DRUG REVIEW

Strontium Ranelate

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Introduction

Postmenopausal osteoporosis is a major public health problem. The objective of treatment is to either follow anti-resorptive or bone forming strategies (1). Currently available medications, such as bisphosphonates, selective estrogen receptor modulators, and teriparatides, have shown their ability to reduce vertebral and/or nonvertebral fractures. But it remains sub-optimal. There is, therefore, an urgent need of new effective, safe, and user-friendly medications to optimize the treatment of postmenopausal osteoporosis. Among these recent advances strontium ranelate(Sr) has gained importance in the treatment and prevention of osteoporosis (2).

The di-strontium salt strontium ranelate, a novel orally active agent consisting of two atoms of stable strontium and the organic moiety ranelic acid, has been developed for the treatment of osteoporosis (3, 4).Strontium ranelate is a new antiosteoporotic treatment with a dual mode of action, both increasing bone formation and decreasing bone resorption, which rebalances bone turnover in favour of bone formation and increases bone strength. It has been shown to enhance osteoblastic cell replication and increase collagen synthesis while it decreases pre-osteoclast differentiation and bone-resorbing activity of mature osteoclasts in vitro. Studies performed at preclinical level have shown that strontium ranelate not only increases bone mass at various skeletal sites but also improves mechanical properties of femoral, humeral and vertebral bones. (3, 4).

In a short 24 months trial, daily oral doses of 125mg, 500mg or 1gm of Sr ranelate significantly increased bone mineral density of the spine and femur in early postmenopausal woman in comparison to placebo without inducing any significant adverse reactions (5). Similarly, others suggest it to be effective and safe treatment for vertebral and non-vertebral osteoporosis with a unique mechanism of action (6). Femoral neck and total hip BMD also significantly increases at 24 month with SR 1 g/day compared with placebo. SR 1 g/day significantly increases bone alkaline phosphatase at all time points compared with baseline (6).

A mataanalysis by Reginster *et al* (7) showed that in the Prevention of Early Postmenopausal Bone Loss by Strontium Ranelate (PREVOS study), the increase in lumbar BMD from baseline in the 1 g/day group significantly differed from the decrease in the placebo group. In the strontium administration for treatment of osteoporosis STRATOS study, the annual increase in lumbar BMD in the 2 g/day group was significantly higher than in the placebo group. There was a significant reduction in the number of patients experiencing new vertebral deformities in the second year of treatment in the 2 g/day group. In both studies, there was a significant increase in the bone formation marker (bone alkaline phosphatase) in the higher-dose group. Urinary excretion of the marker of bone resorption (cross-linked N-telopeptide) was lower with SR than with placebo in the STRATOS study. SR was very well tolerated in both studies (7).

Efficacy of strontium ranelate in preventing vertebral fractures in a phase 3 trial suggested that new vertebral fractures occurred in fewer patients in the strontium ranelate group than in the placebo group, with a risk reduction of 49 percent in the first year of treatment and 41 percent during the three-year study period. Strontium ranelate increased bone mineral density at month 36 by 14.4 percent at the lumbar spine and 8.3 percent at the femoral neck. There were no significant differences between the groups in the incidence of serious adverse events. Hence, the study concluded that treatment of

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postmenopausal osteoporosis with strontium ranelate leads to early and sustained reductions in the risk of vertebral fractures (8)

Another metanalysis study by Adami *et al* (9) showed that phase 3 study, (Spinal Osteoporosis Therapeutic Intervention), evaluating the effect of strontium ranelate 2 g/day on vertebral fracture rates, revealed a significant 41% reduction in the relative risk of patients experiencing new vertebral fracture with strontium ranelate over 3 years. The TROPOS study, which aimed at evaluating the effect of strontium ranelate on nonvertebral fractures, showed a significant reduction in the risk of new nonvertebral fractures and also, in a high-risk subgroup, a significant reduction in the risk of hip fractures. In both studies, the reduction in fracture risk was accompanied by an increase in bone mineral density. The increase remained significant also after correction of the bone mineral density for the higher atomic mass of strontium compared to calcium. Furthermore, an increase in serum levels of a bone formation markers and a decrease in serum levels of a bone resorption markers were observed (9).

The antifracture efficacy of strontium ranelate, 2 g per day orally, in the treatment of postmenopausal osteoporosis has been investigated in a large-scale, international, multicenter, phase 3 programme with more than 7000 patients. A significant early (after 1 year) and sustained (over 3 years) antifracture efficacy of strontium ranelate, compared with placebo, was demonstrated in patients with prevalent vertebral fracture with reductions in risk of new vertebral fracture of 49% after 1 year. In addition, the relative risk of clinical vertebral fracture was significantly reduced by 52% after 1 year and by 38% over 3 years in the strontium ranelate group compared with placebo. Strontium ranelate was also demonstrated to significantly decrease the relative risk of vertebral fractures by 45% in patients without prevalent vertebral fracture over 3 years, vs. placebo. Bone mineral density was linearly increased during 3 years of treatment with strontium ranelate in comparison with placebo. Strontium ranelate was well tolerated throughout the entire duration of the clinical trials (10).

Side effects of strontium ranelate comprise mild diarrhea, particularly within the first weeks of treatment, and also a slightly increased risk of venous thromboembolic events (9).Strontium causes a 50% increase in the risk of venous thromboembolism (including pulmonary embolism). Strontium also increases serum creatine kinase activity in 30% of patients. Strontium can affect mental functions, and this effect needs to be quantified. Neurological and muscular adverse effects are also inadequately documented. The long-term adverse effects of strontium on bone (osteomalacia, pathological fractures, etc.) are unknown (11).

Conclusion : Strontium ranelate thus appears to be a new, effective treatment to prevent fractures in postmenopausal osteoporosis with a novel dual mechanism of action. It can be expected in the near future that clinical use of strontium ranelate will increase. But only more experience will decide future fate of this drug.

References

1. Sharma S, Tandon V, Mahajan A. Therapeutic strategies for postmenopausal osteoporosis: Present and future. *Obs & Gynae Today* 2004 ; 9(11) : 758-62.
2. Burlet N, Reginster JY. Strontium Ranelate: The First Dual Acting Treatment for Postmenopausal Osteoporosis. *Clin Orthop Relat Res* 2006 ; 443 : 55-60
3. Dimai HP.Strontium ranelate : a novel concept for the treatment of osteoporosis] *Wien Klin Wochenschr* 2005 ; 117(21-22) : 728-38.
4. Marie PJ. Strontium ranelate: A physiological approach for optimizing bone formation and resorption. Bone 2006 Jan 23 ; [ahead of print]
5. Reginster JY, Spector T, Badurski J *et al*. A short-term run-in study can significantly contribute to increasing the quality of long-term osteoporosis trials. The strontium nanelate phase III program. *Osteoporos Int* 2002 ; 13 : S30.
6. Reginster JY, Deroisy R, Dougados M *et al*. Prevention of early postmenopausal bone loss by strontium ranelate: a randomized two-year, double-blind, dose-ranging, placebo-controlled trial. *Osteoporosis Int* 2002 ; 13 : 925-31.
7. Reginster JY, Meunier PJ. Strontium ranelate phase 2 dose-ranging studies: PREVOS and STRATOS studies. *Osteoporos Int* 2003 ;14 (Suppl 3) : S56-65.
8. Meunier PJ, Roux C, Seeman E, Ortolani S, The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004 ; 350(5) : 459-68.
9. Adami S. Protelos: Nonvertebral and hip antifracture efficacy in postmenopausal osteoporosis. *Bone* 2006 Jan 21; [ahead of print]
10. Ortolani S, Vai S. Strontium ranelate: An increased bone quality leading to vertebral antifracture efficacy at all stages. *Bone* 2006 ; 38(2 Suppl 1) : 19-22.
11. [No authors listed]. Strontium: new drug. Postmenopausal osteoporosis: too many unknowns. *Prescrire In*t 2005 ; 14(80) : 207-11.