Selective estrogen receptor modulators in post-menopausal osteoporosis

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ABSTRACT

Osteoporosis (OP) is a chronic disease that occurs when the balance between the processes of bone formation and resorption is lost. OP is characterized by a decrease in bone quality and an increased risk of fractures. In post-menopausal women, as a result of decreased estrogen levels, there is bone loss. Hormone replacement therapy was initially used for the management of OP in post-menopausal women but was soon abandoned due to the occurrence of significant side effects. This shifted research toward the development of a class of drugs called selective estrogen receptor modulators (SERMs). These drugs always act through estrogen receptors (ERs), but as agonists or antagonists depending on the tissue under consideration. In particular, SERMs at the level of bone tissue behave as agonists of ERs but, as they do not result in the occurrence of estrogen side effects, they are widely used in the therapy of post-menopausal OP. This review provides a brief summary of the characteristics of SERMs employed in the treatment of post-menopausal OP.

KEYWORDS

Osteoporosis, menopause, estrogen receptors, SERMs.

Introduction

In bone tissue a balance is established between bone resorption and bone formation. This balance is critical for maintaining bone density and mineral homeostasis. Bone remodeling is a phenomenon finely regulated by hormones and local regulators synthesized in bone, among which estrogens have been identified as key players [1].

To date, the most prevalent disorder affecting the skeleton is osteoporosis (OP), which affects an estimated 200 million people worldwide [2]. According to the International Osteoporosis Foundation, one in three women and one in five men over the age of 50 will develop a fracture caused by OP [3].

OP is a chronic metabolic disorder characterized by decreased bone mass and deterioration of bone tissue microarchitecture, resulting in decreased bone quality and increased bone fragility.

In fact, the main complication of OP is bone fractures, which, although they can occur in any bone, are more common at the hip and vertebrae [4].

OP can be primary or secondary [5]. Primary OP is age-related and generally occurs in individuals over 50 years of age. The most common form of primary OP is post-menopausal (PM) osteoporosis (PMOP). Secondary OP, on the other hand, occurs when, as a result of medications and medical conditions, there is a decrease in bone mineral density (BMD) [6]. An example of secondary OP is that which occurs as an unwanted effect of the prolonged use of glucocorticoids, which are used to treat inflammation and various forms of allergy [7].

Treatment of OP is intended to prevent fractures and must be individualized according to the patient's characteristics (cardiac history, risk and type of fractures). It is a long-term therapy and there is an inverse relationship between the length of treatment and the risk of mortality [8]. It is important to start treatment as soon as the diagnosis of OP is received (an observational study showed that in the United States 64% do not start treatment within one year of diagnosis) or at least after the first fracture (because treatment prevents the occurrence of subsequent fractures) [9,10].

It is critical to follow such treatment consistently over time because poor adherence is associated with an increased risk of fractures, mortality, and hospitalizations [11].

Treatment of OP consists of non-pharmacological and pharmacological interventions. The former includes calcium and vitamin D supplementation, exercise, and healthier living choices (smoking cessation). Pharmacological interventions, approved by the Food and Drug Administration (FDA), fall into two categories: antiresorptive agents, which slow bone resorption, and anabolic agents, which stimulate bone formation (teriparatide) [12,13]. Antiresorptive agents include bisphosphonates (risedronate, alendronate, zoledronate and ibandronate), receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor (denosumab, romosozumab), and selective estrogen receptor modulators (SERMs) (raloxifene, bazedoxifene) [14].

Article history
Received 12 Jul 2022 – Accepted 16 Sep 2022

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In this concise review we analyze PMOP in women and the characteristics of SERMs, a class of drugs used in the treatment of PMOP.

Estrogen and PMOP

Three estrogenic molecules (estrone, 17-β-estradiol, and estriol) are found in women [7]. Of these, 17-β-estradiol is the most potent.

In bone, under normal conditions, 17-β-estradiol regulates osteoclast activity, stimulating osteoblast and osteocyte proliferation, and vitamin D3 and calcitonin synthesis through interaction with specific estrogen receptors (ERs) in bone, thus protecting against the risk of fractures. During puberty, estrogen contributes to the development of the pubic epiphyses and long bones [15].

In women, the sharp drop in estrogen levels during the PM period results in cardiovascular and metabolic changes, mood swings, memory problems, hot flashes, and at bone level there is an alteration in the activity of both osteoclasts and osteoblasts. This is reflected in an increased risk of fractures, sensitivity to parathyroid hormone, and loss of bone tissue as a result of increased osteoclast number and activity [16]. Decreased estrogen levels have also been shown to result in increased levels of two pro-inflammatory cytokines, tumor necrosis factor-α and interleukin-6, which induce bone resorption [17]. All this leads to the development of PMOP.

PMOP can be divided into a first period (of 3 to 5 years), in which trabecular bone loss occurs, and a second period (of 10 to 20 years), in which there is age-dependent bone loss involving not only trabecular but also cortical bone [15].

In addition, increased cardiovascular disease has also been shown in women with PMOP and a high percentage of adipose tissue [18].

Treatment of PMOP

Hormone replacement therapy has been used to treat OP in the past, but today its clinical use is precluded by the occurrence of major side effects (increased risk of breast cancer, deep vein thrombosis, and stroke) [19].

This has shifted research toward new therapeutic strategies and promoted the development of a class of drugs known as SERMs [6].

SERMs have a non-steroidal structure and behave, depending on the tissue, as agonists or antagonists of ERs [20]. There are two ER subtypes, ER-α and ER-β, which belong to the nuclear steroid/thyroid hormone receptor family. These receptors are located in the cytoplasm. Following ligand binding, they undergo conformational changes, dimerize and translocate to the nucleus, where the receptor-ligand complex binds to specific DNA sequences (called estrogen-responsive elements - EREs) and result in transcription of new proteins [21-24].

The different tissue-dependent actions exerted by SERMs have been hypothesized to be associated with the conformations of ER dimerization induced by binding to SERMs themselves and the different expression of the two ER subtypes [25].

The two subtypes differ in ligand binding site and size (ER-α is larger than ER-β) [15]. Although they are expressed in almost all cells, ER-α and ER-β show different tissue distribution. ER-α is predominantly expressed in bone, liver, breast tissue, the uterus, and the cardiovascular system, and ER-β in the colon, vascular endothelium, and prostate. ER-α is expressed in cortical bone cells and ER-β in trabecular bone.

Non-classical estrogen actions (fast responses involving transcription of genes not included in EREs) have been identified [3,26-28].

SERMs decrease bone resorption by inhibiting the release of RANKL, but at the same time do not increase the risk of breast cancer in women with PMOP because they act as antagonists at the level of breast tissue [29].

SERMs are grouped into three generations. Tamoxifen, raloxifene, and bazedoxifene belong to the first, second, and third generations, respectively, whose characteristics are listed in Table I [30].

Table I Summary of the tissue-dependent actions of tamoxifen, raloxifene, and bazedoxifene.

	BONE	BREAST	ENDOMETRIUM	CARDIOVASCULAR SYSTEM
Tamoxifen	+	-	+	+
Raloxifene	+	-	Neutral	+
Bazedoxifene	+	-	-	+
+: agonist; -: antagonist				

Tamoxifen has been approved for the prevention and treatment of breast cancer in PM women. Although tamoxifen inhibits osteoclast activity *in vitro* and *in vivo* in PM women while maintaining bone integrity, it can stimulate bone loss in pre-menopausal women based on menstrual status [15]. Indeed, tamoxifen has been shown to protect PM women with estrogen-dependent breast cancer from bone loss, but conversely, it causes a significant decrease in bone loss when administered to pre-menopausal women [31,32].

Because following treatment with tamoxifen for 5 years, compared with placebo, there was a decrease in mortality but also in the risk of breast cancer recurrence, it soon became one of the most prescribed anti-cancer drugs and was added to the World Health Organization's "List of Essential Medicines" [33,34].

In addition, tamoxifen acts as an ER agonist in the cardiovascular system, and results in an increase in coagulation factors and a decrease in low-density lipoprotein [35].

The risk of fractures was evaluated in a clinical trial in which 13000 women were divided into a placebo group and a tamoxifen group; after a follow-up period of 7 years, statistically fewer fractures at the spine, hip, and radius were recorded in the tamoxifen group than in the placebo group [36].

Tamoxifen, however, increases endometrial cancer, pulmonary embolism, and uterine weight [20]. Because of these side effects, tamoxifen is not considered, among the various SERMs, to be the first-line drug for the prevention and treatment of OP.

Raloxifene has been approved for the prevention and treat-

ment of OP in PM women at high risk of ER-positive breast cancer without leading to the development of breast cancer [15,37].

In clinical trials, compared with tamoxifen, raloxifene resulted in increased BMD, decreased risk of invasive breast cancer, and decreased risk of developing endometrium cancer [30]. Raloxifene decreases the incidence of spinal fractures by increasing BMD of the spine but has only a protective effect on non-spinal fractures (such as hip fractures). It also reduces total low-density lipoprotein and serum cholesterol levels [16].

The bioavailability of raloxifene is low due to both the high first-pass effect and its poor solubility. To overcome the problem of the first-pass effect and to increase adherence to therapy, Muhindo *et al*. developed subcutaneous cylindrical solid implants loaded with raloxifene and polycaprolactone/polyethylene glycol, which can be used for the treatment and prevention of PMOP [38]. By studying the release of raloxifene from such implants, they showed that they are capable of covering a time period of thirty days. Thus, since implantable systems allow controlled drug release over time and excellent adherence to therapy, these may represent a delivery modality to be investigated in the future.

Also, for the same purpose, Yang *et al*. developed human serum albumin-based raloxifene nanoparticles for intravenous administration [19]. They showed that the nanoparticles, after encapsulation, were stable over time, and both bio- and hemo-compatible, but also with improved bioavailability of raloxifene following intravenous administration to rats. This may thus represent a viable strategy for intravenous administration of this drug.

In the literature there are conflicting data regarding the use of raloxifene after discontinuation of denosumab, which is associated with increased bone turnover. Therefore, it is necessary to start therapy with another antiresorptive drug after discontinuation of denosumab. Ha *et al*. conducted a retrospective observational study in women with PMOP who started 12 months of raloxifene therapy following discontinuation of denosumab [39]. From this study, it was found that although no vertebral fractures were recorded, lower BMD was measured with raloxifene than after the last denosumab treatment, and increased levels of bone turnover markers. Thus, overall, raloxifene is unable to block the "rebound phenomenon" of denosumab. Hong *et al*. also compared BMD between PM women who started raloxifene therapy after discontinuation of denosumab and those who did not take any therapy [40]. In both groups there was a significant decrease in BMD but raloxifene protected against bone loss in the spine, indicating the efficacy of raloxifene after discontinuation of denosumab in PM women.

Some cases of stroke and a slightly increased risk of venous thrombosis have been demonstrated following clinical use of raloxifene [2,15].

Bazedoxifene acts as an agonist of ERs in bone and as an antagonist in breast and endometrium [37]. It interacts with both ER-α and ER-β, and specifically down-regulates ER-α and promotes its degradation [37]. It has been approved for the treatment of PMOP. It can be used alone or in combination with estrogen and the FDA has approved a combination of bazedoxifene and conjugated estrogen for the treatment of vasomotor systems and the prevention of osteoporosis in PM women [2].

Bazedoxifene increases BMD and prevents vertebral and nonvertebral fractures [41,42]. It has similar efficacy to raloxifene in decreasing fracture risk but has fewer side effects than raloxifene, exerting no negative actions at the level of breast tissue and endometrium [43]. Gustafsson *et al*. investigated the relationship between mER-α signaling and the action of bazedoxifene and lasofoxifene (other third-generation SERMs) in C451A mice, which, due to a mutation on the palmitoylation site, lack mER-α signaling [42]. Treatment with the two SERMs resulted in increased cortical thickness in vertebrae and cortical bone in the femur similarly to 17-β-estradiol in control mice, whereas no effect was recorded in C451A mice. This demonstrated that the effects of SERMs are dependent on mER-α signaling.

Recent studies have shown that bazedoxifene has potent anticancer activity in several types of cancer [30,44]. These properties, which are now being studied both *in vitro* and *in vivo*, make bazedoxifene a promising anticancer drug.

Conclusions

To date, we have effective drugs available for the treatment of OP but it is important to emphasize that drugs classified as bone resorption inhibitors are unable to reverse the osteoporotic process that has already begun. SERMs, a class of drugs that act as agonists or antagonists of ERs, are also used in PMOP. Raloxifene and bazedoxifene act as ER agonists in bone and decrease the risk of fractures. They do, however, present side effects, and the goal is to develop others that are equally effective for the prevention and treatment of PMOP but have no or at least insignificant side effects. Therefore, further knowledge of the cellular and molecular mechanisms underlying OP is needed.

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Author Contributions: *Each author contributed equally and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.*
Funding: *This research received no external funding.*
Institutional Review Board Statement: *Not applicable.*
Informed Consent Statement: *Not applicable.*
Data Availability Statement: *Not applicable.*
Acknowledgments: *This research was supported by F.I.R.M.O. Italian Foundation for the Research on Bone Disease, Florence, Italy.*
Conflicts of Interest: *The authors declare no conflict of interest.*