Clinical Medicine Insights: Women’s Health 2011:4 1–8
doi: 10.4137/CMWH.S5149
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**Introduction**

The worldwide incidence of osteoporosis is increasing and with it, the incidence and burden of osteoporotic fractures,\textsuperscript{2–4} which are associated with pain, deformity, disability, dependence and even mortality.\textsuperscript{5} It has been estimated that up to half of all postmenopausal women will suffer at least one such fracture.\textsuperscript{1} Fortunately several drugs are now available for preventing the occurrence of fractures. Most of them are antiresorptive drugs such as bisphosphonates (alendronate, risedronate, ibandronate and zoledric acid) and selective-estroegen receptor modulators. Their efficacy is however variable according to the type of fracture taken into consideration. For example ibandronate and raloxifen did not demonstrate any efficacy for preventing hip fractures. Moreover their mechanism of action explain that these drugs do not increase bone mass, whereas osteoporosis is defined particularly by low bone mass.

In this context strontium ranelate, a new antios- teoporotic drug available in European countries since 2004 offers several advantages.

**Mechanism of Action**

First, at the opposite of numerous antiosteoporotic treatments SR has a unique mode of action: increasing bone formation and reducing bone resorption leading to balance bone remodeling in favour of bone formation. This unique and original mechanism of action was investigated in non-clinical and clinical studies. SR was shown to increase the recruitment and activity of osteoblastic cells using $^{3}$H-thymidine and $^{3}$H-proline-labeled calvariae of newborn.\textsuperscript{6,7} Recent studies have shown that the activation of osteoblast replication is partly mediated by the calcium sensing receptor (CaR). Indeed SR enhances osteoblast replication obtained from rat calvariae.\textsuperscript{8} Also SR is able to inhibit the recruitment and activity of osteoclasts in a dose-dependent manner, through an increase in osteoprotegerin (OPG) and a decrease in receptor activator of nuclear factor kappa B ligand (RANKL) by osteoblasts.\textsuperscript{9} SR may act by increasing apoptosis of osteoclasts, as shown in rabbit models.\textsuperscript{10} Finally the CaR has also been shown to be involved in the SR-induced osteoclast apoptosis.\textsuperscript{11} The increase in bone formation parameters was also demonstrated in human bone biopsy studies, showing significant increases in osteoblastic surfaces by 38% and in mineral apposition rate for both cancellous and cortical bone by respectively 9% and 10%.\textsuperscript{12} These biopsies were obtained after 3 years of treatment suggesting a sustained effect over time. By contrast bisphosphonates do not have any effect on bone formation.

Also SR is able to inhibit the recruitment and activity of osteoclasts in a dose-dependent manner, throught an increase in osteoprotegerin (OPG) and a decrease in receptor activator of nuclear factor kappa B ligand (RANKL) by osteoblasts.\textsuperscript{13}

**Main Clinical Studies**

Two major randomized, double-blind, placebo-controlled Phase III clinical trials have examined the safety and efficacy of strontium ranelate (SR). This article discusses the findings of these studies, focusing on the effects of SR on the risks of vertebral and non-vertebral fractures in a wide variety of patients.

**Phase III Clinical Trials of SR: Study Designs**

The primary outcome of the Spinal Osteoporosis Therapeutic Intervention (SOTI) study,\textsuperscript{14} was vertebral fracture incidence over 3 years. This study included 72 centres in 11 European countries and Australia, and enrolled 1649 women with osteoporosis who were at least 50 years old and 5 years post menopause, had had at least one confirmed vertebral fracture after minimal trauma, had lumbar spine bone mineral density (BMD) $\leq 0.840 \text{ g/cm}^2$, and had not taken significan anti-osteoporotic treatment in the year before entering the study.

The primary outcome of the TROPOS (Treatment Of Peripheral OSteoporosis) study,\textsuperscript{15} was the incidence over 3 years of non-vertebral fractures related to osteoporosis. This trial enrolled 5091 women who were aged $\geq 74$ years (or 70–74 years with one fracture risk factor such as a prior osteoporotic fracture, residence in a retirement home, frequent falls, or maternal history of major osteoporotic fracture), had femoral neck BMD $\leq 0.600 \text{ g/cm}^2$, and had not taken significant anti-osteoporotic treatment in the year before entering the study.

In both SOTI and TROPOS, patients began with a run-in period during which calcium and Vitamin D levels were normalized as needed before being randomized to receive either SR 2 g daily or placebo for 3 years. All subjects received appropriate calcium and Vitamin D supplementation throughout the study.
BMD was measured at the proximal femur at baseline and every 6 months thereafter by dual-energy x-ray absorptiometry (DEXA); vertebral x-rays and lumbar spine BMD measurements (also at baseline and every 6 months thereafter) were required in SOTI and encouraged in TROPOS.

The protocols, participating centres, and BMD and x-ray reading centres were common to both studies to allow data pooling. The prespecified pooled dataset enabled several analyses, including the effects of SR treatment in elderly women (aged ≥80 years), younger postmenopausal women (aged 50–65 years) and women with osteopenia, as well as the effects of key risk factors for vertebral fracture on SR efficacy. The reduction of hip fracture incidence in women at high risk for hip fracture (aged ≥74 years, with femoral neck BMD T scores less than −2.4SD) was also analyzed.

Effects of SR on the Incidence of Vertebral and Non-Vertebral Fractures

In the SOTI trial, SR reduced vertebral fracture risk by 49% (6.4% vs. 12.2%, P < 0.001), and symptomatic vertebral fracture risk by 52% (3.1% vs. 6.4%, P = 0.003) compared to placebo after only 1 year of treatment. After 3 years, SR treatment had reduced vertebral fracture risk by 41% (20.9% vs. 32.8%, P < 0.001). SR also reduced symptomatic vertebral fracture risk over 3 years by 38% (11.3% vs. 17.4%, P < 0.001). The results after four years of treatment were recently published by Meunier et al. They demonstrated a decrease in the risk of vertebral fracture by 33% as compared with the placebo group. The relative risk reduction was 36% for clinical vertebral fractures.

The TROPOS trial, which focused on non-vertebral fractures, showed that SR treatment reduced the risk of any non-vertebral fracture by 16% (11.2% vs. 12.9%, P = 0.04), and of a major non-vertebral fragility fracture by 19% (8.7% vs. 10.4%, P = 0.031). The risk of hip fracture was reduced by 15% (not significant) in the overall population, but post-hoc analysis (requested by EMEA) demonstrated that in women at high risk for hip fracture as previously described (n = 1977), SR reduced hip fracture risk by 36% (4.3% vs. 6.4%, P = 0.046).

Vertebral x-rays were available for 3640 patients in the TROPOS trial, enabling assessment of vertebral fracture risk. In this group, SR reduced vertebral fracture risk by 45% compared to placebo after 1 year (3.0% vs. 5.3%, P < 0.001), and by 39% over 3 years (12.5% vs. 20%, P < 0.001). Moreover, SR significantly reduced vertebral fracture risk by 45% among those who had no prior vertebral fracture (7.7% vs. 14.0%, P < 0.001) and by 32% among those with a prior vertebral fracture (P < 0.001).

Long Term Effect of SR on the Risk of Fracture

Fracture efficacy for 5 years

TROPOS is the only preplanned randomized, double-blind, placebo-controlled study focused on non-vertebral fractures in osteoporosis to last for 5 years. TROPOS was completed by a substantial number of patients (n = 1384 strontium ranelate 2 g/day, n = 1330 placebo). The fracture efficacy of strontium ranelate was sustained for both vertebral and non-vertebral fracture (including hip in women at high risk according to age and T score). The primary end point of new non-vertebral osteoporotic fracture occurred in 18.6% of the strontium ranelate group versus 20.9% of the placebo group over 5 years (RR, 0.85, 95% CI, 0.73–0.99). Treatment was associated with similar risk reductions for new major non-vertebral osteoporotic fracture (RR, 0.82, 95% CI, 0.69–0.98) and new vertebral fracture (RR, 0.76, 95% CI, 0.65–0.88), as well as hip fracture in a subset of 1128 patients at higher risk (RR, 0.57, 95% CI, 0.33–0.97).

A recent subgroup analysis of 1489 patients in SOTI and TROPOS demonstrated that this fracture efficacy over 5 years was seen in the elderly (aged > 80 years at baseline). Treatment reduced the risk of non-vertebral fracture (RR, 0.73, 95% CI, 0.57–0.95) and vertebral fracture (RR, 0.69, 95% CI, 0.52–0.92).

Fracture efficacy beyond 5 years

The effect of treatment with strontium ranelate has been explored up to 8 years in an open-label extension study, pooling patients from both SOTI and TROPOS. This analysis included 879 patients, who had received continuous treatment with strontium ranelate for 8 years. The absence of a placebo group in this analysis precluded any conclusions on the reduction of risk of fracture at 8 years, though fracture assessment was an end point, and not a safety measurement. However, the cumulative incidence of new fracture between 5 and 8 years of treatment

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was similar to that in the first 3 years of treatment for vertebral fracture (13.7% versus 11.5%, respectively), non-vertebral fracture (12.0% versus 9.6%), and any osteoporotic fracture (21.3% versus 19.2%). BMD continued to increase over 8 years at all sites. While this study suffers the same limitations as the other long-term studies in osteoporosis, with its open-label design and the absence of a placebo control group, it does provide indirect evidence for the long-term impact of strontium ranelate on fractures.

Effects of SR on BMD
Although clinical efficacy of anti-osteoporotic drugs needs to provide anti-fracture efficacy, BMD assessment in the follow-up of treatment is a simple and useful tool. Also we need to have simple tools to follow osteoporotic patients and it is one way for improving compliance and persistence in the field of osteoporotic treatment. In the SOTI trial, the two treatment groups had similar baseline BMD measurements at the lumbar spine, femoral neck and total hip. Treatment with SR steadily increased BMD at all sites over 3 years, by 12.7% at the lumbar spine, 7.2% at the femoral neck and 8.6% at the total hip (all P < 0.001 vs. baseline). In contrast, placebo group BMD declined, so that after 3 years, the differences between SR and placebo groups were 14.4% at the lumbar spine, 8.3% at the femoral neck and 9.8% at the total hip (P < 0.001 for all comparisons). After 4 years, patients in the SR arm were re-randomized to receive either placebo or continuing SR treatment for another year. During this year, BMD decreased significantly in the placebo group (by 3.2% at the lumbar spine and 2.5% at the hip) with a slope mirroring that of the increase seen during the first year of active treatment. In the TROPOS trial, 3 years of SR treatment increased BMD by 5.7% at the femoral neck and 7.1% at the total hip (P < 0.001 vs. baseline), a difference from placebo of 8.2% (7.7–8.7) and 9.8% (9.3–10.4), respectively (P < 0.001).

Relationship Between BMD Gains and Decrease Vertebral Fracture Risk
The precise relationship between increases in BMD and reductions in fracture risk with antiresorptive agents is no so clear. Indeed it has been well demonstrated for bisphosphonates and more generally anti-resorptive drugs that BMD gains on treatment explain a small part of antifracture efficacy. Strontium has an increased x-ray absorption compared with calcium, leading to an amplification of BMD measurement by dual energy x-ray absorptiometry. These effects may account for approximately 50% of the measured changes in BMD. To determine the relationship between changes in measured BMD and fracture incidence in patients treated with Strontium ranelate, a preplanned analysis was conducted on the 1813 SR-treated subjects from the SOTI and TROPOS studies who had undergone both vertebral x-rays and lumbar spine BMD measurements. Patients with any detectable increase in femoral neck BMD after 1 year of treatment had a 21% lower vertebral fracture risk than patients who had not shown an increase after the first year (P = 0.04). Each 1% increase in femoral neck BMD after the first year of treatment was associated with a 3% reduction in new vertebral fractures at 3 years (P = 0.04). Conversely, the gain in femoral neck BMD was significantly less if the patient sustained a new vertebral fracture (4.5% vs. 5.7%, P = 0.03) or a new symptomatic vertebral fracture (3.6% vs. 5.7%, P = 0.009) than if she did not. Increases in femoral neck and total proximal femur BMD were estimated to account for 74%–76% of the reduction in vertebral fractures over 3 years.

Relationship Between BMD Gains and Decrease Hip Fracture Risk
Changes in BMD at the lumbar spine, femoral neck or total proximal femur did not statistically predict the risk of new non-vertebral fractures, probably because other confounding factors such as falls also influence rates of these types of fractures. However, in the analysis of hip fracture incidence among high-risk subjects in the TROPOS trial, a detectable gain in femoral neck BMD (achieved by 49.9% of this group) was associated with a 67% decrease in hip fracture risk over 3 years (1.3% vs. 3.9%, P = 0.08). Femoral neck BMD increased by a mean of 7.23% in the group without a hip fracture, but only 3.41% in the group that suffered a hip fracture (P = 0.02). After adjustment for covariates (age, BMI, baseline BMD and number of prior vertebral fractures), each 1% increase in femoral neck BMD after 3 years was associated with a 7% decline in the risk of hip fracture.
fracture \((P = 0.04)\). Finally, the association between femoral neck BMD and risk of hip fracture held true for the SR-treated cohort in the main TROPOS study \((P = 0.02)\). These results confirm that unlike antiresorptive agents,\textsuperscript{26} SR produces increases in BMD that are directly correlated with clinical protection against new vertebral and to a lesser extent against hip fractures.

**Effects of Risk Factors of Fracture at Baseline and Antifracture Efficacy**

Analyses were also carried out on the pooled dataset of SOTI and TROPOS to discern whether risk factors for fractures impacted the ability of SR to reduce vertebral fracture incidence over 3 years. Age (<70 years vs. 70–80 years vs. \(\geq 80\) years), even advanced age, did not diminish the efficacy of SR. This drug also decreased vertebral fracture incidence in women with osteoporosis and those with osteopenia with similar absolute risk reductions; in addition, the relative risk reductions were similar regardless of the number of prior vertebral fractures. Similarly, baseline body mass index (BMI), smoking status, family history of osteoporosis and prior non-vertebral fracture history had no effect on the risk reduction provided by SR. Hence, SR reduced vertebral fracture incidence regardless of the presence or absence of key risk factors for vertebral fracture, even in the oldest subgroup at the highest absolute risk of vertebral fractures.\textsuperscript{27}

**Efficacy of SR in Patients with Osteopenia**

It has been well demonstrated that the majority of patients with fragility fracture (particularly hip fracture) does have on BMD assessment not an osteoporosis but an osteopenia. Therefore the assessment of the efficacy of treatments for these patients is of interest. An analysis was conducted on the efficacy of SR treatment for women with osteopenia (BMD T scores between −1 and −2.5). These women are of particular clinical interest because although their fracture risk lies between those of women with normal BMD and women with osteoporosis, they are a large group and therefore suffer the most fractures in the community.\textsuperscript{28,29} Yet efficacy data for common anti-osteoporotic agents are scant in this group, only reported in subgroups of patients treated with raloxifene,\textsuperscript{30} alendronate\textsuperscript{31} and risedronate\textsuperscript{32} with lack of proofs in patients with both femoral neck and vertebral osteopenia. Among the 1166 women with osteopenia at the lumbar spine (and any BMD value at the femoral neck), compared to placebo, SR reduced vertebral fracture risk over 3 years by 41%. If the patient had not had a previous fracture, the risk reduction was 59% (3.5% vs. 8.6%, \(P = 0.039\)), and if she had, the risk reduction was 38% (15.5% vs. 23.8%, \(P = 0.008\)). In the 265 women with osteopenia at both lumbar and femoral neck sites, treatment reduced the risk of vertebral fracture by 52% (10.2% vs. 19.3%, \(P = 0.034\)). There were not enough patients to assess the efficacy of SR on non-vertebral fractures in women with osteopenia. This is the first study to report effective reduction in vertebral fracture incidence in women with lumbar spine osteopenia.\textsuperscript{33}

**Efficacy of SR in Younger Postmenopausal Patients**

Younger postmenopausal women (aged 50 to 65 years) are also of particular interest because a first osteoporotic fracture predicts further fractures more strongly in younger patients, and vertebral fractures increase mortality even more in younger than in elderly patients. Despite this, there are few treatment data for women under age 65. The Women’s Health Initiative showed that treatment with estrogen + progestin reduces the incidence of fractures compared with control, but the study was conducted in healthy postmenopausal women.\textsuperscript{34} Several studies have shown the absence of effect of age on response to some anti-osteoporotic treatment, but this point was assessed in population older than 65 years.\textsuperscript{35} A blinded post-hoc subgroup analysis was carried out on 3- and 4-year data from the SOTI trial, involving 353 women aged 50–65 years with severe osteoporosis. Over 4 years, SR reduced vertebral fracture risk by 35%, and clinically diagnosed vertebral fracture risk by 52% compared to placebo. Moreover, SR treatment steadily increased BMD at both lumbar spine and femoral neck over the entire 4-year period while BMD at both sites declined in the placebo group; the difference between treatment groups amounted to 18.2% at the lumbar spine and 9.9% at the femoral neck. The safety of SR in this type of patient was similar to that in the overall population.\textsuperscript{16}
Effects of SR on Height Loss and Back Pain

Height loss and back pain may be related to the occurrence of vertebral fracture. Loss of $\geq 1$ cm of body height was a secondary endpoint in the SOTI trial; after 3 years, SR reduced the risk of height loss by 20% (30.1% vs. 37.5%, $P = 0.003$). It has been suggested that 10%–20% of older women are functionally limited by back pain caused by an unrecognized vertebral fracture; repeated vertebral fractures are one of the main causes of chronic back pain in women with osteoporosis. Back pain frequently appears as the first symptom of established osteoporosis. In the pooled analysis, SR increased the chance of being free of back pain by 29% after only 1 year of treatment (10.2% vs. 13.1%, $P = 0.03$); this effect was maintained over 3 years (11.1% vs. 14.3%, $P = 0.006$).

Safety

Strontium ranelate has a good tolerability profile in the trials to 5 years, and there was no evidence of a change in the long-term trials beyond that. The annual incidence of venous thromboembolism in the Phase 3 studies was 0.9% versus 0.6% in the placebo group. However, concerns surrounding this issue have been allayed by analysis performed within the UK General Practice Research Database. This retrospective cohort study found no difference in the rates of venous thromboembolism in osteoporotic women treated with strontium ranelate (n = 2408) or alendronate (n = 20 084), versus untreated osteoporotic women (n = 11 546). The same study found that osteoporotic women were more likely to suffer venous thromboembolism than their non-osteoporotic counterparts.

Moreover the most common adverse events reported with SR were nausea and diarrhoea. The respective frequencies of the 2 adverse were 7.1% and 7% for patients treated by SR against 4.6% and 5% in the placebo group (P), respectively. Also these 2 adverse events occurred mainly at the start of the treatment. The other adverse events reported were: headaches (3.3% for SR and 2.7% for P), dermatitis (2.3% for SR vs. 2% for P), eczema (1.8% for SR vs. 1.4% for P). Finally other nervous system disorders other than headaches were sometimes reported: disturbances in consciousness (2.6% for SR vs. 2.1% for P), memory loss (2.5% for SR vs. 2% for P) and seizures (0.4% for SR vs. 0.1% for P).

Patients preference and compliance

Adherence is a great concern in the field of osteoporosis. The patient’s choice is therefore a critical issue. For having a high adherence, the patient should be convinced that the treatment is efficacious, well tolerated and easy to take. However it is also important to note that the patient usually doesn’t know the results of the pivotal studies. Moreover the antifracture efficacy is not the same for all the available drugs. Therefore the choice of the prescriber is also relevant obviously. In a cohort of 13,069 patients treated by RS, the persistence of strontium ranelate treatment, estimated through Kaplan-Meyer method was 80% and 70%, respectively 12 and 24 months after the inclusion. The findings suggest a high rate of persistence.

Place in Therapy

Over the last 20 years, several drugs emerged in the field of osteoporosis. The main class is represented by the bisphosphonates. More recently other drugs became available with different mechanisms of action. Among them SR is of interest. Indeed its mechanism of action is unique and original as compared with other drugs. Also is has been shown through very large studies that it is efficacious for preventing both vertebral and non vertebral fractures (particularly hip fracture). Also it dramatically increases BMD and this point should be useful for the follow-up of patients and could improve adherence that is a great concern in the field of osteoporosis. Finally phase III studies and cohort studies showed that the treatment is well tolerated. For all these reasons, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), acknowledges SR as safe and as a very potent anti-osteoporotic treatment.

Conclusion

SR was shown to be safe and broadly effective in two multinational Phase III randomized controlled trials involving over 6000 patients. Based on these data, the recently updated guidance document for the management of postmenopausal osteoporosis, issued by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), acknowledges SR as safe and as a very potent anti-osteoporotic treatment.
vertebral and non-vertebral (especially hip) fracture risk. It should also be useful in a wide variety of patients (including those with pre-existing determinants of fracture risk, those with osteopenia, those aged 50–65 years and over 80 years, and those who suffer a disproportion number of fractures). Finally, it should be safe and well tolerated in the long term, and act to improve quality of life. Since SR fulfills all of these criteria, showing consistent broad spectrum efficacy and safety, it should be considered as a first-line option in the treatment of postmenopausal osteoporosis.

**Disclosure**

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. B. Cortet received consulting fees, paid advisory boards, lecture fees, and/or grant support from Servier, Novartis, Lilly, Amgen, Glaxo-SmithKline, Roche, Nycomed, Merck Sharp and Dohme, Alliance for Better Bone Health, Medtronic. The author confirms that they have permission to reproduce any copyrighted material.

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Cortet


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