Strontium ranelate: a novel treatment for postmenopausal osteoporosis: a review of safety and efficacy

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Abstract: Strontium ranelate is a new orally administered agent for the treatment of women with postmenopausal osteoporosis that reduces the risk of vertebral and hip fractures. Evidence for the safety and efficacy of strontium ranelate comes from two large multinational trials, the SOTI (Spinal Osteoporosis Therapeutic Intervention) and TROPOS (Treatment Of Postmenopausal Osteoporosis) studies. The SOTI study evaluated vertebral fracture prevention in 1649 postmenopausal women with a mean age of 69 y. The subjects all had at least one previous vertebral fracture and a low spine bone mineral density (BMD) (equivalent to a Hologic spine T-score below –1.9). The strontium ranelate group had a 41% lower risk of a new vertebral fracture than the placebo group over the three-year study period (relative risk [RR]=0.59; 95% confidence interval [CI]: 0.48–0.73; p<0.001). The TROPOS study evaluated non-vertebral fracture prevention in 5091 postmenopausal women with a mean age of 77 y. The subjects were aged 74 y and over (or 70–74 y with one additional risk factor) and a low femoral neck BMD (equivalent to an NHANES III [Third National Health and Nutrition Examination Survey] T-score below –2.2). Over the three-year study period there was a 16% reduction in all non-vertebral fractures (RR=0.84; 95% CI 0.702–0.995; p=0.04) and a 19% reduction at the principal sites for non-vertebral fractures. The TROPOS study was not powered to investigate hip fracture risk. However, in a high risk group of women aged 74 y and over and with an NHANES III femoral neck T-score less than –2.4 there was a 36% reduction in hip fracture risk (RR=0.64; 95% CI: 0.412–0.997; p=0.046). The overall incidence of adverse events did not differ significantly from placebo and were generally mild and transient, the most common being nausea and diarrhea. Strontium ranelate is a useful addition to the range of anti-fracture treatments available for treating postmenopausal women with osteoporosis and is the only treatment proven to be effective at preventing both vertebral and hip fractures in women aged 80 y and over.

Keywords: Strontium ranelate, osteoporosis treatment, postmenopausal women, vertebral fracture prevention, hip fracture prevention

Introduction

Strontium ranelate (Les Laboratoires Servier, Neuilly-sur-Seine, France) is a new orally administered agent recently licensed in Europe and Australia for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. As an alkaline earth element, strontium has close similarities with calcium in its absorption in the gut, incorporation into bone, and relatively high renal tubular reabsorption in the kidneys (Marshall et al 1973). Since strontium is naturally present in trace amounts in the human body (Sowden and Stitch 1957), treatment with strontium ranelate is simply making more stable strontium available for incorporation into bone. After 3 years treatment with strontium ranelate, the molar fraction of strontium in bone is about 1%, ie, there is ~1 strontium atom for every 100 calcium atoms in bone tissue (Blake and Fogelman 2005).

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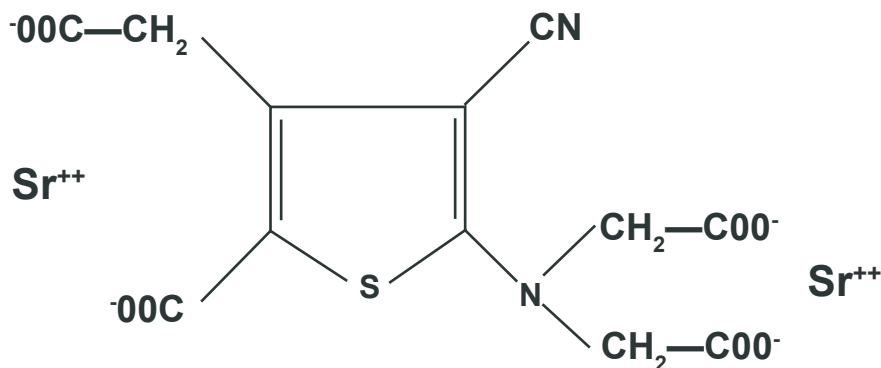**Table 1** Treatments for postmenopausal women with osteoporosis

Strontium ranelate
Bisphosphonates
Alendronate
Ibandronate
Risedronate
Selective estrogen receptor modulators (SERMS)
Raloxifene
Parathyroid hormone (PTH)
Human recombinant PTH (1-34)
Calcium and vitamin D

Strontium ranelate is a useful addition to the range of anti-fracture treatments available for treating postmenopausal women with osteoporosis (Table 1). Its mechanism of action appears to be different from other treatments. Bisphosphonates (BPs) (Liberman et al 1995; Black et al 1996; Harris et al 1999; Chesnut et al 2004) and selective estrogen receptor modulators (SERMs) (Ettinger et al 1999) are antiresorptive agents that are believed to work by suppressing bone remodeling (Eastell et al 2003). In contrast, human recombinant parathyroid hormone (PTH) is an anabolic agent that that works by promoting bone formation (Lindsay et al 1997; Neer et al 2001). Animal models and in vitro studies suggest that strontium ranelate acts in both these ways, having both a mild anabolic effect and a mild antiresorptive effect on bone tissue (Marie et al 1993; Canalis et al 1996). Studies in intact rats given strontium ranelate showed increases in bone resistance, in cortical and trabecular bone volume, and in bone micro-architecture,

indicating an improvement in bone quality (Ammann et al 2004). Treatment with strontium ranelate may therefore serve to uncouple bone resorption and bone formation and rebalance bone turnover in favor of bone formation (SPC 2004).

The chemical structure of strontium ranelate is composed of two atoms of stable strontium combined with organic ranelic acid (Figure 1). Strontium is the bone active component and makes up 34% by weight of the whole molecule, so each 2 g dose of strontium ranelate delivers 680 mg of elemental strontium. The daily dose comes as granules in a sachet that are suspended in water and drunk usually at bedtime. The summary of product characteristics (SPC) gives a figure of 25% for the gut absorption of strontium. This is consistent with the findings of a recent meta-analysis of strontium gut absorption, which reported a log normal distribution with a geometric mean of 22.3% and 95% confidence interval (CI) 10.9% to 45.6%, or about a factor of 2 around the geometric mean (Apostoaei 2002). If strontium ranelate is prescribed with calcium supplements then these latter should be taken at a different time of day (ie, at lunch time) to avoid reducing gut absorption. Similarly, absorption is affected by food, milk, and milk derivatives, and strontium ranelate should be taken at least 2 h after these products. The suspension of strontium ranelate in water is tasteless and the ranelic acid passes through the gut largely unabsorbed (SPC 2004).

The two most important requirements of any treatment for osteoporosis are firstly that it is proven to be safe and secondly that it is effective in reducing fracture risk. Evidence of the safety and efficacy of strontium ranelate comes from two large multinational clinical trials, the SOTI (Spinal Osteoporosis Therapeutic Intervention) (Meunier et al 2004) and TROPOS (Treatment of Peripheral Osteoporosis) (Reginster et al 2005) studies, which were

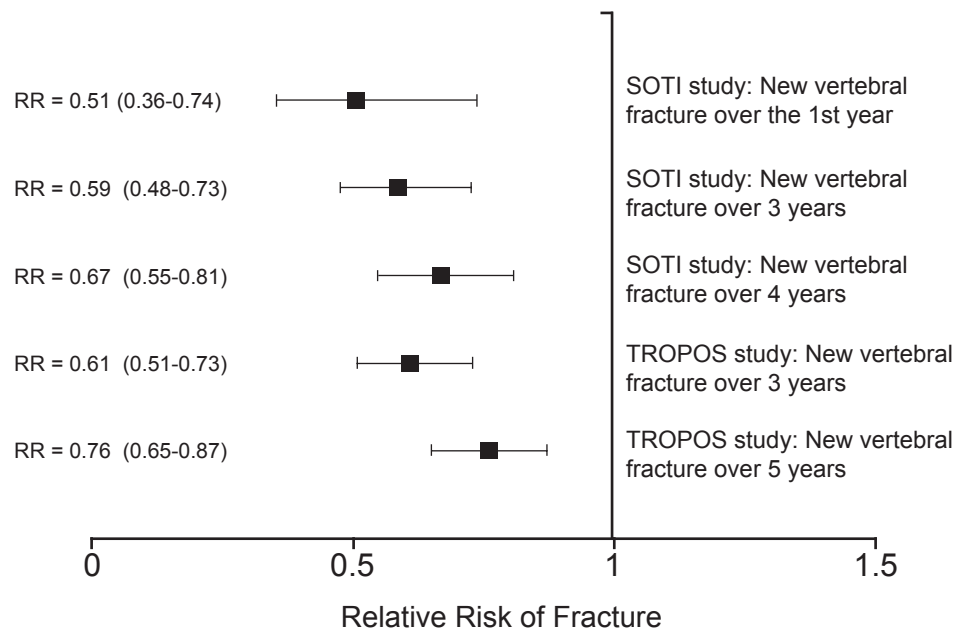**Figure 1** Chemical structure of strontium ranelate (Marie et al 1993).

RR = 0.51 (0.36-0.74)	SOTI study: New vertebral fracture over the 1st year
RR = 0.59 (0.48-0.73)	SOTI study: New vertebral fracture over 3 years
RR = 0.67 (0.55-0.81)	SOTI study: New vertebral fracture over 4 years
RR = 0.61 (0.51-0.73)	TROPOS study: New vertebral fracture over 3 years
RR = 0.76 (0.65-0.87)	TROPOS study: New vertebral fracture over 5 years

Relative Risk of Fracture

Figure 2 Results for vertebral fracture reduction by strontium ranelate treatment in the SOTI and TROPOS studies (Meunier et al 2004; Reginster et al 2005, 2006). Results are shown as the relative risk (RR) and 95% confidence intervals.
Abbreviations: SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, Treatment Of Postmenopausal Osteoporosis.

designed to study vertebral and non-vertebral fractures respectively. Further clinical data is available from two earlier Phase 2 trials, the STRATOS (Strontium Ranelate for Treatment of Osteoporosis) (Meunier et al 2002) and PREVOS (Prevention of Osteoporosis) (Reginster et al 2002) studies. These latter were dose ranging studies that examined the effects of strontium ranelate treatment on bone mineral density (BMD) and biochemical markers of bone turnover in patients with established vertebral fractures and early postmenopausal women respectively. The STRATOS study also provided some fracture data.

Vertebral fracture prevention by strontium ranelate

The evaluation of the efficacy of strontium ranelate treatment in preventing vertebral fractures was the primary aim of the SOTI trial (Meunier et al 2004). A total of 1649 women (mean age 69 y) were enrolled and randomized to receive either strontium ranelate 2 g/day or placebo. All subjects were also given calcium and vitamin D supplements to ensure they received the recommended daily intakes. The women were aged 50 y and over, at least 5 y postmenopausal, had at least 1 previous vertebral fracture and a lumbar spine bone mineral density (BMD) less than 0.840 g/cm^2 (T-score <–2.4 on the Slosman reference range (Slosman et al 1994) used for study inclusion criteria, equivalent to a T-score <–1.9 on the Hologic manufacturer's spine reference range).

Lateral spinal radiographs were performed at baseline and then annually, and were evaluated for evidence of new vertebral fractures using the Genant semi-quantitative method (Genant et al 1993). At the end of the first year of treatment there was a 49% lower risk of a new radiographic vertebral fracture in the strontium ranelate group compared with the placebo group (incidence 6.4% vs 12.2%; relative risk [RR]=0.51; 95% CI: 0.36–0.74; p<0.001). The risk of a clinically symptomatic vertebral fracture was 52% lower (3.1% vs 6.4%; RR=0.48; 95% CI: 0.29–0.80; p=0.003). Over the main three-year study period the strontium ranelate group had a 41% lower risk of a new radiographic vertebral fracture than the placebo group (incidence 20.9% vs 32.8%; RR=0.59; 95% CI: 0.48–0.73; p<0.001), while the incidence of clinically symptomatic vertebral fracture was 38% lower (11.3% vs 17.4%; RR=0.62; 95% CI: 0.47–0.83; p<0.001). Over this period the number of patients treated to prevent one vertebral fracture (NNT) was 9. The four-year SOTI study fracture data were recently published in a conference abstract (Reginster et al 2006) and show a 33% reduction in the risk of a new vertebral fracture in the strontium ranelate group compared with placebo (RR=0.67; 95% CI: 0.55–0.81; p<0.001). The 1 y, 3 y, and 4 y data are summarized in Figure 2.

The TROPOS study provided further data on the vertebral fracture efficacy of strontium ranelate (Reginster et al 2005). Although not primarily intended to study vertebral fractures,

3640 out of 5091 women enrolled in the TROPOS study (71%) had annual spinal radiographs. Of these 3640 patients, two-thirds (66.4%) had no prevalent vertebral fracture at inclusion. Over three years the overall reduction in vertebral fracture risk was 39% (RR=0.61; 95% CI: 0.51–0.73; p<0.001), and in the first year the reduction was 45% (RR=0.55; 95% CI: 0.39–0.77; p<0.001). The anti-fracture efficacy at 3y was similar for patients with and without vertebral fractures at baseline. The pooled 3-year data from the SOTI and TROPOS studies gave a total population of 5082 women for the evaluation of vertebral fracture risk and showed an overall reduction in fracture risk of 40% over three years (RR=0.60; 95% CI: 0.53–0.69; p<0.001) (Roux et al 2006). The recently presented 5-year TROPOS data show a 24% reduction in vertebral fracture risk (RR=0.76; 95% CI: 0.65–0.87; p<0.001) (Reginster et al 2006). Although both the SOTI and TROPOS data show a slight decline in antifracture efficacy the longer treatment is given (Figure 2), such a trend is expected since with the Kaplan-Meier analysis patients are censored after their first fracture and with time the remaining subjects in the treated and placebo groups become less well matched.

One interesting aspect of the SOTI and TROPOS studies compared with previous osteoporosis trials was the relatively advanced age of many of the subjects (Seeman et al 2006). Taken together, the two studies enrolled 1556 patients over 80 years at inclusion (23.1% of the entire study population) (SPC 2004). The pooled analysis of the studies for vertebral fracture risk showed no evidence of a treatment-by-age interaction (p=0.652). The RR reduction was 37% (p=0.003) in the younger women (<70 years), 42% (p<0.001) in women 70–80 years of age, and 32% (p=0.013) in the elderly (women ≥80 years of age) (Roux et al 2006).

Some vertebral fracture data was also published for the STRATOS study (Meunier et al 2002). However, this was a much smaller study with only 90 patients in each of four groups (placebo, 0.5, 1 and 2 g/day strontium ranelate) and over the full 2-years of the trial the results were not statistically significant (2 g/day group at 2 y: RR=0.77; 95% CI: 0.54–1.09).

Non-vertebral fracture prevention by strontium ranelate

The efficacy of strontium ranelate treatment in preventing non-vertebral fractures was investigated in the TROPOS trial, a study of 5091 women with a mean age of 77 y (Reginster et al 2005). Women were eligible for this study if they had a femoral neck BMD less than $0.600\,g/cm^2$ (T-score <–2.5 on the Slosman reference range [Slosman et al 1994] used for study inclusion criteria, equivalent to a T-score <–2.2 on the widely adopted NHANES III (Third National Health and Nutrition Examination Survey) hip reference range [Looker et al 1998]) and were aged 74 y or over, or were between 70 y and 74 y and had at least one additional risk factor such as a history of previous osteoporotic fracture or a maternal history of fracture. As in the SOTI trial, the subjects were randomized to receive either strontium ranelate 2 g/day or placebo, and also received calcium and vitamin D supplements. All non-vertebral fractures were recorded with the exception of the coccyx, skull, jaw, face, phalanx (fingers and toes) and ankle, since these latter were not regarded as being related to osteoporosis. Over the main 3 year follow-up period there was a 16% reduction in all non-vertebral fractures (incidence 11.2% vs 12.9%; RR=0.84; 95% CI: 0.702–0.995; p=0.04; number needed to treat [NNT]=59) (Figure 3). For the principal non-vertebral fracture sites (hip, wrist, pelvis, sacrum, ribs, sternum, clavicle, humerus) there was a 19% reduction in fracture risk (incidence 8.7% vs 10.4%; RR=0.81; 95% CI: 0.66–0.98; p=0.031; NNT=59). Overall the relative risk of hip fracture was reduced by 15%, but this figure was not statistically significant and the trial was not powered to investigate anti-fracture efficacy at this site. However, in a subgroup of high risk patients aged 74 y and over and with an NHANES III femoral neck T-score <–2.4 there was a 36% reduction in hip fracture risk (incidence 4.3% vs 6.4%; RR=0.64; 95% CI: 0.412–0.997; p=0.046; NNT=48) (Figure 3). The 5-year results of the TROPOS study show continuing long-term efficacy with a 15% reduction in non-vertebral fractures (RR = 0.85; 95% CI: 0.73–0.99; p=0.03) (Reginster et al 2006) (Figure 3).

The smaller SOTI study (Meunier et al 2004) was not powered to investigate non-vertebral fracture risk. Non-vertebral fractures were recorded in 234 women (112 in the strontium ranelate group and 122 in the placebo group) over the 3-year study (incidence 15.5% vs 16.8%; RR=0.90; 95% CI: 0.69–1.17). In the analysis of the pooled data from the SOTI and TROPOS studies the overall reduction in non-vertebral fracture risk was 15% (incidence 11.6% vs 13.1%; RR=0.85; 95% CI: 0.74–0.99; p=0.03) (Roux et al 2006). In the cohort of SOTI and TROPOS women aged 80 years and over at enrolment the reduction in non-vertebral fracture risk was 31% (incidence 14.2% vs 19.7%; RR=0.69; 95% CI: 0.52–0.92; p=0.011) (Seeman et al 2006).
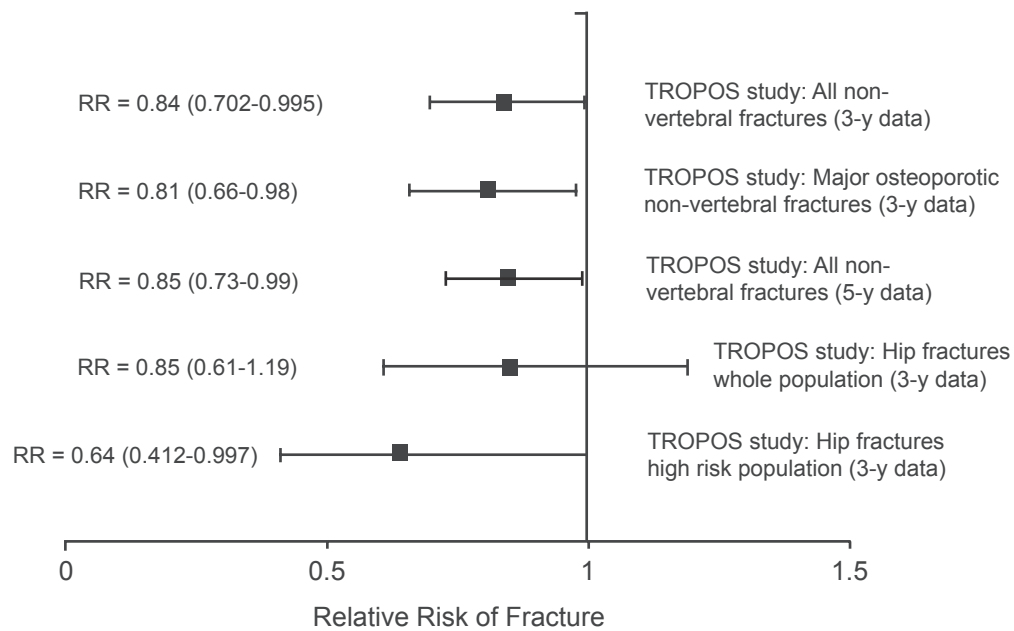
Figure 3 Results for non-vertebral fracture reduction by strontium ranelate in the TROPOS study (Reginster et al 2005, 2006). Results are shown as the relative risk (RR) and 95% confidence intervals.
Abbreviations: TROPOS, Treatment Of Postmenopausal Osteoporosis.

Patient safety in the strontium ranelate trials

During the SOTI and TROPOS trials a total of 3352 patients were exposed to strontium ranelate, 2315 of them for at least 36 months (Meunier et al 2004; Reginster et al 2005). The overall incidence of adverse events did not differ significantly from placebo and were generally mild and transient. The most common were nausea (6.6% of patients taking strontium ranelate vs 4.3% in those taking placebo) and diarrhea (6.5% vs 4.6%). However, if constipation is reduced the latter effect may be beneficial. The adverse reactions in the two studies thought possibly attributable to strontium ranelate are listed in Table 2. After 3 months there were no differences between strontium ranelate and placebo groups with respect to nausea and diarrhea. In both studies a small decrease in serum calcium concentration and a small increase in serum phosphate was noted in the strontium ranelate group, but these and other small changes in biochemistry were without clinical consequence (SPC 2004).

In the two Phase 3 studies strontium ranelate treatment was found to be associated with an increase in the annual incidence of venous thromboembolism (VTE) including pulmonary embolism (SPC 2004). This effect was observed over 4 years and was approximately 0.7% with a RR of 1.42 (95% CI: 1.02–1.98; p=0.036). The cause of this finding is unknown. The SPC advises that strontium ranelate should be used with caution in patients at increased risk of VTE, including patients with a previous history of VTE.

The SPC also states that strontium ranelate is not recommended in patients with severe renal impairment (glomerular filtration rate below 30 mL/min). Plasma strontium levels will be higher in such patients and the implications for bone safety are not known.

The effect of strontium ranelate treatment on bone mineral density

All the clinical trials of strontium ranelate (Meunier et al 2002, 2004; Reginster et al 2002, 2005) show impressive increases in BMD compared with BPs (Liberman et al

Table 2 Adverse events pooled for the SOTI (Meunier et al 2004) and TROPOS (Reginster et al 2005) studies

Adverse event	Strontium ranelate (N=3352)	Placebo (N=3317)
Nausea	222 (6.6%)	142 (4.3%)
Diarrhea	219 (6.5%)	154 (4.6%)
Loose stools	36 (1.1%)	6 (0.2%)
Headache	101 (3.0%)	79 (2.4%)
Dermatitis	69 (2.1%)	54 (1.6%)
Eczema	50 (1.5%)	40 (1.2%)
Allergic dermatitis	33 (1.0%)	18 (0.5%)

Abbreviations: SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, Treatment Of Postmenopausal Osteoporosis.
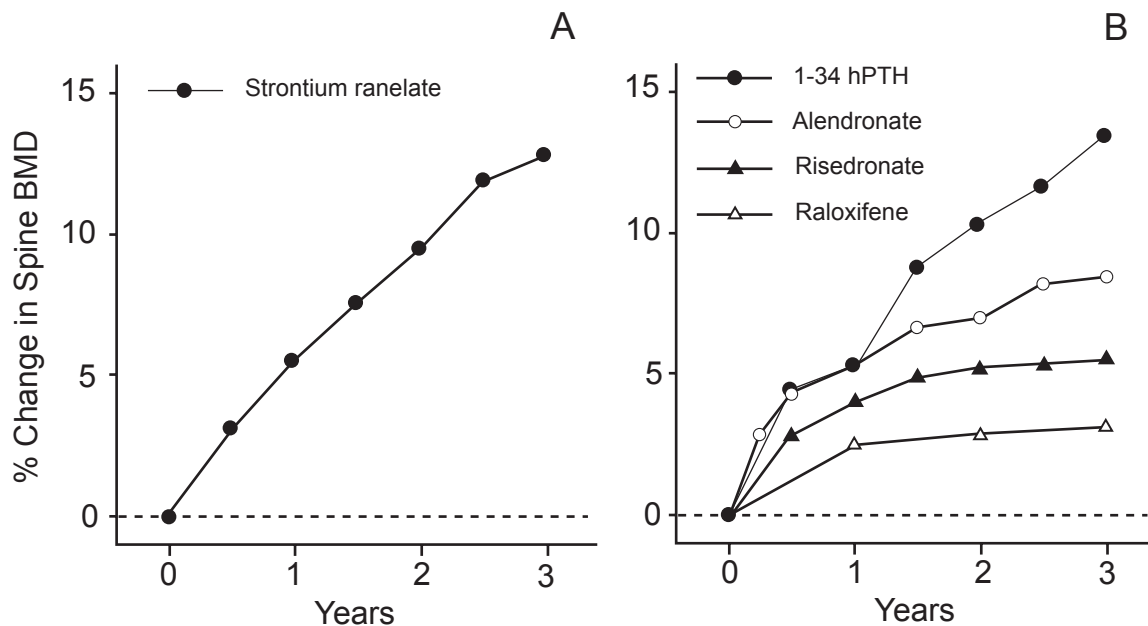
Figure 4 (A) Data from the SOTI study (Meunier et al 2004) showing the effect of 3 years treatment with strontium ranelate (2 g/day) on spine bone mineral density (BMD). The BMD values have not been adjusted for the bone strontium content. (B) Mean percentage changes in spine BMD from baseline to 3 years in patients receiving active treatment in four clinical trials: (i) raloxifene (60 mg/day) (Ettinger et al 1999); (ii) risedronate (5 mg/day) (Harris et al 1999); (iii) alendronate (10mg/day) (Liberman et al 1995); (iv) hPTH(1-34) and oestrogen (Lindsay et al 1997).
Abbreviations: hPTH, Human recombinant parathyroid hormone; SOTI, Spinal Osteoporosis Therapeutic Intervention.

1995; Black et al 1996; Harris et al 1999; Chesnut et al 2004) and SERMs (Ettinger et al 1999), and comparable with PTH (Lindsay et al 1997; Neer et al 2001) (Figure 4). After 3 years treatment the SOTI data showed BMD increases compared with placebo of 14.4% at the spine, 9.8% at the total hip site, and 8.3% at the femoral neck (Meunier et al 2004). These large changes may provide a useful way of monitoring patient compliance (Fogelman and Blake 2005). However, caution is necessary in interpreting the BMD increases as a real change in bone mass because much of the effect is due to the higher atomic number of strontium (Z=38) compared with calcium (Z=20) (Blake and Fogelman 2005). When BMD is measured by dual energy X-ray absorptiometry (DXA), strontium atoms in bone attenuate X-rays more strongly than calcium causing BMD to be overestimated. This effect was studied quantitatively by Pors Nielsen et al (1999) who constructed phantoms containing mixtures of calcium and strontium hydroxyapatite that were scanned on different manufacturers' DXA systems. They concluded that the same factor (a 1% molar ratio of Sr/(Ca+Sr) causing a 10% overestimation of BMD) applied to all the DXA brands studied. Since 3 years treatment with strontium ranelate results in a molar ratio of ~1%, it is clear that a significant percentage of the BMD increase in the clinical trial data can be explained by the increased

attenuation due to the bone strontium content (Blake and Fogelman 2006).

The most detailed discussion of the size of the BMD artefact produced by strontium ranelate treatment is that included in the report of the STRATOS trial (Meunier et al 2002). In this study 17 patients had iliac crest bone biopsies to measure bone strontium content (BSC) at 1 year and 64 patients at 2 years. At each time point a linear relationship was found between the iliac crest BSC and the area under the curve of strontium plasma concentration against time (AUC), and this was used to predict BSC values in patients who did not have a bone biopsy. For the 2 g/day strontium ranelate group it can be inferred from the raw and corrected STRATOS study BMD data that the mean iliac crest BSC was 0.8% at 12 months and 1.3% at 2 years. These BSC values were corrected by a factor of 0.61 for the ratio of spine to iliac crest BSC measured in female monkeys (Dahl et al 2001), and then combined with the phantom data of Pors Nielsen et al (1999) to adjust the raw spine BMD measurements. The strontium ranelate SPC document cites a factor of 50% for the correction of the measured BMD changes at the end of 3 years of treatment to allow for this effect. This should be taken into account when interpreting BMD changes during treatment with strontium ranelate. Radionuclide studies of the long-term retention of strontium

in bone using whole body counters (Marshall et al 1973) suggest that much of this BMD artefact will persist for at least 10 years after patients discontinue treatment (Blake and Fogelman 2006).

The effect of strontium ranelate treatment on biochemical markers of bone turnover

Follow-up measurements of changes in bone resorption and bone formation have played an important part in characterizing the clinical response in trials of other treatments for postmenopausal osteoporosis (Black et al 1996; Lindsay et al 1997; Harris et al 1999; Ettinger et al 1999; Eastell et al 2003; Chesnut et al 2004). For example, with the more potent BPs there is an almost immediate (within 1 month) reduction of 30%–50% in biochemical markers of bone resorption followed by a similar but delayed (3 to 6 month) reduction in markers of bone formation (Garnero et al 1994). For the potent anabolic agent human recombinant PTH there is an increase of about 50% in markers of both bone formation and bone resorption within 6 months of patients starting treatment. Based on pre-clinical studies, strontium ranelate is believed to exert an uncoupling effect on bone turnover by enhancing bone formation at the same time that it suppresses bone resorption (Marie et al 1993). It was therefore of interest to see whether the strontium ranelate trials provided confirmation of this behaviour.

Biochemical marker measurements were reported for the SOTI study (Meunier et al 2004) but not TROPOS (Reginster et al 2005). Unfortunately, the SOTI biochemical marker data were affected by some unexplained variations affecting the measurements for both the strontium ranelate and placebo groups. Nevertheless, the SOTI study authors inferred that after 3 months of treatment the serum concentration of bone specific alkaline phosphatase (BSAP), a bone formation marker, increased by 8.1% in the strontium ranelate group compared with placebo (p<0.001) while the concentration of serum C-telopeptide cross-links (CTX), a bone resorption marker, was lower by 12.2% (p<0.001), and these changes were sustained throughout the 3-year study. The biochemical marker data from the SOTI study therefore appeared to confirm the expected effect of a mild (compared with a potent anabolic agent) promotion of bone formation, and a mild (compared with potent antiresorptive agents) suppression of bone resorption, and are in line with

the results of pre-clinical animal and in vitro studies (Marie et al 1993; Canalis et al 1996; Ammann et al 2004).

Biochemical marker data were also reported for the STRATOS (Meunier et al 2002) and PREVOS (Reginster et al 2002) trials. However, both these studies were smaller than the SOTI trial with patients randomized to a range of treatment doses. In the STRATOS study BSAP increased by 11% at 24 months in the 2 g/day group (p<0.05), while urinary excretion of type 1 collagen cross-linked N-telopeptide pyridinoline (NTX) was reduced by 10.1% compared with placebo at the same time point. In the PREVOS study similar trends were seen, but most of the differences were not statistically significant.

The effect of strontium ranelate treatment on bone histomorphometry

A considerable effort was made in the strontium ranelate trials to obtain transiliac bone biopsies to evaluate bone safety and assess the mechanism of action at the bone tissue level (Meunier et al 2002, 2004; Reginster et al 2005). Bone histomorphometry data from the STRATOS, SOTI, and TROPOS patients at baseline, 1 y, 2 y, 3 y, 4 y and 5 y from the start of treatment were reviewed by Arlot et al (2005). Data were available for 49 patients treated with strontium ranelate for between 1 y and 5 y, and for 87 patients either at study baseline or in those randomized to the placebo group. The positive effect of strontium ranelate on bone formation was confirmed by a higher osteoblastic surface area (Ob.S/BS) in treated compared with untreated patients (+38%; p=0.047) and a greater mineral apposition rate (MAR) in trabecular (+8%; p=0.008) and cortical (+11%; p=0.033) bone. There was no significant change in activation frequency. The effect on bone resorption consisted of trends towards lower endosteal eroded surfaces, endosteal and trabecular osteoclast surfaces, and osteoclast numbers, none of which were statistically significant. In terms of bone safety, osteoid thickness was found to be significantly lower and MAR significantly higher in treated patients with no change in osteoid volume or mineralization lag time demonstrating that primary mineralization was not impaired. Overall, the results are consistent with the mild stimulation of bone formation.

Conclusions

The results of the SOTI and TROPOS studies confirm that strontium ranelate is a safe and effective treatment to prevent

vertebral fractures and hip fractures in women with postmenopausal osteoporosis. The 40% reduction in vertebral fracture risk found in the pooled analysis (Roux et al 2006) is similar to that found in trials of other osteoporosis treatments including alendronate (Black et al 1996), risedronate (Harris et al 1999), ibandronate (Chesnut et al 2004), and raloxifene (Ettinger et al 1999). Strontium ranelate has also been proven to reduce non-vertebral fracture risk by 15% (Roux et al 2006). This includes the prevention of hip fractures in older patients with a femoral neck BMD T-score consistent with the diagnosis of osteoporosis. Interestingly, because of the generally elderly population enrolled in the SOTI and TROPOS studies, strontium ranelate is the only treatment proven to be effective at preventing both vertebral and non-vertebral fractures in patients aged 80 years and over (Seeman et al 2006). Data from bone biopsies and biochemical markers of bone turnover seem to confirm the hypothesis that strontium ranelate may have a dual mode of action that has the effect of rebalancing bone turnover in favor of bone formation. No studies have yet examined the benefit of combining strontium ranelate with another treatment, for example a BP. Theoretically the administration of strontium ranelate in combination with a potent BP could have an adverse effect on both the uptake and the pharmacological action of strontium in bone because of the reduction in osteoblastic activity by the BP. In many patients strontium ranelate treatment has an impressive effect on BMD, and the large BMD increase may prove a useful way of monitoring patient response (Fogelman and Blake 2005). However, clinicians should be aware that at least 50% of the observed BMD increase is an artefact caused by the high bone strontium content (SPC 2004). This artefact will persist for many years after the patient discontinues therapy and will need to be taken into account in the interpretation of future BMD scans in patients who have previously been treated with strontium ranelate (Blake and Fogelman 2006).

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