions

Further investigation into new SERMS is warranted to more clearly define the bone and gynecologic safety and potential effects on both breast cancer and cardiovascular risk. It is clear that SERMS differ in their efficacy and safety profiles.

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