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EMAS clinical guide: Selective estrogen receptor modulators for postmenopausal osteoporosis

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ABSTRACT

Osteoporosis and the resulting fractures are major public health issues as the world population is ageing. Various therapies such as bisphosphonates, strontium ranelate and more recently denosumab are available. This clinical guide provides the evidence for the clinical use of selective estrogen modulators (SERMs) in the management of osteoporosis in postmenopausal women.

1. Introduction

Osteoporosis and subsequent fractures have a major impact on morbidity and mortality worldwide [1].

Thus the World Health Organization has included fracture prevention in its list of public health priorities [2].

World-wide, osteoporotic fractures accounts for 0.83% of the global burden of non-communicable disease, and 1.75% of the global burden in Europe [3]. In Europe, osteoporotic fractures account for more Disability Adjusted Life Years (DALYs) lost than common cancers with the exception of lung cancer. For chronic musculo-skeletal disorders the DALYs lost in Europe due to osteoporosis (2.0 million) are less than for osteoarthritis (3.1 million) but greater than for rheumatoid arthritis (1.0 million). The economic burden is considerable and it has been estimated that the direct cost of osteoporotic fractures in Europe is about €36 billion [4]. Furthermore, in the absence of a significant treatment impact on the global burden of fractures, these costs are set to increase two-fold or more by 2050.

Various therapies such as bisphosphonates, strontium ranelate and more recently denomsumab are available [5,6]. However concerns have been raised regarding safety such as oesophageal cancer, osteonecrosis of the jaw (ONJ) and subtrochanteric fractures with bisphosphonates and venous thromboembolism with strontium ranelate [5,7]. This guidance aims to summarise the evidence on SERMs as the European Medicines Agency (EMA) has approved the use of bazedoxifene and lasofoxifene for the treatment of osteoporosis.

2. Selective estrogen receptor modulators

SERMs are chemically diverse compounds that lack the steroid structure of estrogens, but interact with estrogen receptors (ERS)

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as agonists or antagonists depending on the target tissue. The agonist and antagonist properties of SERMs derive from differentially expressed ERs, ligand-dependent receptor conformational changes, interactions with various coactivators and corepressors expressed and recruited in different tissues, and subsequent changes in gene transcription. Differential gene regulation with different SERMs ultimately contributes to the different cell- and tissue-specific activities of SERMs [8].

The early SERMs tamoxifen, toremifine and raloxifene were originally developed for the prevention and treatment of breast cancer and were subsequently found to conserve bone mass [8]. Tamoxifen has been used for several decades. Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women in the United States and Europe. Toremifine will not be discussed further as data regarding osteoporosis are scant. Two new SERMs, bazedoxifene and lasofoxifene, are now licensed in Europe.

3. Tamoxifen

Tamoxifen is a triphenylethylene derivative with a particular affinity for estrogen receptors. While it has anti-estrogenic properties in the breast it acts as an agonist in some tissues such as the endometrium increasing the risk of cancer [8].

Tamoxifen is used as adjuvant treatment for node-positive and node-negative breast cancer to reduce risk of invasive breast cancer, and also to reduce breast cancer incidence in high-risk women [9,10]. A meta-analysis of 55 trials of 37,000 women demonstrated that the risk of breast cancer recurrence was significantly reduced by 18%, 25% and 42% following 1, 2, or 5 years, respectively, of adjuvant tamoxifen therapy compared with no treatment [11].

Ding and Field reviewed the effect of tamoxifen on bone health in postmenopausal women with early breast cancer and found that bone mineral density (BMD) was conserved at the spine and hip but not the wrist [12]. While there is no evidence that tamoxifen reduces the risk of fracture the incidence of fractures is lower in tamoxifen compared with aromatase inhibitor users [13]. Tamoxifen is not indicated for the prevention or treatment of postmenopausal osteoporosis.

4. Raloxifene

This benzothiophene was originally designed as a drug to treat breast cancer. Nevertheless, its clinical development focused afterwards on the prevention and treatment of postmenopausal osteoporosis and it became the first licensed SERM for this indication [8].

Raloxifene (RLX) is indicated for the prevention and treatment of osteoporosis in postmenopausal women in the United States and Europe [8]. Since raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer, in the United States, it is also indicated for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and those at high risk for invasive breast cancer [8].

According to a meta-analysis including seven clinical studies, RLX in dose of 60 mg or 120/150 mg daily reduced the risk for vertebral fracture by 40% (RR, 0.60; 95% CI, 0.49–0.74) and 49% (RR, 0.51; 95% CI, 0.41–0.64) respectively [14]. It significantly reduced the risk of invasive breast cancer but only for estrogen receptor positive tumors (RR, 0.24; 95% CI, 0.15–0.40 [15].

Furthermore in a 5-year study of postmenopausal women ($n = 19{,}747$) at high risk of breast cancer, both raloxifene and tamoxifen were similarly effective in reducing the risk of invasive breast cancer [16]. However raloxifene had a significantly lower risk of endometrial hyperplasia, thromboembolic events, and cataracts than tamoxifen. An update of this study showed a reduced risk of endometrial cancer in raloxifene users [17]. With regard to cardiovascular events, raloxifene has no clear benefits on coronary heart disease and increases the risk of stroke and venous thromboembolism [18,19].

Raloxifene use has been associated with an increase in vasomotor symptoms, particularly hot flushes. A meta-analysis of the pooled adverse event data from all osteoporosis prevention trials reported a 7% increase in incidence of hot flushes using raloxifene (24.6%) vs. placebo (18.3%), although some RCTs did not observe this higher frequency or severity of vasomotor symptoms [20]. It has been reported that slow-dose escalation decrease the number of symptomatic patients when starting RLX [21].

Thus RLX 60 mg daily reduces the risk of vertebral but not nonvertebral fracture and its ability to reduce the risk of breast cancer without increasing the risk of endometrial cancer may be an advantage for some women.

5. New generation SERMs

5.1. Bazedoxifene

Bazedoxifene (BZA) is an indole-based third-generation SERM, with the phenyl rings serving as union receptor sites. It was developed for the prevention and treatment of postmenopausal osteoporosis [8].

5.1.1. Trial efficacy data

Bazedoxifene was evaluated in two phase III studies. In a 2-year prevention trial 1583 healthy postmenopausal women with low or normal BMD received daily doses of BZA of 10, 20, 40 mg; 60 mg of RLX or placebo, and all took 600 mg of elemental calcium daily [22]. All three doses of BZA and RLX were similarly effective at conserving BMD at the hip, lumbar spine, femoral trochanter and femoral neck. Within a six-month period, the three doses of BZA had already demonstrated a significant reduced BMD loss compared to placebo. The differences in mean percentage of BMD in the lumbar spine with respect to baseline at 24 months using 10, 20, and 40 mg BZA, vs. placebo, were $1.08 \pm 0.28\%$, $1.41 \pm 0.28\%$ and $1.49 \pm 0.28\%$, respectively (with a statistical significance of $p < 0.001$ for all of them).

A pivotal phase III clinical study was undertaken to evaluate the effectiveness and safety of BZA in preventing fractures in postmenopausal women with osteoporosis (55–85 years of age) [23]. Participants received daily treatment of BZA 20 mg ($n = 1886$) or 40 mg ($n = 1872$), RLX 60 mg ($n = 1849$) or placebo ($n = 1.885$), as well as a daily supplement of 1200 mg calcium and 400–800 IU of vitamin D. Among 6847 subjects in the intent-to-treat population, the incidence of new vertebral fractures was significantly lower ($p < 0.05$) with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), and raloxifene 60 mg (2.3%) compared with placebo (4.1%), with relative risk reductions of 42%, 37%, and 42%, respectively. The treatment effect was similar among subjects with or without prevalent vertebral fracture ($p = 0.89$ for treatment by baseline fracture status interaction). The incidence of nonvertebral fractures with bazedoxifene or raloxifene was not significantly different from placebo. In a post hoc analysis of a subgroup of women at higher fracture risk (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or multiple mild vertebral fractures; $n = 1772$), bazedoxifene 20 mg showed a 50% and 44% reduction in nonvertebral fracture risk relative to placebo ($p = 0.02$) and raloxifene 60 mg ($p = 0.05$), respectively.

The 2-year extension included a total of 4216 women providing 5 year data [24]. The raloxifene arm was discontinued after