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Reference studies for strontium ranelate in the treatment of osteoporosis

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Introduction

Strontium ranelate is an agent used for the treatment of osteoporosis. It consists of two atoms of stable strontium and an organic part: ranelic acid. Simultaneously, it stimulates the formation of new bone and reduces bone resorption, resulting in a deviation from the balance of bone turnover towards formation¹. These actions are effected by improving the replication of pre-osteoblastic cells and the differentiation of osteoblasts, as well as reducing their capacity to induce the osteoclasts through the receptor sensors of calcium (CaR) and increase the range OPG/RANKL². Its effectiveness in animals has been widely studied, it having been shown to augment bone mass in ovariectomised rats and to increase bone resistance in normal animals³⁻⁵. The action mechanism of strontium ranelate, as well as its effect on bone quality, is studied in greater detail in other chapters of this monograph.

Reference studies for strontium ranelate. The SOTI and TROPOS study

Design. Objectives

The objective of any anti-osteoporotic treatment is to prevent all fractures, whatever their location. Phase 3 of the study of strontium ranelate consisted of two parallel international studies to evaluate its anti-fracture effect both vertebral, in the study Spinal Osteoporosis Therapeutic Intervention (SOTI)⁶, and non-vertebral in the Treatment of Peripheral Osteoporosis Study (TROPOS)⁷ (Table

1). Both studies were prospective, randomised, double blind and controlled by placebo. For this reason these publications permit us to determine the efficacy of strontium ranelate in the reduction of all fractures related to osteoporosis, both of the axial and extra-axial skeleton.

It is necessary to clarify that the TROPOS study was designed in 1996, more than a year before the first guide to osteoporosis was published by the Committee of Medical Products for Human Use (CHMP). Even so, non-vertebral fractures including hip and other major fractures were documented separately as the CHMP guide of 2001 advised⁸. In addition, it was designed to evaluate the relative risk of non-vertebral fractures between the two groups. As such, the study was not designed to demonstrate the anti-fracture efficacy in each individual location, but its anti-fracture efficacy in non-vertebral locations in general. To adapt the study to the recommendations of the 2001 CHMP guide, and to enable an evaluation of the effect of strontium ranelate in reducing the risk of hip fracture, a sub-group of high risk patients was created. Established as criteria for this group were that the subjects be aged 74 or more, with a bone mineral density in the femoral neck with a T-score of -3 or less, such as those used for the Hip Intervention Study earlier⁹.

Criteria for inclusion and exclusion

As far as the design of the SOTI and TROPOS studies are concerned, the criteria for inclusion differ between the two studies. In SOTI were included postmenopausal women from 11

European countries and Australia who were at least 50 years of age, having been postmenopausal for at least 5 years, having had at least one fracture confirmed by a spinal x-ray after a minimal trauma, and having a bone mineral density in the lumbar spinal column of 0.840 g per square centimetre or less. In TROPOS however, the criteria for inclusion were the following: they had to be women of 74 years or more, but also being between 70 and 74 years old, but with an additional risk factor for fracture. Understood as additional risk factors were a previous history of fracture after menopause, living in an old people's home, suffering frequent falls or having a maternal history of osteoporotic fractures of the hip, wrist or vertebrae. Additionally, a high risk subgroup was created whose criteria for inclusion have already been stated above. Similarly, the patients had to have a bone mineral density in the femoral neck of 0.600 g per square centimetre or less, this measure corresponding to a T-score of less than -2.5 in accord with data for normality¹⁰. In both cases the bone mineral density was measured with Hologic instruments.

With respect to the criteria for exclusion, both studies excluded those patients with serious diseases, or diseases which interfered with bone metabolism. Similarly, those patients having taken oestrogens, calcitriol or calcitonin for more than one month in the previous 6 months, as well as biphosphonates for more than 14 days in the previous 12 months, were excluded. In addition, in SOTI, those patients having taken fluoride salts for 14 days in the previous 12 months, were excluded.

Baseline characteristics of the populations and protocol of treatment

The baseline characteristics of the populations (shown in Table 2) differ, since the criteria for inclusion are very different with regard to age and this means that the other parameters, since they are dependent on it, also differ. As we have already said, in SOTI the age for inclusion was from 50 years while in TROPOS the minimum age was 70, for which reason it is not strange that in the latter study, the time passed since the menopause being greater, the bone mineral density would be lower in all locations.

The protocol for treatment was similar in both investigations. The subjects were submitted to an initial period of 2 to 24 weeks, in depending on the severity of their initial deficiency in calcium and vitamin D, until their levels were normalised. Once the study commenced they received daily supplements of calcium with food: up to 1,000 mg of elemental calcium dependent on their dietary intake of calcium, in order to reach 1,500 mg/day (SOTI) or 1,000 mg/day (TROPOS). They also received vitamin D supplements: 400 to 800 UI, according to their baseline blood concentration of 25-hydroxyvitamin D.

After the initial period, the patients were assigned randomly to receive 2 g daily of strontium ranelate or placebo powder for a period of 3

years. Both preparations were presented in envelopes as a powder which the patients had to mix with water. Similarly, they had to choose if they wanted to take the preparation (2 envelopes) once during the day at night, or twice a day (one envelope half an hour before breakfast and the other at night). Approximately 90% chose the single dose in both studies.

Biochemical determinations. Markers for remodelled bone

The patients attended for a review every 3 months for the first 6 months, and then every 6 months until the end of the study. During these reviews samples were taken of blood and urine, frozen at -80°C and analysed in a central laboratory. In both studies the concentrations of PTH were measured with an immuno-radiometric assessment (N-tact, DiaSorin), of 1.25 dihydroxyvitamin D with an assessment by radioreceptor (DiaSorin) and of 25-hydroxyvitamin D, with radioimmuno-assessment (DiaSorin).

In SOTI, in addition, the specific concentrations of alkaline phosphatase in the bone, were measured with an immuno-radiometric assessment (Tandem-R, Ostase, Hybritech), of the crossed links of C-telopeptide with an immuno-absorbent assessment linked to an enzyme (Serum Crosslaps, Osteometer Biotech), and of calcitonin with an immuno-radiometric assessment (BioSource). Similarly, the strontium content of blood and bone was measured by inductively coupled plasma atomic emission spectrophotometry (BARC).

Radiological study. Assessment of vertebral fracture. Bone densitometry

With respect to radiographical studies, in SOTI 3 lateral spinal X-rays (thoracic, lumbar and the thoracic-lumbar joint) were obtained: baseline, annual, and baseline anteroposteriors also. The X-rays were evaluated centrally by radiologists who knew the time sequence but not the assignment of treatment. They were studied to see if there were indications of vertebral fractures: acute back pain, reduction in the body height of at least 1 cm, or both.

Similarly, in TROPOS, despite the fact that the study was meant to evaluate non-vertebral fractures, they tried to carry out baseline and annual spinal column X-rays in the greatest possible number of women who belonged to a sub-group of 3640 patients (71% of the total submitted to analysis by the intention to treat).

For the SOTI study, two methods were used to evaluate vertebral fractures. In the first place a method of semi-quantitative visual evaluation¹¹ was carried out by the same assessor for each vertebra from T4 to L4. In the second place, a quantitative evaluation was carried out which consisted of measuring the anterior, middle and posterior heights of each vertebra.

In TROPOS the principal evaluation criterion was the incidence of non-vertebral fractures. These types of fracture were evaluated by the

Table 1. Comparison of differences between SOTI and TROPOS studies

	SOTI ⁶	TROPOS ⁷
Fractures studied	Vertebral	Non-vertebral
Criteria for inclusion	> 50 years + menopause > 5 years + vertebral fx + BMD of < 0.840 g/cm ²	> 74 years, or 70-74 + risk factor for osteoporosis + BMD in femoral neck < 0.600 g/cm ² = > 2.5 in T-score
Excluding treatment	Fluoride salts or biphosphonates > 14 days in the last 12 months or oestrogens, calcitriol, calcitonin for > 1 month in last 6 months	Biphosphonates > 14 days in the last 12 months or oestrogens, calcitriol, calcitonin for > 1 month in last 6 months
Number of patients	1,649 population of analysis by intention to treat 1,260 completed the follow up	4,932 population of analysis by intention to treat 3,320 completed the follow up
Parameters analysed in blood and urine	Alkaline phosphatase C-telopeptide, PTH, 25-vitD, calcitonin, 1.25-vitD	PTH, 25-vitD, 1.25-vitD

researched based on documentation written, with facilitation, by the patients, such as information on accidents or their traumatology. Facial fractures, fractures of the coccyx, of the cranium, jaw and phalanges were not considered to be related to osteoporosis, and as such, were not taken into account.

The bone mineral density of the lumbar spinal column and of the femur were measured by double energy X-ray absorptiometry (Hologic) at the baseline visit and every six months, at centralised facilities.

Results. Methodology

Both studies performed similar statistical analyses, carrying out the principal analysis of efficacy based on intention to treat. To compare the two groups, and to estimate the relative risks and confidence interval of 95%, an unadjusted Cox model was used as the main tool for statistical analysis.

Bilateral Student T tests were used to compare the percentage changes from the baseline in independent samples, Pearson's chi squared test was used to compare the number of patients with at least two new vertebral fractures (SOTI) and the number of patients with a specific adverse event, and the intervals of confidence of 95% were determined from the difference between the groups with respect to the average changes in the blood levels of calcium, phosphorus and parathyroid hormone. For the percentage change from baseline value of bone mineral density at each visit, a descending hierarchy procedure, based on an increase in the effect of treatment over time, was carried out. The average values in the two groups for each visit were compared with unilateral Student T tests with a Type 1 error index of 2.5 percent. The P values presented in both investigations corresponded to a bilateral test at a threshold of 5 percent.

In SOTI the intention to treat population was formed by those subjects who had taken at least one dose of treatment and those who had obtained at least one X-ray of the spinal column after the baseline X-ray. In TROPOS it was formed from those who had taken at least one dose of treatment and in whom had been carried out an assessment of non-vertebral fractures. Similarly, every time an X-ray was carried out, the Kaplan-Meier product-limit estimate of the incidence of new fractures was calculated.

In TROPOS the incidence of patients with non-vertebral fractures was estimated through Kaplan-Meier analysis and, simultaneously, a Cox model adjusted for age, with the BMD of the femoral neck, body mass index and country of residence recorded.

Changes in markers for remodelled bone

Strontium ranelate provokes changes in the blood concentrations of certain markers for remodelled bone which, in the studies with which we are concerned, were similar. In the case of blood calcium, this diminished in the group taking strontium ranelate, as blood phosphate levels increased. PTH reduced slightly in both groups, although to a more pronounced extent in the strontium ranelate group. The variations in these parameters did not have clinical consequences.

No changes were observed in blood levels of 25-hydroxyvitamin D, 1.25-hydroxyvitamin D or calcitonin. Similarly, in SOTI an increase in concentrations of blood creatine kinase to twice the upper limit of the normal interval (145 UI per litre) were found in 3.4 percent of subjects in the strontium ranelate group, and in 1.8 percent of the placebo group. However, the majority of these increases were transitory and no muscular symptoms were observed.

Table 2. Comparison of the differences in baseline conditions of the populations

	SOTI ⁶		TROPOS ⁷	
	Strontium (N= 719)	Placebo (N= 723)	Strontium (N= 2479)	Placebo (N= 2453)
Age (years)	69.4 ± 7.2	69.2 ± 7.3	76.7 ± 5.0	76.8 ± 5.0
Time since the menopause (years)	22.1 ± 8.8	21.6 ± 7.2	28.4 ± 7.3	28.5 ± 7.5
BMD T-score in lumbar spinal column	- 3.5 ± 1.3	- 3.6 ± 1.2	- 2.8 ± 1.6	- 2.8 ± 1.6
BMD T-score in femoral neck	- 2.8 ± 0.8	- 2.8 ± 0.8	- 3.1 ± 0.5	- 3.1 ± 0.6
BMD T-score in total hip	- 2.4 ± 1.1	- 2.4 ± 1.1	- 2.7 ± 0.9	- 2.7 ± 0.9

Reduction in risk of new fractures

SOTI and TROPOS demonstrated the efficacy of strontium ranelate in reducing the risk of osteoporotic vertebral and non-vertebral fractures (Table 3). The results obtained in SOTI with respect to vertebral fractures reveal that, after 3 years, the drug reduces the relative risk of suffering a new vertebral fracture in 41 percent of patients compared with the placebo group; from this we can conclude that 9 patients should have been treated over 3 years with strontium ranelate to prevent one patient having a vertebral fracture [95% CI, 6-14]. In addition, the prevalence of patients with more than one new vertebral fracture was 6.4 percent in the strontium ranelate group and 9.8 percent in the placebo group (RR 0.62 [95% CI 0.44 to 0.93]; P= 0.02). The loss of body height of at least one centimetre occurred with less frequency in the strontium ranelate group (P= 0.003), as well as symptomatic fractures (RR 0.62; [95% CI 0.47 to 0.83]; P<0.001).

The results obtained in TROPOS confirm the efficacy of strontium ranelate in the prevention of non-vertebral fractures concluding that, in the intention to treat population, the risk of suffering a non-vertebral fracture is reduced in 16% of cases after 3 years of follow up. The reduction is greater, 19%, if only major non-vertebral fractures are taken into account. The relative risk of suffering a hip fracture was reduced by 15% but without statistical significance, since, as has already been stated, the TROPOS study was not designed to assess this parameter. In those women who formed the high risk sub-group (women of 74 years or greater, with a bone mineral density in the femoral neck with T-score of -3 or less), the risk of suffering a hip fracture was reduced in 36 percent of cases.

Both investigations, after an initial period of 3 years, extended the period of following up their patients up to the end of 5 years. In the case of SOTI², the methodology changed with respect to the initial methodology: up to the fourth year the patients continued to take 2 g of strontium, or the

placebo, daily, according to the random selection at the start of the study. However, once the fourth year had ended, the subjects in the strontium ranelate group were randomly selected again to form two groups: one which would continue with the strontium (SR/SR 50% group) and the other which would change to taking the placebo (SR/placebo 50% group). Similarly, all the subjects in the original placebo group changed to taking the strontium ranelate (placebo/SR group).

At the end of the fourth year the primary criterion for efficacy was the incidence of patients with a new vertebral fracture, whilst at the end of the fifth year, it was bone mineral density in L2-L4.

The intention to treat population studied during the fourth year were those subjects who had taken at least one dose of the product and having had at least two X-ray vertebral assessments in the four years. However, the intention to treat population studied in the fifth year were those patients who had made a visit in the first month of this fifth year, having taken at least one dose of the product in the first four years and another one during the fifth, and, in addition having had a measurement of bone mineral density in L2-L4 in the first four years and another during the fifth year.

In terms of the statistical analysis, it is worth noting that, in this case, the incidence of vertebral fractures was adjusted for age, country, body mass index and bone mineral density in the femoral neck.

At the end of the 4 year period of study the risk of suffering a new vertebral fracture was reduced in 33% of the strontium ranelate group with respect to the placebo group (RR 0.67; [95% CI 0.55-0.81], P<0.001). Thus, the number of patients who it would be necessary to treat in order to prevent one fracture from occurring would be 11 (as opposed to the 9 which was calculated for the first period of 3 years). The total number of fractures was significantly less in the strontium ranelate group (p<0.001). In terms of bone mineral density, this increased in all locations measured in the strontium group but

Table 3. Comparison of RR published by SOTI and TROPOS

	SOTI ⁶			TROPOS ⁷		
	RR	IC (95%)	P value	RR	IC (95%)	P value
New vertebral fracture	0.59	0.48-0.73	< 0.001	0.61	0.51-0.63	< 0.001
1st vertebral fracture	0.59	0.48-0.73	< 0.001	0.55	0.42-0.72	< 0.001
New non-vertebral fracture	0.90	0.69-1.17	NS	0.84	0.70-0.99	0.04
Hip fractures in high risk sub-group				0.64	0.41-0.99	0.046

slightly diminished in the placebo group. The difference between the two groups increased to 14.6% in the lumbar measurement, 8.7% in the femoral neck and 9.8% in the total hip (all $p < 0.01$).

Results at 5 years

At the end of 5 years of study the pattern of change in bone mineral density was modified depending on the group: the increase in bone mineral density continued in the SR/SR group with an additional increase of $1.2 \pm 5.8\%$ between the first and last months of the fifth year. In the SR/placebo group, the increase in density began to reverse ($-3.2 \pm 5.8\%$) between the first and last months of the fifth year ($p < 0.001$), although this was higher at the end of the 5 years (0.819 ± 0.147 g/cm²) than at the start of the study (0.734 ± 0.123 g/cm², $p = 0.002$). In the third group, the placebo/SR group, the bone mineral density increased between the first and last months of the fifth year ($5.3 \pm 7.3\%$). The changes observed in other locations were similar to those found in L2-L4.

In the extension of the follow up period, in TROPOS the design was maintained without changes, and the results were published after 5 years¹³ from the start of the study, following the same methodology as in the first 3. 4,935 patients were included in the study, of whom 2,714 (53%) had completed 5 years. After this time a 15 percent reduction in the risk of suffering a new non-vertebral fracture was observed (RR 0.85; 95% CI [0.73-0.99]), $P = 0.032$). Also, the number of patients who it would be necessary to treat to prevent one fracture from occurring was 44 (95% CI 20-191). While it is not one of the aims of TROPOS, it was observed that the risk of a new fracture occurring was diminished by 24% (RR 0.76 [95% CI 0.65-0.88], $P < 0.001$) and, if we take into account both types of fracture, in the strontium ranelate group, it diminishes by 20% (RR 0.20 [95% CI 0.71-0.90], $P < 0.001$). In terms of bone density, this was increased in the strontium ranelate group in the lumbar spinal column, femoral neck and total hip, whilst in the placebo group, it remained stable or slightly diminished.

Follow-up at 8 years

After this period of 5 years both studies came together to continue until the end of a total of 8 years¹⁴. In this case the criteria of inclusion consisted in having participated in SOTI or TROPOS during the first 5 years, although also included were those patients who had interrupted their treatment or who had been withdrawn from the study, provided that this had happened in the 6 months prior to the last visit of the 5 years.

The procedure followed to evaluate both vertebral and non-vertebral fractures was the same as that which was used in the first 5 years. For the statistical analysis only those fractures occurring in the final 3 years were taken into account, excluding those which had occurred in SOTI or TROPOS in their first 5 years. Spinal X-rays were taken, as well as bone densitometry (lumbar, femoral neck and total hip) at the start and every year to the end of the follow-up period.

The Complete Analysis Group (CAG) was defined as those patients who had taken at least one dose of strontium ranelate after their inclusion in the study with at least one lumbar L2-L4 densitometry at the start and at least one assessment of incidence of fracture. Of the 2,055 patients included in the extension of the studies, 892 were treated with strontium ranelate from the start of SOTI ($n = 164$) or TROPOS ($n = 739$). Of these 879 were included in the CAG; the 13 remaining patients were excluded for not having had a good assessment of efficacy of treatment at the start, or after their inclusion in the extended study. The population is representative of the total sample of SOTI and TROPOS and its baseline characteristics were very similar to theirs.

In those patients who had been treated continuously with strontium ranelate the cumulative incidence of patients with at least one new osteoporotic fracture was 28.8% at the start of the study and 41.1% at the end of 8 years. However, the difference between this cumulative incidence and that obtained in the first 3 years of SOTI and TROPOS are not statistically significant, which suggests that the anti-fracture efficacy of strontium ranelate is maintained for 8 years.

If we focus on bone mineral density, in the three locations measured it increased in all patients treated with strontium ranelate, and the annual relative change was statistically significant at all the annual visits, except at 8 years in the femoral neck and in the total hip. The bone density in the lumbar spinal column increased 0.4 ± 0.08 g/cm² during the last 3 years, which corresponds to an average increase of $4.4 \pm 8.4\%$. This supposes a lower increase in bone mineral density in the lumbar spinal column than in the first 3 years of SOTI (12.7%); in the femoral neck and the total hip the same tendency to a lower increase in bone mineral density in the long term was observed.

The relationship between the changes in bone mineral density and the incidence of fractures was studied in the CAG sub-population with those subjects who had had a densitometry and data on fractures at 6 and 8 years (n= 417). After adjusting for age, body mass index and fractures at the start, there was no significant association between the change in bone density in the lumbar spinal column at 6 and 8 years and the incidence vertebral fractures during the same period of time. However, there was an association between the change in bone density in the proximal femur and the incidence of vertebral fracture (P= 0.02). Every 1% of increase in bone density in the proximal femur was associated with a 5% reduction in risk of vertebral fracture (95% CI 1-10). However, in this final study there was no placebo group, which prevents direct comparisons of indices of fracture being made.

It has been shown repeatedly that the risk of vertebral or non-vertebral fractures multiplies with age¹⁵, as well as there being a reduction in bone mineral density¹⁶. Given that in SOTI and TROPOS the risk of fracture remained stable within the first and last 3 years, this reduction in risk could be attributed to an indirect effect of strontium ranelate. Similarly, as an agent that has been shown to increase bone mineral density, we can confirm that the administration of strontium ranelate in the dose indicated results in a significant reduction in risk of fracture in both vertebral and non-vertebral fractures in postmenopausal women, and that after 8 years this benefit continues to be maintained.

With the intention of verifying the long term benefits, we should take into account that this is the fourth study on anti-osteoporotic agents which has a duration longer than 5 years¹⁷⁻¹⁹. In the early studies, alendronate and risedronate did not show an increase in bone mineral density beyond 4 years, for which reason it was concluded that there was no benefit in administering them beyond this period. The other agent studied is raloxifen which, while it did demonstrate a steady increase in vertebral and hip bone mineral density, it did not show a diminution of the risk of non-vertebral fracture.

Safety and tolerance

With respect to the safety and tolerance of strontium ranelate, the study of the dose-response

showed a good tolerance of the product, the dose with the best efficacy-safety relationship being 2 g per day²⁰. In SOTI and TROPOS, the incidence of secondary effects is balanced between the two treatment groups. Those most common –nausea, diarrhoea, headache and dermatitis– were those most frequent in the strontium ranelate group in the first 3 months, but once this period was passed there were no differences between the groups. Adherence to treatment was 87.5%, similar to that found in the studies with risedronate, although one should bear in mind the fact that those in the extended study were patients who had decided to take the treatment. A rebound in fractures in patients on anti-osteoporotic treatments has been observed, and one of the risk factors most associated is low adherence, especially with bisphosphonates²¹. The scarcity of secondary effects and the comfortable dosage are highly favourable for adherence in treatment with strontium ranelate.

Conclusion

Strontium ranelate is a drug which has shown a reduction in all fragility-related fractures: vertebral, non-vertebral and hip, in women and men, and with a very good safety margin and few secondary effects. All this makes it a drug of first choice in the treatment of osteoporosis.

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