

# Strontium ranelate: short- and long-term benefits for post-menopausal women with osteoporosis

C. Roux

Strontium ranelate is a bone-seeking element that has been assessed in post-menopausal osteoporosis in two large double-blind, placebo-controlled studies. This treatment is able to decrease the risk of vertebral fractures, by 41% over 3 yrs, and by 49% within the first year of treatment. This risk of non-vertebral fractures is decreased by 16% and, in patients at high risk for such a fracture, the risk of hip fracture is decreased by 36% over 3 yrs. Recent 5-yr data from these double-blind, placebo-controlled studies show that the anti-fracture efficacy is maintained over time. Treatment efficacy with strontium ranelate has been documented across a wide range of patient profiles: age, number of prevalent vertebral fractures, BMI, as well as family history of osteoporosis and addiction to smoking are not determinants of anti-fracture efficacy. During these clinical trials, safety was good. Its large spectrum of efficacy allows the use of strontium ranelate in the different subgroups of patients with post-menopausal osteoporosis.

**KEY WORDS:** Osteoporosis, Vertebral fracture, Non-vertebral fracture, Strontium ranelate, Anti-fracture efficacy.

## Introduction

Osteoporosis is characterized by an increase in bone fragility due to low bone mass and deterioration of bone quality, occurring during ageing and after menopause, and leading to an increase in the risk of fractures. An optimal treatment of osteoporosis would increase trabecular and cortical bone strength and decrease the risk of fracture.

The efficacy of strontium ranelate, a drug registered in the treatment of post-menopausal osteoporosis to reduce the risk of vertebral and hip fractures, has been assessed in two multicentre, randomized, double-blind, placebo-controlled trials, scheduled for 5 yrs. The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial studied strontium ranelate's effect on the risk of vertebral fractures [1]. The Treatment of Peripheral Osteoporosis (TROPOS) trial studied the effect of strontium ranelate on the risk of non-vertebral fractures [2]. These studies were preceded by a short run-in period called FIRST (Fracture International Run-in Strontium Ranelate Trial), designed to normalize the calcium/vitamin D status. The main efficacy criterion (effect of treatment on vertebral, hip and non-vertebral–non-hip fractures) was assessed at 3 yrs. Five-year data are now available from SOTI (including 4 yrs against placebo) and from TROPOS (5 yrs against placebo). Moreover, because the procedures of acquisition and central readings were the same, data can be pooled in order to obtain a large database in which subanalyses can be conducted to assess appropriately the determinants of efficacy and safety of strontium ranelate.

## SOTI study

The SOTI trial included 1649 post-menopausal women aged 70 yrs on average with osteoporosis defined by a lumbar BMD  $\leq 0.840$  g/cm<sup>2</sup> and/or at least one prevalent vertebral fracture (this last criterion being present in 87.5% of included patients).

The primary efficacy analysis was the incidence of patients with new vertebral fracture over 3 yrs. Strontium ranelate (2 g/day) reduced the risk of new vertebral fracture of 49% at 1 yr, as compared with placebo [relative risk (RR)=0.51; 95% CI 0.36,0.74;  $P \leq 0.001$ ]. The benefit after 3 yrs of strontium ranelate

was a reduction of 41% (RR = 0.59; 95% CI 0.48, 0.73;  $P \leq 0.001$ ) [1]. The risk of clinical vertebral fracture was reduced to 52% after 1 yr of treatment (RR = 0.48; 95% CI 0.29, 0.80;  $P = 0.003$ ) and to 38% after 3 yrs, as compared with the placebo group (RR = 0.62; 95% CI 0.47, 0.83;  $P \leq 0.001$ ). The number of patients that need to be treated during 3 yrs to prevent one vertebral fracture is nine (95% CI 6, 14). Over 4 yrs, data were available in 1445 patients for the intent-to-treat analysis (87.6% of randomized patients). The decrease in vertebral fracture risk over 4 yrs was 33% (RR = 0.67, 95% CI 0.53, 0.81,  $P < 0.001$ ) (Table 1).

Administration of strontium ranelate results in an increase in levels of serum bone alkaline phosphatase compared with the placebo group from the third month (8.1%;  $P \leq 0.001$ ), this difference persisted at each assessment over 3 yrs, while the serum telopeptide of type I collagen decreased from the third month (–12.2%;  $P \leq 0.001$ ) [1]. The changes are moderate, but opposite and concomitant, and consistent with the potential mechanism of action of the drug.

## TROPOS study

Efficacy of strontium ranelate on non-vertebral fractures has been evaluated in the TROPOS trial, which included 5091 osteoporotic post-menopausal women aged 74 yrs (or 70 yrs with one risk factor of osteoporotic fracture), with a femoral neck BMD  $\leq 0.600$  g/cm<sup>2</sup>. The primary efficacy analysis was incidence over time of patients with at least one osteoporotic peripheral fracture [2].

The TROPOS study showed a significant reduction in the risk of non-vertebral fractures by 16% (RR = 0.84; 95% CI 0.702, 0.995;  $P = 0.04$ ) in the group treated with strontium ranelate throughout the 3-yr study compared with placebo. The relative risk was reduced by 19% ( $P = 0.031$ ) for major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus) in patients treated with strontium ranelate, compared with the placebo group [2]. An *a posteriori* analysis was performed on a subgroup of patients ( $n = 1977$ ) at high risk of hip fracture [ $t$ -score  $\leq -2.4$  according to national health and nutrition survey (NHANES) reference, and age  $\geq 74$  yrs]. Over 3 yrs of treatment, strontium ranelate reduced the risk of hip fracture in this subgroup by 36%, compared with the placebo group (RR = 0.64; 95% CI 0.412, 0.997;  $P = 0.046$ ). Efficacy of strontium ranelate in reducing the risk of vertebral fracture (secondary efficacy end-point) was confirmed in this study with a reduction in risk of 39% (RR = 0.61; 95% CI 0.51, 0.73;  $P \leq 0.001$ ) over 3 yrs in the 3640 patients with available X-rays (Table 1).

Rheumatology Department, Paris Descartes University, Cochin Hospital, Paris, France.

Submitted 31 January 2008; revised version accepted 1 April 2008.

Correspondence to: C. Roux, Rheumatology Department, Paris Descartes University, Cochin Hospital, Paris, France.  
E-mail: christian.roux@cch.ap-hop-paris.fr

TABLE 1. Anti-fracture efficacy of strontium ranelate

Fracture	Duration (yrs)	RR (95% CI)
Vertebral	1	0.51 (0.36, 0.74)
Vertebral	3	0.59 (0.48, 0.73)
Vertebral	4	0.67 (0.53, 0.81)
Clinical vertebral	1	0.48 (0.29, 0.80)
Clinical vertebral	3	0.62 (0.47, 0.83)
Non-vertebral	3	0.84 (0.70, 0.99)
Non-vertebral	5	0.85 (0.73, 0.99)
Hip ( <i>post hoc</i> ) <sup>a</sup>	3	0.64 (0.41, 0.99)
Hip ( <i>post hoc</i> ) <sup>b</sup>	5	0.57 (0.33, 0.97)

<sup>a</sup>Age >74 yrs; *t*-score hip  $\leq -2.4$  (NHANES). <sup>b</sup>Age >74 yrs; *t*-score hip and spine  $\leq -2.4$  (NHANES).

Over 5 yrs, data were available in 4935 patients for intention-to-treat analysis [3]. There was a 15% decrease in the risk of non-vertebral fractures over 5 yrs (RR = 0.85; 95% CI 0.73, 0.99;  $P = 0.032$ ). There was a 43% decrease in the risk of hip fracture in a subset of 1128 patients defined as having a high risk of fractures, i.e. an age of 74 yrs or more, and a BMD *t*-score  $\leq -2.4$  at both the lumbar spine and the femoral neck; in this subset, the RR was 0.57 (95% CI 0.33, 0.97;  $P = 0.036$ ). Although these results were obtained in a *post hoc* analysis, it should be pointed out that no other trial has been conducted so far versus placebo during 5 yrs with non-vertebral fracture incidence as an end-point (Table 1).

### Pooled data

The study design, centres, BMD central reading centre and the X-ray central reading centre were common to both SOTI and TROPOS studies. Thus, a pre-determined analysis of pooled data was performed to increase the assessment of the treatment effect estimate compared with the individual phase III studies [4].

### Age

This was, in particular, an opportunity to assess the efficacy of strontium ranelate according to age (three subgroups of patients: aged <70 yrs, between 70 and 80 yrs (exclusive) and  $\geq 80$  yrs), which is a strong risk factor for fracture. Over the 3-yr follow-up period, in each subgroup of age, there was a decrease in risk of incident vertebral fracture in the strontium ranelate group relative to placebo, and there was no treatment-by-age interaction ( $P = 0.652$ ) [4]. The RR reduction was 37% ( $P = 0.003$ ) in the younger women (<70 yrs), 42% ( $P < 0.001$ ) in women 70–80 yrs of age and 32% ( $P = 0.013$ ) in the elderly (i.e. women  $\geq 80$  yrs of age).

Despite the important contribution of this age group to the public health burden due to their increase in the risk of fractures, few studies have focused on fracture prevention in the elderly. SOTI and TROPOS populations included 1556 (23%) patients who were  $\geq 80$  yrs of age (mean age,  $84 \pm 3$  yrs): in the intention-to-treat (ITT) population, within the first 6 months of treatment, non-vertebral fractures occurred in 3.7% of the women receiving placebo and 2.1% of women receiving strontium ranelate: the risk reduction was 44% ( $P = 0.066$ ) [5]. Over 3 yrs, these proportions were 19.7% of women receiving placebo and 14.2% of women receiving strontium ranelate; i.e. a risk reduction of 31% ( $P = 0.011$ ).

Over 3 yrs, hip fractures occurred in 7.4% of the women receiving placebo and in 5.2% of women receiving strontium ranelate, and this difference did not reach statistical significance ( $P = 0.11$ ). Over 3 yrs, major non-vertebral fractures (hip, wrist, pelvis and sacrum, ribs–sternum, clavicle or humerus) occurred in 17.7% of the women receiving placebo and in 11.5% of those receiving strontium ranelate: a risk reduction of 37% ( $P = 0.003$ ). This efficacy in this specific age group is sustained over 5 yrs of

treatment. A pre-planned analysis showed in the intent-to-treat population that strontium ranelate reduced the risk of vertebral fracture by 31% (RR = 0.69; 95% CI 0.52, 0.92;  $P = 0.010$ ), and of non-vertebral fracture by 26% (RR = 0.74; 95% CI 0.57, 0.95;  $P = 0.019$ ), compared with placebo [6].

The SOTI and TROPOS populations also included 353 patients who were 50–65 yrs old. These patients had severe osteoporosis: baseline lumbar spine *t*-score was  $-3.7$ , and the incidence of vertebral fractures in the placebo group over 3 yrs was 29.6%. Strontium ranelate decreased the risk of such fractures by 47% (RR = 0.53; 95% CI 0.33, 0.85;  $P = 0.006$ ) over 3 yrs. This efficacy in reducing the risk of vertebral fractures was sustained over 4 yrs of treatment with a reduction by 40% (RR = 0.60; 95% CI 0.39, 0.92;  $P = 0.017$ ) in these early post-menopausal women.

### Determinants of fracture

The current perspective is to use the clinical risk factors to determine the individual risk of fracture and thus, the therapeutic threshold. Thus, it is relevant to check for any effect of these risk factors on the anti-fracture efficacy of the chosen drug. This has been done, using the large database of pooled SOTI and TROPOS data, assessing BMD, prevalent vertebral fracture, family history of osteoporosis, baseline BMI and addiction to smoking [4] as potential determinants of strontium ranelate efficacy.

There was an increase in the incidence of vertebral fractures according to the number of prevalent vertebral fractures in the placebo group: 25.2% in patients having only one prevalent fracture (1110 patients in total, 577 in the placebo group) and 40.3% in patients having two or more prevalent fractures (1365 patients in total, 683 in the placebo group). In each of those subgroups, there was a decrease in risk of incident vertebral fracture in the strontium ranelate group relative to placebo. The risks of experiencing a first vertebral fracture, a second vertebral fracture, or more than two vertebral fractures were reduced by 48, 45 and 33%, respectively (all of them with  $P < 0.001$ ) with strontium ranelate. Baseline BMD, family history of osteoporosis, baseline BMI and addiction to smoking were not determinants of anti-fracture efficacy [4].

The role of BMD changes in the assessment of strontium ranelate effects warrants details. During treatment, there is a large increase in BMD. In SOTI, after 3 yrs, the lumbar spine BMD increased in the patients treated by strontium ranelate compared with the placebo group (12.7% vs  $-1.3\%$ ,  $P \leq 0.001$ ). The gain of femur BMD was also significant (8.3% compared with the placebo group). In TROPOS, at 3 yrs, the BMD in the strontium ranelate group had increased from baseline by 5.7% at the femoral neck and 7.1% at the total hip ( $P \leq 0.001$ ), compared with the placebo group. The greater attenuation of X-rays by strontium overestimates the actual BMD. However, and more relevant for the clinical practice, there is a pragmatic approach looking at the relationships between the increase in BMD, which in this situation appears directly linked to compliance, and the decrease in fracture risk. Thus, it has been observed in SOTI and TROPOS pooled data that the higher the increase in femoral neck BMD, the lower the incidence of vertebral fracture [7].

There was no link with the incidence of non-vertebral fractures, which can be explained by the absence of assessment of falls in this population, and no link between changes of BMD at the spine and vertebral fractures, which may be related to the artefactual effect of lumbar spine OA. Among patients treated with strontium ranelate, those sustaining new vertebral fractures gain less BMD ( $+4.5 \pm 9.1\%$ ) than patients without incident vertebral fractures ( $+5.7 \pm 7.4\%$ ). After controlling for covariates, patients with an improvement of at least 3% in femoral neck BMD were at a lower risk of sustaining new vertebral fractures (odds ratio 0.62; 0.42, 0.81) than patients without such improvement. Of the patients treated with strontium ranelate, 45.7% experienced an absolute gain of  $0.033 \text{ g/cm}^2$  in femoral neck BMD after 3-yr treatment,

corresponding to the smallest detectable difference in femoral neck measurement. The risk of a new vertebral fracture in these patients was reduced by 24% (2–41%) ( $P=0.03$ ), compared with patients without such gain in BMD. These analyses indicate that the increase in BMD is directly correlated with a better anti-fracture efficacy. Although the increase in BMD at 1 yr was also, in the same study, an indicator of a decreased fracture risk, a BMD measurement at 1 yr in clinical practice for monitoring of patients cannot yet be recommended, as there is no evidence that this may improve patients' long-term persistence, and, as a consequence, long-term efficacy of the treatment.

Another question is the persistence of the gain in BMD after stopping the treatment. In SOTI, treated patients were randomized at the end of the fourth year to placebo or strontium, for a fifth year. In patients who switched from strontium ranelate treatment to placebo, there was a significant BMD decrease by 3.2 and 2.5% at lumbar spine and hip, respectively. This decrease in BMD in the year following the treatment seems to have the same slope as the one observed for annual increase in BMD during the first year of treatment. This phenomenon probably reflects the bone clearance of strontium, and the change in bone remodelling induced by the end of the treatment.

### Safety

In SOTI, tolerability was similar in the strontium ranelate group and the placebo group. The most common adverse events consisted of nausea and diarrhoea (6.1% vs 3.6% in the placebo group). The difference between the two groups disappeared after the first 3 months. In TROPOS study conducted in 77-yr-old patients on average, nausea (7.2% vs 4.4%), diarrhoea (6.7% vs 5.0%), headache (3.4 vs 2.4%) and dermatitis and eczema (5.5% vs 4.1%) were reported more commonly in the strontium ranelate group, but, again, only during the first 3 months of treatment, without difference for gastrointestinal disorders between groups afterwards. Actually, as anti-osteoporotic drugs are administered to a large number of women, it is important to check for adverse events in the largest possible population in Phase 3 studies. That is why the safety of strontium ranelate was evaluated in the pooled SOTI and TROPOS populations. For adverse events having an incidence higher than 2%, only nausea and diarrhoea were different between strontium ranelate and placebo. There was a small and transient rise in serum creatine phosphokinase concentrations, which had no clinical consequence during the studies. A slight increase in the annual incidence of venous thromboembolism (0.9% vs 0.6%) was observed at 3 yrs, and unchanged since the third year, without any underlying potential mechanism, as there is no known interaction between strontium ranelate and parameters of haemostasis.

During post-marketing surveillance, isolated cases of hypersensitivity syndrome or DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have been reported. These syndromes are defined by the presence of skin reactions, fever and systemic findings, hypereosinophilia, hepatic abnormalities and renal impairment being the most prominent but inconstant. The clinical manifestations typically occur within 2–6 weeks after initiating therapy and in most cases resolved upon discontinuation.

The mechanism has not been elucidated. This syndrome has been very rarely reported so far (16/570 000 patient-years). However, due to the potential fatal outcome linked to this syndrome, the treatment should be discontinued immediately and

permanently in case of skin rash, with initiation of an adapted treatment and medical follow-up.

### Quality of life

Few data exist on effects of anti-osteoporotic drugs on quality of life (QOL). In SOTI, QOL was assessed 6-monthly during 4 yrs using the generic SF-36 questionnaire, and a specific questionnaire for assessment of QOL in osteoporosis, QUALIOST® (Boston, USA). Qualiost has been validated for internal consistency, reliability and reproducibility. It is a 23-item module resulting in a total score and two subscores, one emotional and one physical. There was no effect of strontium ranelate on SF-36 changes. In contrast, strontium ranelate prevented the slight deterioration of QOL assessed by Qualiost observed in the placebo group: mean baseline total score was  $38.5 \pm 21$  and  $40.3 \pm 22$  in the strontium ranelate and placebo groups, respectively; the magnitude of the difference in the change of QOL reached 2 ( $P < 0.05$ ) over 4 yrs. Similar differences were also observed for the two subscores of Qualiost.

### Conclusion

Strontium ranelate reduces both the risk of vertebral fracture over 4 yrs and the risk of non-vertebral fractures over 5 yrs. In the context of clinical trials, safety was good. Its large spectrum of efficacy allows the use of strontium ranelate in the different subgroups of patients with post-menopausal osteoporosis.

#### Rheumatology key messages

- Strontium ranelate has long-term efficacy in vertebral and non-vertebral fracture risk.
- Strontium ranelate is effective in the treatment of post-menopausal osteoporosis.

*Disclosure statement:* C.R. has received grants and research support from Servier.

### References

- 1 Meunier PJ, Roux C, Seeman E *et al*. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459–68.
- 2 Reginster JY, Seeman E, De Vernejoul MC *et al*. Strontium ranelate reduces the risk of non vertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816–22.
- 3 Reginster JY, Felsenberg D, Boonen S *et al*. Effects of long-term strontium ranelate treatment on the risk of non-vertebral and vertebral fractures in post menopausal osteoporosis: results of a 5-year, randomized, placebo-controlled trial. *Arthritis Rheum* 2008, in press.
- 4 Roux C, Reginster JY, Fechtenbaum J *et al*. Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. *J Bone Miner Res* 2006;21:536–42.
- 5 Seeman E, Vellas B, Benhamou C *et al*. Strontium ranelate reduces the risk of vertebral and non vertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006;21:1113–20.
- 6 Seeman E, Vellas B, Benhamou C *et al*. Sustained 5-year vertebral and non-vertebral fracture risk reduction with strontium ranelate in elderly women with osteoporosis. *Osteoporosis Int* 2006;17(Suppl 2):abstract OC39.
- 7 Bruyère O, Roux C, Detilleux J *et al*. Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. *J Clin Endocrinol Metab* 2007;92:3076–81.