Osteoporosis is characterized by a decrease in bone mass and a deterioration in skeletal micro architecture. One of the major determinants of skeletal weakness is bone loss that occurs after menopause. The bone loss is a consequence of an increased osteoclastic resorption that is only partially compensated by a moderate rise in the rate of bone formation by osteoblasts. The bone loss is a consequence of an agonism in one or more desired targeted tissues (SERMs) and second and third generation agonist receptor modulators (SERMs). This article highlights some of these promising agents in the treatment of osteoporosis.

Raloxifene
SERMs are defined as compounds that produce estrogen agonism in one or more desired targeted tissues (e.g., bone, liver) together with estrogen antagonism and/or minimal agonism in reproductive tissues, such as the breast or uterus. Raloxifene and its hydrochloride salt form are benzothiophene derivatives. On a molecular basis, raloxifene activates the gene encoding transforming growth factor beta, which together with other growth factors and cytokines, induces production of osteoblasts and inhibits the activity of osteoclasts thereby shortening their life span.

Raloxifene and estrogen have shown to inhibit with similar potency and magnitude, the interleukin (IL-6) induced differentiation and resorptive activity of mammalian osteoclasts. In the human-female derived SaOS-2 osteoblast-like cell line, raloxifene has been shown to stimulate creatine kinase activity, a marker of cell division in a dose dependent manner. The beneficial estrogen agonist like effects have been characterized extensively in ovariectomized rats and several clinical trials have been depicting the same.

The MORE (Multiple Outcomes of Raloxifene Evaluation) trial was a randomized, placebo controlled study of raloxifene 60 or 120 mg/day involving 7705 women who were at least 2 years menopause. The primary end point of MORE was the determination of the percentage of women taking raloxifene who had at least one new vertebral fracture, as compared to the control group. Secondary end points were the relative risk (RR) of nonvertebral fracture, breast cancer and cardiovascular events. In overall cohort, the risk of nonvertebral fractures for raloxifene (60 mg/day and 120 mg/day) vs placebo did not differ significantly (RR=0.9, 95% CI=0.8-1.1). However, while assessing separately women whose fracture severity grades, at baseline, corresponded to an estimated decrease in vertebral height of >40% (grade 3), raloxifene 60 mg/day significantly decreased the risk of new vertebral fracture (RR=0.73, 95% CI=0.54-0.99) and nonvertebral fracture (RR=0.53, 95% CI=0.29-0.99) at 3 years. It reduced the risk of estrogen receptor positive invasive breast cancer by 84% (RR=0.16, 95% CI=0.09-0.30). It also significantly reduced the risk of cardiovascular events in a subset of women with increased cardiovascular risk. Thus, it appears that raloxifene can be targeted to postmenopausal women with osteopenia with a risk for hip fracture (RR=2.6) and to women aged 65 or older or at a high risk (RR 3.0) for hip fracture.

Strontium Ranelate
Strontium (Sr) is a trace element that is distributed throughout the geosphere and biosphere. Sr greatly stimulates the formation of steroid tissue and tends to repress the resorptive process in bones. Sr ranelate is composed of an organic moiety (ranelic acid) and 2 atoms of stable non radioactive Sr.

In vitro, Sr ranelate increased DNA synthesis by 3-4 fold in rat cell population enriched with fibroblast and preosteoblastic cells. It also increased collagen and non collagenic protein synthesis by 34% in mature osteoblast enriched cells. On basis of in vitro results, Sr ranelate appeared to have a particular profile characterized by an inhibition of bone resorption and stimulation of bone formation. Targeting this mechanism of action-uncoupling the bone remodeling process-presents a novel means to treat osteoporosis. Sr ranelate is the first agent with this potential to be investigated. In experimental studies, it was found to be linked to an increase in femoral bone mineral content (BMC) which was associated to an increase in trabecular number and an unchanged trabecular thickness. Bone resorption was also slightly decreased. It was also found that Sr was able to prevent the change in bone turnover induced by estrogen deficiency.

In a 24 month, double blind placebo controlled, prospective, randomized study, daily oral doses of 125 mg, 500 mg or
1 gm of Sr ranelate was compared with placebo. In conclusion, the percent variation of lumbar adjusted BMD from baseline was +1.41% in group receiving 1gm/day Sr; that was significantly different as compared to –0.98% in placebo. Significantly increasing BMD of the spine and femur in early postmenopausal women, 1g/day Sr ranelate as compared to placebo, did not induce any significant adverse reactions. In Sr ranelate, treated women, there was a dose-dependent deposition into compact and cancellous bone, with significantly higher contents in new bone that in old one.

Sr ranelate is being investigated in a large phase 3 program initiated in 1996 that includes two extensive clinical trials for the treatment of severe osteoporosis. The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial will assess the effect of Sr ranelate on the risk of vertebral fractures. The Treatment of Peripheral Osteoporosis Study (TROPOS) will evaluate the effect of Sr ranelate on peripheral (nonspinal) fractures. It is proposed that Sr ranelate is a new effective and safe treatment of vertebral and nonvertebral osteoporosis, with a unique mechanism of action.

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References

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