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Prevention and Treatment of Osteoporosis with Selective Estrogen-Receptor Modulators (SERMS) – a revival?

S. Rozenberg, M. Eyckerman

This review analyses the efficacy of selective estrogen-receptor modulators (SERMs) in postmenopausal osteoporosis treatment based on meta-analyses or randomized controlled trials (RCTs). We also refer to a consensus paper [1].

Tibolone

Tibolone is viewed by some as a menopause hormone therapy rather than as a SERM. Tibolone is not viewed as a first-line therapy for osteoporosis treatment, although there are data to sustain its antifracture efficacy in elderly women: Cummings et al [2] evaluated tibolone (1.25 mg/day, i.e., half the conventional dosis) as compared to placebo. After a median time of 34 months of treatment, the tibolone used had a decreased risk of vertebral fracture (RR, 0.55; 95% CI, 0.41–0.74; $p < 0.001$) and a decreased risk of nonvertebral fracture (RR, 0.74; 95% CI, 0.58–0.93; $p = 0.01$). Interestingly, tibolone users also had a decreased risk of invasive breast cancer (RR, 0.32; 95% CI, 0.13–0.80; $p = 0.02$) and colon cancer (RR, 0.31; 95% CI, 0.10–0.96; $p = 0.04$). However, because an increased risk of stroke in tibolone users was observed (RR, 2.19; 95% CI, 1.14–4.23; $p = 0.02$), the study was stopped prematurely.

Raloxifen

Seeman et al [3] reported in a meta-analysis including seven clinical studies, that raloxifen (RAL) 60 mg reduced the risk for vertebral fracture by 40% (RR, 0.60; 95% CI, 0.49–0.74) and RAL 120/150 mg by 49% (RR, 0.51; 95% CI, 0.41–0.64). An additional benefit is the breast cancer reduction. After 8 years (4 years in MORE, 3 years in CORE, plus nearly 1 year inbetween without SERM therapy), the reduction in invasive breast cancer amounted to 66% (RR, 0.34; 95% CI, 0.22–0.50). This reduction in cancer risk is only seen in invasive estrogen receptor-positive breast cancers (RR, 0.24; 95% CI, 0.15–0.40), but not in invasive estrogen-receptor-negative breast cancers. In contrast to tamoxifen, there is no increased risk in endometrial pathology (vaginal bleeding, hyperplasia and cancer).

A non-significant increase in the risk of deep venous thrombosis persisted in the CORE study (RR, 2.17; 95% CI, 0.83, 5.70) [4]. In the RUTH-RCT (10,101 postmenopausal women with either coronary disease or an increased risk for coronary disease), RAL (60 mg/day) failed to protect coronary events. There was, however, in women assigned RAL versus placebo, a higher incidence of fatal strokes (RR, 1.49; 95% CI, 1.0–2.24) [5, 6]. There was also an increased risk of venous thromboembolism (RR, 1.44; 95% CI, 1.06–1.95). Still this study confirmed a reduction in the risk of invasive breast cancer (RR, 0.56; 95% CI, 0.38–0.83) and of vertebral fractures (RR, 0.65; 95% CI, 0.47–0.89) [5]. In the STAR-study (Tam versus RAL in 19,647 postmenopausal women with increased 5-year breast cancer risk), RAL was shown to be as effective as tamoxifen in reducing the risk of invasive breast cancer but not non-invasive breast cancer, but RAL was associated with a higher safety (lower risk of thromboembolic events and cataracts) [7]. A more recent meta-analysis by Kanis et al [8] evaluated the distribution of fracture risk assessed at baseline using the FRAX tool in RCT with RAL in the MORE-trial and determined the efficacy of RAL as a function of baseline fracture risk. The efficacy of RAL on vertebral fracture risk was significantly greater at lower ages [8].

In conclusion, RAL at a daily dose of 60 mg reduces significantly the vertebral fracture risk in postmenopausal women with densitometric osteoporosis (T-score ≤ -2.5) and fracture-related and risk-related osteoporosis. Data on non-vertebral fracture are lacking. An important clinical advantage is the co-existing reduction in invasive breast cancer risk. RAL does not confer cardiovascular prevention, but is like other SERMS associated with small but significant increases in risk of fatal strokes and venous thromboembolism.

Bazedoxifene

Bazedoxifene (BZA) is a novel selective estrogen-receptor modulator. BZA prevents bone loss and reduces bone turnover. In a 3-year RCT, (N = 7,492; mean age, 66.4 years randomized to daily doses of BZA 20 or 40 mg, RAL 60 mg, or placebo) the safety was similar for BZA as for placebo group, but the incidence of hot flushes and leg cramps was higher with BZA or RAL compared with placebo, as were the venous thromboembolic events. BZA showed a neutral effect on the breast and an excellent endometrial safety profile [9]. In a 3-yr RCT (BZA 20 or 40 mg/d, RAL 60 mg/d, or placebo) in postmenopausal women with osteoporosis (6847 subjects 55–85 yr of age), the incidence of new vertebral fractures was significantly lower ($p < 0.05$) with BZA 20 mg (2.3%), BZA 40 mg (2.5%), and RAL 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 fractures. The incidence of nonvertebral fractures with BZA or RAL was not significantly different from placebo [10]. When data were analysed as a function of fracture risk, the results suggested that BZA should be targeted preferentially to women at high fracture risk [11]. Because of the increase in hot flushes, BZA has also been successfully studied in combination with small doses of conjugated estrogens for climacteric and osteoporosis treatment.

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Lasofoxifene

Lasofoxifene is a SERM in development that has been shown also to decrease bone resorption, bone loss, and have a favourable lipid profile in postmenopausal women. In the „Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene“ (PEARL) trial lasofoxifene at a dose of 0.5 mg per day was associated with reduced risks of vertebral fractures (hazard ratio, 0.58; 95 % CI, 0.47 to 0.70), non-vertebral fracture (hazard ratio, 0.76; 95 % CI, 0.64 to 0.91), ER-positive breast cancer, coronary heart disease, and stroke but with an increased risk of venous thromboembolic events [12].

Conclusion

SERMs have a place in the prevention and treatment of osteoporosis and breast cancer in postmenopausal women.

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