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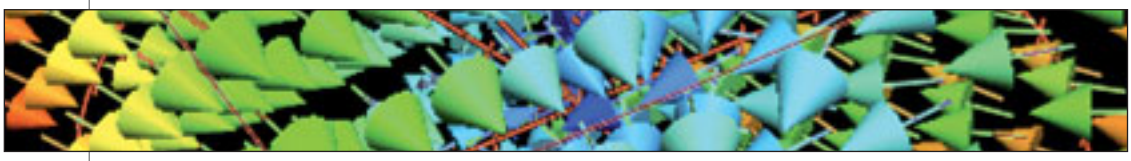

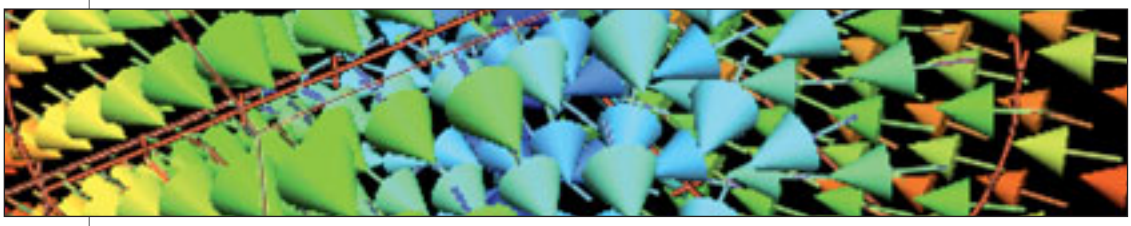

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Action mechanism of strontium ranelate

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Characteristics of strontium

Strontium was discovered in 1790 in a mine close to the Scottish village Strontian and was isolated in 1808. Strontium is one of the alkaline earth metals and is never found in its free form in nature because it easily oxidises, forming strontium oxide. Strontium, along with calcium and magnesium belongs to group 2 of the periodic table which are divalent cations, which, in biological liquids can have different degrees of bonds with blood proteins. The binding to proteins of strontium is in the same order of magnitude as that of calcium[1]. In the human body there are only traces of strontium. A normal diet supplies from 2 to 4 mg of strontium per day, although the quantity can be higher if the diet is rich in cereals or vegetables.

Given the similarity in the behaviour of both elements, the radioisotopes of strontium have been used for kinetic studies of the metabolism of calcium. However, there are important biological differences between them, which are in part explained by the greater molecular weight of strontium. Common transportation pathways have been described, for example strontium competes with calcium in intestinal absorption and in renal tubular reabsorption[1]. Strontium is absorbed less than calcium, this difference in the intestinal tract could be due, in part, to the smaller size of the calcium atom. On the other hand, the renal clearance of strontium is nearly three times greater than that of calcium, perhaps due to a greater secondary tubular absorption because of the larger size of the strontium atom.

Relationship of strontium with bone

The quantity of strontium in the skeleton is very small, and represents only 0.035% of the content of calcium. After its administration it is deposited almost exclusively in bone. Like sodium and lead, strontium can substitute for calcium in the position which it occupies in hydroxyapatite.

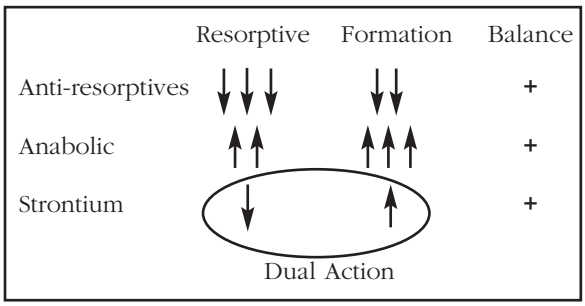
In 1952, Shorr and Carter demonstrated that the addition of a moderate quantity of strontium lactate improves the deposition of calcium in the bone[2]. One can say that this observation was the first suggestion in the literature that strontium could be useful in the treatment of alterations in bone metabolism. In 1959, McCaslin showed in a small study that in patients with osteoporosis strontium lactate reduced bone pain, at the same time as improving the X-ray images of demineralisation[3]. However, these observations did not awaken great interest in the researchers of that time, probably due to the mineralisation defects which a high dose of strontium was known to produce.

Subsequently, in the 90s, from the study of Marie et al.[4], various researchers confirmed progressively and uniformly, that strontium ranelate reduced bone resorption, maintaining formation and increasing bone volume without inducing mineralisation defects[5,6].

The effect of strontium ranelate on markers for bone formation and resorption

Anti-resorptive and anti-catabolic drugs prevent the destruction of bone by reducing the rate of

Figure 1. Classification of different drugs for the treatment of osteoporosis by function of their effects on remodelled bone



bone remodelling, as is reflected in the decrease in markers for bone resorption and formation[7]. The bone formation drugs such as teriparatide and PTH 1-84, increase bone formation and secondarily, an increase in bone resorption is observed[8,9]. However, the action mechanism of strontium ranelate is different to that of other drugs; in fact, by its action in opposing resorption and formation, it has been classified within a new group: dual action[10,11], Figure 1.

One of the studies (randomised, double blind, of 3 years duration)[12] which was carried out, for the registration of the drug, in 1649 postmenopausal women with osteoporosis and at least one vertebral fracture, after 3 months of treatment, found in the group taking strontium ranelate an increase in bone-specific alkaline phosphatase and a decrease in C-telopeptide, compared with the placebo group. These changes, although more pronounced during the first six months of treatment, persisted throughout the study, remaining statistically significantly different from the placebo group during the three years of the study.

Target molecules for strontium ranelate

There is no doubt as to the clinical efficacy of this drug which, thanks to the carful design of the studies for its registration (SOTI and TROPOS)[12,13], has shown long term (5 years) beneficial effects on vertebral and non-vertebral fractures compared with a placebo[14-17]. However, there remain doubts over the molecular signalling mechanisms which come to produce the observed effects on osteoblasts, osteocytes, osteoclasts and definitively on bone metabolism.

The similarities of strontium with calcium, already mentioned at the start of this review[1-3], have generated many studies intended to investigate if the final action mechanism of strontium shares signalling pathways with calcium, involving the receptor-sensor of calcium (CaSR) in these responses[18]. *In vitro* studies show that strontium activates CaSR[19-22], in turn it has been shown that CaSR is implicated in the replication of pre-osteoblasts and osteoblasts induced by strontium ranelate[22,23].

However, the activation of CaSR is not the only mechanism which has been implicated in the signalling pathways of strontium. Other parallel mechanisms could exist through the cation receptor-sensors, similar to CaSR[23]. Among the activated pathways are found protein kinase C, protein kinase D and p38, signals involved in cellular replication induced by strontium ranelate[23].

Recent data obtained in cultures of human primary osteoblasts stimulated with strontium ranelate have strengthened the idea of the involvement of CaSR in the molecular signalling pathways of this drug[24,25]. Strontium ranelate has shown itself to be capable of increasing the levels of ARNm and of the protein of osteoprotegerin (OPG), in turn suppressing RANKL (receptor activator of NF-kB ligand). In addition, strontium ranelate also stimulates osteoblast replication and differentiation, increasing cellular survival under stress. These positive effects of strontium ranelate are suppressed when CaSR is partially silenced, suggesting the significant involvement of CaSR in these responses[25].

General effects of strontium in experimental models

The action mechanism of strontium ranelate is based on its capacity to increase the formation, and reduce the resorption, of bone simultaneously, but to a moderate extent, restabilising the balance between the two processes in the same way as that observed in women before the menopause. This dual action mechanism also has positive effects on bone resistance[10,11,26].

The preclinical development of strontium ranelate included numerous *in vitro* and *in vivo* studies, with experimental models[5,6,27,28]. The results have been consistent and reproducible and, very importantly, the concentration of strontium ranelate used in most of the experimental studies has been within similar ranges as those used in patients.

In normal female rats, strontium ranelate increases bone formation and reduces bone resorption, resulting in an increase in bone mass at the same time as conserving of bone mineralisation[27]. In addition, in both normal male and female rats, treated with strontium over prolonged periods, an increase in the parameters of bone formation and a decrease in the parameters of bone resorption is observed[28].

In ovaryectomised rats treatment with strontium reduces the number of osteoclasts and the osteoclastic surface, whilst increasing the osteoblastic surface and the rate of bone formation with a magnitude of response similar to that obtained by administering oestrogens. This effect of strontium succeeds in preventing the loss of bone mass in both femur and vertebrae[4]. Also, in immobilisation models, when bone resorption is high and formation low, strontium ranelate has been successful in correcting both effects and in conserving bone mass[29].

In spleen cells and in murine primary osteoblasts and osteoclasts derived from cranial vault, strontium ranelate has been capable of stimulating

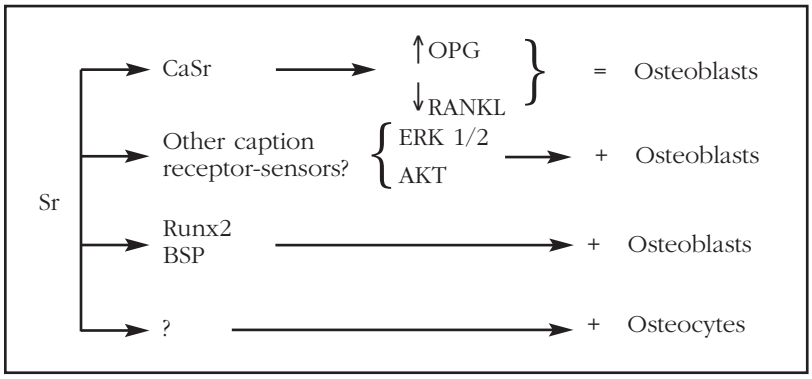
the formation of osteoblasts and inhibiting osteoclast formation, independently of the degree of proliferation and differentiation in which the cells are found[30].

Specific effects of strontium on osteobastic proliferation and osteocytes

In vitro, strontium ranelate has been shown to exert a positive effect on the replication of osteoprogenitor cells and preosteoblasts at the same time as it increases the syntheses of collagen and non-collagen proteins in cells from the cranial vault and in mature osteoblasts in rats[31]. In addition, strontium ranelate stimulates the differentiation of osteoblastic precursors or mature osteoblasts capable of intervening in bone mineralisation. Strontium ranelate has also been capable of increasing the expression of critical genes in osteoblastic differentiation, such as Runx 2 and BSP (bone sialoprotein)[32]. On the other hand, it has not shown any effect on the gene for osteocalcine, the protein implicated in the regulation of the osteoid matrix. The effects of strontium ranelate are not equal in all the cell lines studied, its impact on gene expression varies according to the cell type, as has been demonstrated with preosteoblasts U-33 or in mature osteoblasts OB-6. In general, strontium ranelate has always been more efficacious at the level both of the cellular response and of mineralisation (measured by Von-Kossa), in less differentiated cells. Therefore, one of its important properties appears to be its capacity to stimulate osteoblastic differentiation. In summary, the association and sum total of the effects of strontium ranelate on preosteoblasts and osetoblasts, and their beneficial consequences on mineralisation, explain in great measure the positive action of the drug on bone formation.

At the present time there is a growing interest in the role which the osteocytes play in the health of bone, and their potential as therapeutic targets[33]. The osteocytes are not inactive residual cells, resulting from active osteoblasts trapped in newly-formed bone, but play an important role in structural remodelling. They are responsible for the initiation of bone repair in response to micro cracks[34], and for the formation of new bone in response to an increase in load[35]. The reduced density of osteocytes has been associated with osteoporotic fractures[36], and it has been speculated that if the osteocytes have a mechanico-sensory function, their decrease could imply a lower capacity to detect micro-lesions in the bone matrix, and as a consequence result in a higher accumulation of micro-lesions and material fatigue with age[37]. Strontium ranelate has shown itself capable of favouring the differentiation of human osteoblasts to osteocytes. In cultures, in conditions of mineralisation, treatment with strontium ranelate increases, dose and time dependently, osteoblastic replication, inducing a phenotype similar to the osteocyte and increasing the expression of alkaline phosphatase, of STRO-1, of ARNm of the matrix protein of dentin and of sclerostin, markers which support the existence of a phenotypic change to osteocyte[25]. Figure 2.

Figure 2. Possible regulation pathways of strontium ranelate on bone cells. CaSR: receptor sensor of calcium, OPG: osteoprogerine, ERK: kinase regulators of extracellular signal, Runx2: transcription factor of the Runx family associated with osteoblast differentiation, BSP: bone sialoprotein



Specific effects of strontium on osteoclasts and bone resorption

The positive effects of strontium ranelate on bone metabolism does not only depend on its effect as a stimulator of bone formation, but also on its capacity to reduce bone resorption.

Given the known effect of oestrogen deficiency on the increase in bone resorption and as a consequence, in the loss of a neutral balance between bone formation and resorption, oestrogen deprivation in rats has been the model most commonly used to study the effects of anti-osteoporotic drugs. Strontium ranelate has shown in histomorphometric studies to reduce bone resorption (number of osteoclasts and osteclastic surface) with final results similar to those observed in rats in which ovaryectomies have not been carried out[4].

The inhibition of bone resorption obtained with strontium ranelate could be explained through the inhibition of both the differentiation of the osteoclasts and their capacity for resorption. In rat osteoclast cultures strontium inhibits, in a dose-dependent way, in previously stimulated osteoclasts, the expression of carbonic anhydrase II and the receptor for vitronectin. This resorption inhibitor effect increases when the incubation is prolonged[38].

As has already been commented on, there are data which indicate that strontium ranelate could also have the effect of stimulating the production of OPG, a known inhibitor of osteoclastogenesis[39]. Primary cultures of adult human osteoblasts trea-

ted with strontium ranelate under conditions of mineralisation showed a time dependent increase in the expression of ARNm of OPG. The effect of strontium ranleate on the expression of RANKL does not appear to be uniform and is usually less that the changes observed in OPG, suggesting that strontium ranelate could have an inhibitory effect on osteoclastic differentiation fundamentally through its action on the osteoblasts[25].

Summary

It is 50 years since it was suggested for the first time that strontium could have a positive effect on bone metabolism, improving the incorporation of calcium in the bone[1,2]. However, it was the start of the 90s, with the initiation of studies with strontium ranelate, when the real knowledge of its biological and clinical effects began.

The efficacy of strontium ranelate in the treatment of postmenopausal osteoporosis has been widely proven: for vertebral and non-vertebral fractures, in all age ranges and in the presence of all risk factors for osteoporosis[12,13,40-43]. The result of its administration is an increase in bone formation and a reduction in bone resorption, both moderate, in an almost physiological range, equal to that of calcium. The effect on remodelled bone results in increases in bone mass, an increase in bone resistance and, as a final result, a reduction in the risk of fractures.

The final, close up action mechanism seems clearly to involve CaSR (in its effect as a modulator of osteclastogenesis) and other cation sensors (which are to be found in the different maturation of osteoblasts) which seem to be crucial in the molecular signalling pathways of this drug. This will bring a higher capacity for bone synthesis and mineralisation, with a positive balance in each remodelling cycle, with the end result of an improvement in bone resistance.

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Bone quality and strontium ranelate

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Introduction

The current definition of osteoporosis, which considers the disease to be a systemic alteration characterised by low bone resistance[1], indicates also that this resistance basically depends on the integration of two variables: the quantity and quality of the bone. Whilst the quantity is directly related to the mineral density of the bone tissue, the quality depends on variables such as the chemical composition of the organic and inorganic materials which make up its matrix (material properties) and the resulting spatial structure of these materials (structural properties), all of which factors depend to a greater or lesser degree on bone remodelling[2].

Starting from this definition, the ideal therapeutic profile for an anti-osteoporotic drug would be one which on the one hand is shown to increase bone resistance (increasing the BMD and correcting osteoporotic material and structural alterations) and on the other hand, would reduce the incidence of fractures related to fragility of this kind in the axial and peripheral skeleton, be they the first or successive[3,4].

These days there is a series of medications which, by means of different action mechanisms and effects on bone remodelling, are capable of mitigating and/or repairing the physiopathological changes which osteoporosis induces in the determinants of bone resistance.

Among these, and depending on the mechanism or type of action which they exert on remodelling, the determinants of resistance and their effector cells, are found the anticatabolics or antiresorptives and the anabolics or bone formers. Whilst the first [oestrogens, modulators of the oestrogen receptors (SERMs), calcitonin and biphosphonates] are characterized as being capable of reducing accelerated bone remodelling by reducing the number of newly activated basic multicellular units (BMU) and the level of their osteoclastic activity, the second type (PTH 1-34 and PTH 1-84) increase bone remodelling by increasing the number of newly activated BMUs and the level of their osteoblastic activity[5].

However, nowadays, in addition to these large groups of anti-osteoporotic drugs, a third group of medicines should be considered with a mixed anticatabolic-anabolic action mechanism, which in some way combine the effects of antiresorptive drugs with those which form bone.

Strontium ranelate (SR), an oral medicine active against osteoporosis, acts with this combined effect on bone metabolism, on the one hand diminishing resorption, while on the other, increasing bone formation, for which reason it is considered to be a dual action bone agent[6,7].

Action mechanism

One of the most significant characteristics recently discovered concerning the action mechanism of SR seems to indicate that this medicine stimulates the receptor sensitive to calcium (CaSR) expressed in the osteoblasts, thus inducing in them the production of inositol 1,4,5-triphosphate and the activation of the mitogenic protein-kinase signalling pathway, a situation which promotes cellular proliferation[8,9]. Experiments carried out with rats with a genetic absence of CaRS, have also been able to demonstrate the involvement of different CaRS receptors in the stimulatory effect of SR on the replication of the pre-osteoblasts[10].

However, in addition to this action, recent data indicates that SR can also activate osteoprotegerin (OPG), a cytokine which impedes the conversion of macrophages into osteoclasts. This activation of OPG reduces the expression of the ligand bound to the receptor activator of nuclear kappa B factor

(RANK-L), the trans-membrane receptor implicated in the differentiation and maturation of the osteoclasts, so suggesting that SR can reduce bone resorption by modulating the RANK/RANK-L/OPG system, essential for osteoclastogenesis[11].

Even more recently, through the cultivation of specific cell lines, the role that SR plays in the differentiation of the osteoblasts and osteoclasts has become clearer. For example, Bonnelye and collaborators have shown that SR stimulates the differentiation of the osteoblasts and the formation of bone nodules already from the 5th day of culture, whilst in the control cultures this does not happen until at least 22 days have passed. At the same time the authors show that in cultures of osteoclasts SR achieves a diminution in cellular differentiation in a dose-depended way, resulting, with this drug, in a lower number of cells than in the controls at 8 days of cultivation. In addition to this diminution, its resorptive action on the osteoid matrix also appears to reduce in a dose-dependent way[12].

All these characteristics of the action mechanism of SR, mediated therefore through a series of effects on the osteoblasts (stimulation of the differentiation of the pro-osteoblasts, increase in the proliferation of osteoblasts, increase in osteoblastic activity and increase in the synthesis of the bone matrix) and on the osteoclasts (inhibition of cellular differentiation, reduction in osteoclastic resporptive activity and increase in osteoclast apoptosis)[13] rebalancing bone turnover in favour of bone formation, a situation which results analytically in statistically significant increases in the markers for bone formation (bone alkaline phosphatase) and decreases, also significant, in markers for resorption (C-telopeptide)[6], while quantitatively this is characterised by increases in bone mineral density (BMD) and qualitatively by an improvement in the structural and material properties of bone[14].

Effects of SR on bone quantity

The effects of SR on the quantity of bone, have been testified to in different preclinical and clinical studies.

In experimental animals (female rats), and in a dose dependent way (225, 450 and 900 mg/kg/day), treatment over 2 years with SR increased significantly, with respect to the controls ($p<0.05$), BMD in the lumbar spinal column and femoral neck[9].

In clinical trials in humans, SR has also demonstrated a significant increase in BMD, both in the lumbar spinal column and in the femoral neck, statistically significant increases even after adjusting the mineral density due to the content and molecular weight of strontium. This adjustment was considered necessary since, due to the homogeneous distribution of this element in bone and its greater absorption of X rays, the values of BMD obtained by means of dual photonic densitometry become magnified by at least 50%[15].

In the SOTI (Spinal Osteoporosis Therapeutic International) study, a clinical trial, phase III, in which 1,649 postmenopausal women over 50 years of age with osteoporosis (BMD of lumbar spinal column ≤ 0.84 g/cm^2) and at least one vertebral fracture, SR at a dose of 2 g/day over 3 years, participated, there was a significant increase ($p<0.001$ in comparison with the placebo) in the non-adjusted BMD in the lumbar spinal column (DBMD: 14.4%), in the femoral neck (DBMD: 8.3%) and in the whole hip (DBMD: 9.8%)[16].

The TROPOS (Treatment of Peripheral Osteoporosis) study, a clinical trial in which the anti-non-vertebral fracture effect of the administration of 2 g/day of SR in osteoporotic women (BMD <-2.5 DE) older than 73 years, or between 70 and 74 years old with an additional risk factor was evaluated, found at three years of treatment an increase in non-adjusted BMD with respect to the placebo both in the spinal column (DBMD: 14.7%) and in the total hip (DBMD: 8.2%) (adjusted DBMD in LV: 4.1%, adjusted DBMD in FN: 4.9%).

A prolongation of the same study has shown that at 5 years of treatment SR maintains to a statistically significant extent its positive effect on BMD both in the femoral neck (DBMD: 1.8%) and in the total hip (DBMD: 2%)[17].

Effects of SR on bone quality

SR has shown equally, in different animal experimentation models and in clinical studies in humans, its capacity to improve all hierarchical levels of bone, the structural characteristics and the material properties, contributing in such a way as to the augment its resistance and, as such, to reducing the risk of fractures[18].

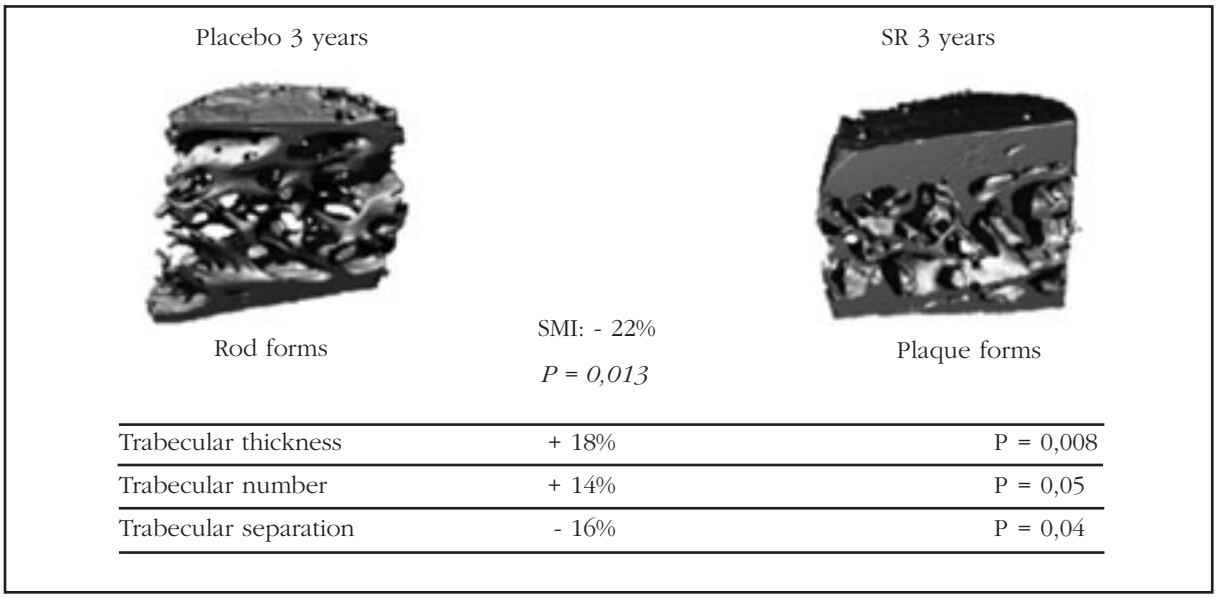
SR and structural properties

At the macrostructural level, SR has shown itself capable of increasing the cortical thickness and the area of transversal section of osteoporotic bone, both in experimental animals[9] and in humans[19].

Thus, recently Briot and collaborators analysed, using Hip Structural or Strength Analysis (HSA), the proximal extremity of the femur of 483 women with postmenopausal osteoporosis (BMD ≤ -2.6 DE) and with an average age of 75.9 years, all of whom were part of the prolongation to 5 years of the TROPOS study. The authors showed that, as opposed to the controls, in patients treated with SR, a significant decrease in the endocortical diameter (ØEC) and significant increases in cortical thickness (CTh), of the area of transversal section (AST), of the moment of inertia of the transversal section (MIST) and of the module of the section (MS) were confirmed, as was a significant diminution in the buckling ratio, all these variables being intrinsically related to an improvement in total bone resistance[19] (Table 1).

At the microstructural level, various animal experimentation studies have demonstrated that SR improves to a significant degree the trabecular microarchitecture. Thus, Ammann and collaborators, in intact rats, have shown through histomorphometry of the proximal tibia, that the adminis-

Figure 1. Microstucture 3D after 3 years of treatment with SR in women with postmenopausal osteoporosis. (Modified by Arlot et al. 2008)



Trabecular thickness	+ 18%	P = 0,008
Trabecular number	+ 14%	P = 0,05
Trabecular separation	- 16%	P = 0,04

tration of SR over 2 years has a favourable effect on the trabecular and cortical microarchitecture, inducing a significant increase in bone volume (BV/TV), and in the number (TbN) and the thickness of the trabeculae (TbTh), without it implying a significant increase in the thickness of the osteoid, which appears to indicate a neutral effect of the molecule on bone mineralisation. Equally, in their study the authors showed that due to these microarchitectural changes the biomechanical resistance of the vertebral bodies and of the femur of the rats increased significantly with respect to the controls[14].

The same group of authors showed in ovaryectomised rats (the model which most simulates postmenopausal osteoporosis) that the administration of SR mitigates the physiopathological changes induced by an accelerated bone remodelling, preserving both the bone mass and the microarchitectural properties of the bone[20].

Very recently, Cattani-Lorentea and collaborators evaluated, by means of computerised microtomography (µ-TC), standard biomechanical trials and techniques of nanoindentation, the capacity of SR, administered in an isolated form or in association with alendronate or PTH, to improve the intrinsic quality of newly-formed bone in intact or ovaryectomised rats. After 8 weeks of treatment, the authors found that while the SR-alendronate association was exclusively capable of preserving the bone microstructure, augmenting maximum bone resistance only comparatively with the group of ovaryectomised rats, the SR-PTH association was able to increase significantly bone volume (BV/TV) and the thickness of the trabeculae (TbTh), increasing significantly the maximum bone resistance in both intact and ovaryectomised rats, at levels also above those obtained with the administration of PTH alone[21].

In humans, different types of studies have also been carried out which ratify the favourable effects of this molecule on the microarchitecture of osteoporotic bone.

Arlot and collaborators, in an analysis carried out by µ-TC of trans-iliac biopsies obtained after three years of treatment with SR, found significant changes in trabecular architecture resulting in the treated group in an increase in cortical thickness (DCTh: 18%) and in the number of trabeculae (DTbN: 14%), as well as significantly lower intertrabecular separation (DTbSp: -18%), or, which is the same, a higher trabecular connectivity[22], changes noted previously with the same technique by other authors in isolated biopsies of patients participating in randomised double blind clinical trials with SR[23].

However, in addition, in Arlot's study the administration of this drug induced a significant change in the proportions between trabeculae with plaque forms and those with rod forms (DSMI: -22%), which indicates clearly a structural and biomechanical improvement in the trabecular tissue (Figure 1). All these data bring the authors to the conclusion that the decline in the rate of vertebral and non-vertebral fracture experienced by those osteoporotic patients treated with SR is intimately related to an improvement in the microstructural characteristics of the bone[22,23].

Very recently, Rizzoli and collaborators, in 88 women with postmenopausal osteoporosis (aged 63.7 ± 7.4 years and T-score in CL and CT: -2.7 ± 0.9 and -2.0 ± 0.8, respectively), compared directly through high resolution peripheral computerised tomography (CTp-AR, XtremCT® Scanco

Medical) the effects on the microarchitecture of the distal extremity of the tibia induced by 2 g per day of SR or 70 mg per week of alendronate. After one year of treatment, and in comparison with baseline values, SR increased significantly the cortical thickness (DCTh: 5.3%; p<0.001), while in those patients treated with alendronate no significant increase was noted (p= 0.045). In addition, in the group treated with SR significant increases in bone volume (DBV/TV: 2.0%; p= 0.002) and trabecular density (DTb Dens: 2.1%; p= 0.002) were found, while in the alendronate group no significant variations were found (p= 0.725 y p= 0.645, respectively)[24] (Table 2).

Table 1. SR and HSA (Modified by Briot et al. 2009)

HSA	SR (n= 251)	Placebo (n= 232)	Value p
CTh	10,27 ± 11,57	-4,02 ± 9,33	< 0,001
ØEC	-1,93 ± 3,19	0,01 ± 3,59	< 0,001
AST	9,05 ± 10,65	-4,06 ± 8,82	< 0,001
MIST	8,60 ± 14,06	-4,81 ± 14,63	< 0,001
MS	11,07 ± 14,03	-4,72 ± 14,77	< 0,001
Rate pandeo	-10,32 ± 10,08	5,93 ± 22,00	< 0,001

Table 2. SR vs Alendronate in women with postmenopausal osteoporosis (Modified by Rizzoli et al. 2009)

	Strontium ranelate		Alendronate		#	
	Average	DE	Average	DE	considered	95% CI
Tb. N (N/mm)	4,2	8,2	4,3	10,7	0,05	(-4,0;4,2)
Tb. Sp (mm)	-3,7	8,3	-3,1	9,8	-0,65	(-4,6;3,3)
C. Th (mm)	5,3	10	1,3	6,0	3,9	(0,1;7,7)
Tb. Th	-1,6	8,6	-2,8	8,3	1,2	(-2,6;5,0)
BV/TV	2,0	5,3	0,6	3,6	1,7	(0,0;3,3)
Tb. Dens	2,1	5,2	0,6	3,8	1,8	(0,1;3,4)
Cort. Dens	1,1	2,7	0,5	2,0	0,6	(-0,4;1,7)

SR and material properties

From the point of view of the material properties of bone, SR has been shown in different studies, both experimental and clinical, to be capable of preserving the degree of bone mineralisation and the crystaline characteristics of bone.

Farlay and collaborators, through microanalysis of X-ray diffraction and quantitative microradiographs evaluated in cynomolgus monkeys the effect which SR, at doses of 200-1,250 mg/day, had on bone mineralisation and the physical characteristics of the hydroxyapatite crystals, showing that after 52 weeks of treatment with strontium they are deposited in the cortical and trabecular bone in a dose-dependent way, distributed uniformly in all the bone tissue, already in the remodelling or quiescent phase. In the study, both the characteristics of the crystals, and the average degree of bone mineralisation and index of heterogenicity of the distribution of strontium resulted in being similar to those animals in the control group[25].

Very recently, Boivin and collaborators analysed through the same techniques the deposition of strontium, its focus of distribution and the degree of bone mineralisation in biopsies from patients with postmenopausal osteoporosis treated with SR over more than 3 years, all women, pertaining to phase II or III of the clinical trials. In all the biopsies the total strontium contented was also evaluated. In addition, in some of the cases, the general distribution of strontium in the whole sample was analysed, by means of X-ray cartography, to calculate the percentage of bone surface which contained this element. The authors found that, in a dose-dependent way, the strontium was deposited exclusively in bone newly-formed during the period of treatment, so that a greater concentration was found in the new UBM than in the old, even after 3 years of treatment with the drug. In this study the total content of strontium in the bone reached a plateau at 3 years of treatment with the drug, which for the authors showed that the strontium does not substitute for calcium ions, but that it is absorbed in the bone mineral surface. The cartographic analysis of the samples showed that the bone formation activity during the treatment with SR was greater in the trabecular bone than in the cortical, the degree of bone mineralisation remaining homogeneous during the period of treatment. The authors conclude that due to all these characteristics SR is an efficacious and safe drug from the point of view of bone material quality[26].

Effects of SR on bone resistance

In addition to the stated effects of SR on the structural and material properties of bone, the improvement in bone quality which SR can induce in bone resistance has been underlined in different studies and through different types of biomechanical tests.

In animal experimentation models (female rats), treatment over 2 years with SR increased significantly compared to controls ($p<0.05$) total bone resistance measured both with techniques of biomechanical resistance to vertebral compression (DRO: 20%) and in flexion tests at three points of the femoral diaphysis (DRO: 14%), this increase in the final force of fracture is directly ($r= 0.739$) and significantly ($p<0.0001$) related to the increases achieved in DMO[9,14].

Recently Ammann and collaborators, using nanoindentation techniques, showed a significant increase in the elasticity, the toughness, and the capacity to dissipate energy of impact in the trabecular and cortical bony nodes of the vertebrae of rats treated for 104 weeks with different daily doses of SR. For the authors, these results showed for the first time the direct action of SR on the biomechanical quality of bone tissue. This increase in bone resistance induced by SR was responsible finally for the reduction in the risk of fracture in women with menopausal osteoporosis treated with SR[27].

Conclusions

SR, a dual action drug capable of dissociating remodelled bone, rebalancing it towards bone formation, acts at the level of each and every one of the determinants of bone resistance, increasing significantly and promptly BMD, improving qualitatively the structure of cortical and trabecular bone, and preserving mineralisation, the size and structure of the mineral crystals, even at high doses. Thus SR, by improving significantly the biomechanical properties of bone, reduces significantly the risk of fractures in women with postmenopausal osteoporosis.

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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 formation[1]. 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/RANKL[2]. Its effectiveness in animals has been widely studied, it having been shown to augment bone mass in osteopenic animals, to prevent bone loss in ovaryectomised rats and to increase bone resistance in normal animals[3-5]. 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 advised[8]. 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, bu 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 earlier[9].

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 normality[10]. 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–hydoxycolecalciferol.

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 -80ºC 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 evaluation[11] 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 perfomed 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 SOTI[12], 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 ± 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 ± 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/cm^2) than at the start of the study (0.734 ± 0.123 g/cm^2, 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 ± 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 years[13] 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 years[14]. 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/cm^2 during the last 3 years, which corresponds to an average increase of 4.4 ± 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 at 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 age[15], as well as there being a reduction in bone mineral density[16]. 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 years[17-19]. 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 day[20]. 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 biphosphonates[21]. 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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Other studies with strontium ranelate: Analysis of efficacy

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Introduction

The efficacy of strontium ranelate (SR) in the reduction of fractures having already been described in another chapter of this monograph, we are going to analyse other important aspects of the studies which support the assessment of its efficacy. These aspects are:

1. Quality of life in the short and long term in treatment with SR.
2. Efficacy of SR in patients over 80 years of age.
3. The relationship of the basleline state of bone turnover to anti-fractural efficacy.
4. Baseline risk factors and anti-fractural efficacy of ST.

Quality of life in the short and long term in treatment with SR

Osteoporosis is characterised by a decrease in bone mass and a deterioration in the microarchitecture of bone tissue, which explains the weakness of the bone and the consequent risk of fractures.

Epidemiological studies have confirmed that postmenopausal osteoporosis is a very extensive and prevalent disease[1]. The morbidity of osteoporosis is due, above all, to fractures of the hip, vertebrae and distal radial extremities. Hip fractures produce acute pain and loss of function and almost always result in hospital admission. Recuperation rates are low and rehabilitation is often incomplete. Many patients end up staying in a centre for the chronic sick. Vertebral fractures can produce acute pain and loss of function but are also associated with serious symptoms. Vertebral fractures often recur, and the consequent incapacity increases with their number. Fractures of the distal radial extremities also produce acute pain and loss of function but recuperation is usually satisfactory.

In addition to the pain and functional changes, the fractures can reduce mobility and social relations and result in emotional problems. All these characteristics shape the quality of life.

Quality of life covers all aspects of life, including health, the environment, economic matters and human rights. Health-related quality of life (HRQL) is a subgroup of quality of life which affects physical, emotional and social well-being.

Clinical trials concerning osteoporosis carried out to date, have been based on variables measured with imaging techniques. However, these measurements do not adequately reflect the degree to which the daily activities of the patient come to be affected and, as a result, are not appropriate for the evaluation of their incapacity and its symptoms[2-5]. The quality of life has, in recent years, become an important variable in clinical trials. To assess the repercussions of a fracture due to osteoporosis on the quality of life and the effects of different treatments for osteoporosis specific questionnaires which relate quality of life to health (HRQL) have been used as the main criteria for the assessment of clinical trials for osteoporosis[6].

Quality of life questionnaires have been classified as generic, specific to a disease, or specific to a study. Generic questionnaires contain general questions on state of health and can be used for different diseases. Some generic questionnaires

regarding HRQL, such as SIP (Sickness Impact Profile), SF-36 or NHP (Nottingham Health Profile), have been used with more frequently to understand the effect of osteoporosis on HRQL[7]. These questionnaires can be applied to any population or disease, which allows a comparison to be made between those suffering different diseases. However, they show serious limitations because they do not explore in detail specific aspects of osteoporosis. For example, in some studies it has been confirmed that certain aspects, such as fear of falling and its consequent fracture, the ability to dress oneself without help, the impossibility of correctly carrying out housework, and desperation before an uncertain future, causes these patients suffering[8].

These matters are not included in generic questionnaires and their omission could result in an incomplete evaluation or bias in the HRQL of patients with osteoporosis.

There are also questionnaires specific to osteoporosis, such as OPTQoL (Osteoporosis Targeted Quality of Life)[9], OPAQ (Osteoporosis Assessment Questionnaire)[10], QUALEFFO (Quality of life questionnaire of the European Foundation for Osteoporosis[11], OQLQ (Osteoporosis Quality of Life Questionnaire)[12] and OFDQ (Osteoporosis Functional Disability Questionnaire)[13]. The QUAlity of Life questionnaire in Osteoporosis (QUALIOST)[14] has been developed as a metric for quality of life specifically for osteoporosis used in conjunction with one of those most widely-used as a generic tool – SF-36. QUALIOST is a questionnaire valid for 23 items which are expressed as a global assessment, and two sub-assessments (physical and emotional).

QUALIOST® and strontium ranelate (SR)

SR is a new anti-osteoporotic preparation studied in two broad phase 3 programmes called the SOTI (Spinal Osteoporosis Therapeutic Intervention) study[15] and the TROPOS (Treatment of Peripheral Osteoporosis) study[16]. In the SOTI study, an international clinical trial, double blind and placebo controlled, 1,649 postmenopausal women with osteoporosis were examined; SR reduced the risk of vertebral fracture. This efficacy in relation to fractures results in clinical benefits, for example a 20% decrease in the rate of reduction in height and a 29% increase in the number of patients without back pain. Quality of life constitutes a secondary variable, assessed through two questionnaires: SF-36 and QUALIOST® at baseline and every 6 months. The main analysis is carried out after a 3 year follow up[17-19]. The change in the general scores revealed an improvement in the HRQL in the group treated with SR and a deterioration in the placebo group (p= 0.03). This improvement in quality of life of the SR group was confirmed by the change in the emotional and physical scores in this group, in comparison with the placebo group (p= 0.04 and p= 0.05 respectively), indicating beneficial effects on emotional and physical functions. The majority of the patients with SR (+31%) were without lumbar pain after three years of the study, compared with the placebo group (p= 0.005). The rates of therapeutic completion surpassed 80% in the phase III studies, which reflects the profile of tolerance, safety, and ease of administration of this medication[20]. There are more long term (4 years) data from the SOTI study in which 1,250 patients (87% of the intention to treat population) were followed[21]. Both SF-36 and QUALIOST questionnaires were analysed. In relation to the SF-36 questionnaire, significant differences were found between baseline values and those after treatment both in the individual dimensions of SF-36 (p= 0.043) and the General Perception of Health dimension (p= 0.012). The global score of QUALIOST was lower (indicating a better quality of life) in the group treated with SR than in the placebo group, and the differences between the baseline and final values were -0.06 in the SR group and 1.92 in the placebo group (p= 0.02). When the emotional and physical dimensions of QUALIOST are considered separately, a statistically significant difference between the baseline changes and those post-treatment is found in the group treated with SR with respect to the placebo group, both in the emotional (p= 0.012), and in the physical variable (p= 0.034).

The proportion of patients free from lumbar pain after four years of treatment was 28% higher in the group treated with SR than in the placebo group, (p= 0.005). In fact 14.6% of the patients who received SR, vs 11.2% of those who received the placebo, were without lumbar pain after 4 years (RR= 1.28; 95% CI [1.08, 1.52]).

Efficacy of strontiun ranelate in older people

Around 25-30% of the population which suffers fractures due to fragility in the community occurs in women over 80 years of age, due to the fact that this population has a high risk of all types of fracture, particularly non-vertebral fractures. In spite of this, there is little evidence that the existing therapies for osteoporosis reduce the risk either of vertebral or non-vertebral fractures in this age group.

A study has been carried out based on a preplanned analysis of the results of two international studies, phase III, randomised, controlled by placebo, double blind – the SOTI (Spinal Osteoporosis Therapeutic Intervention) study[15], and the TROPOS (Treatment Of Peripheral Osteoporosis) study[16] which included 1,488 women, aged between 80 and 100 years, followed for three years[22]. An annual X-ray of the spinal column was carried out in 895 patients Only non-vertebral fractures confirmed radiologically were included. The results of this study showed that at baseline, there were no differences between the group which received the placebo and that which received treatment. In the intention to treat analysis, the risk of vertebral, non-vertebral and clinically symptomatic fractures (vertebral and non-vertebral) was reduced in one year by 59% (p= 0.002), 41% (p= 0.027), and 37% (p= 0.012), respectively. At the end of the third

year, the risk of vertebral, non-vertebral and clinical fractures was reduced by 32% (p= 0.013), 31% (p= 0.011) and 22% (p= 0.040), respectively. The medication was well tolerated and its safety profile was similar to that of young patients. What this shows is that, even in very old people, it is never too late to reduce the risk of fracture.

Relation of the baseline state of bone turnover with anti-fractural efficacy

The intensity of bone turnover is variable among women at risk of osteoporotic fractures. Strontium ranelate is an anti-osteoporotic treatment which increases bone formation and reduces bone resorption. It has been hypothesised that the already demonstrated anti-fractural efficacy of SR could be independent of the baseline levels of bone turnover. To check this hypothesis, the mixed data from the two randomised, double blind trials, SOTI and TROPOS, carried out with SR in women with osteoporosis, have been analysed. The patients were stratified in terciles, in accordance with baseline values of the biochemical markers for bone remodelling: bone alkaline phosphatase (b-ALP, as marker for bone formation, n= 4,995), and blood C-terminal telopeptide (sCTX, as marker for bone resorption, n= 4,891). After three years of treatment with 2 g/day of SR, or placebo, the risk of vertebral fracture and the bone mineral density (BMD) in the lumbar region were assessed[23].

In the placebo group, the relative risk of vertebral fracture increased in relation to the level of the tercile of the markers, it being 32% and 24% for the patients in the higher tercile for b-ALP and CTX respectively. In the SR group, the incidence of vertebral fracture was not significantly different between the different terciles. A significant reduction in vertebral fractures was observed in the three terciles of both markers, with a reduction of relative risk of fracture of 31% to 47% in relation to the placebo group. The reduction of risk did not differ between the different terciles (p= 0.513 for b-ALP, p= 0.290 for sCTX).

We can conclude that the efficacy of SR in reducing vertebral fractures is independent of the baseline values of the markers for bone turnover, supporting the idea that SR offers clinical benefits to osteoporotic women, independent of their metabolic state.

Baseline risk factors and the anti-fractural efficacy of ST

At present there are diverse treatments which have demonstrated their efficacy in the treatment of OP. It is possible that the therapeutic response to these treatments depends on the initial BMD or age of the patients, or that it could be dependent on other factors. SR has demonstrated, in two extensive international studies in postmenopausal women (SOTI and TROPS), its efficacy in the reduction of vertebral and non-vertebral fractures.

An earlier analysis[24] has grouped the data of these two studies (SOTI and TROPOS) (5082 patients, 2,536 treated with SR and 2,546 receiving the placebo), with an average age of 74 years and followed up over 3 years, and in which the influence of different baseline risk factors (age, baseline BMD, prevalent fractures, family history of OP, body mass index (BMI), and tobacco habit) in the efficacy of the treatment were analysed. The intention to treat principle was used, as well as the Cox model in the comparisons and the calculations of relative risk.

We know that SR reduces the risk of vertebral fractures (relative risk (RR = 0.60 [0.53-0.69]). The reduction in risk of vertebral fracture was 37% (p= 0.003) in women aged less than 70 years, 42% in women of between 70 and 80 years and 32% (p= 0.013 in those of at least 80 year of age, without any difference in the three groups. The RR of vertebral fractures was 0.28 (0.07-0.99) in the women with osteopenia, and 0.61 (0.53-0.70) in the case of osteoporosis and the baseline BMD was not a determinant of efficacy. The incidence of vertebral fractures increased in the placebo group in relation to the number of previous fractures, but this was not a determinant of the efficacy of SR. In 2,605 patients, the risk of presenting a first vertebral fracture was reduced in 48% (p<0.001). The risk of suffering a second vertebral fracture decreased in 45% (p<0.001; 1,100 patients). Also, the risk of presenting more than two vertebral fractures was reduced in 33% (p<0.001; 1,365). Family antecedence of OP, baseline BMI, and smoking were not determinants of the efficacy of SR, from which we can conclude that the efficacy of SR in reducing vertebral fractures in postmenopausal women is independent of baseline risk factors for OP.

Conclusions

Patients treated with SR have a reduced number of vertebral and non-vertebral fractures and this effect is independent of age, continuing in women of over 80 years of age, independent of BMD previous to the treatment, and independent of baseline risk factors. In addition, it has been shown that, in treated patients, SR improves the quality of life in an objective way.

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Safety and results for strontium ranelate

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Introduction

Strontium ranelate is a therapeutic agent introduced in recent years for the treatment of osteoporosis with dual action on bone metabolism. The conditions which need to be satisfied by any drug for its use in the treatment of osteoporosis include safety and efficacy in the prevention of fractures. The evidence in relation to strontium ranelate come principally from the two multi-centric, clinical reference trials in phase 3, the SOTI (Spinal Osteoporosis Therapeutic Intervention)[1] study and the TROPOS (Treatment of Peripheral Osteoporosis) study[2]. The first was designed to access the preventative effect on vertebral fractures, whilst the second had as an objective the evaluation of non-vertebral fractures. These are the anti-osteoporotic drug trials which give results over the longest term, 4 years for the first and 5 for the second[3]. Additional data comes from other older trials in phase 2, the STRATOS (Strontium Ranelate for Treatment of Osteoporosis) trial[4] and the PREVOS (Prevention of Osteoporosis) trial[5] which had the objective of assessing the effect on bone mass and biochemical markers for bone turnover in patients with established vertebral fractures in the first, and in the second, in women in the first years of menopause.

Safety of strontium ranelate

The SOTI and TROPOS studies included 3,352 women who received treatment with strontium ranelate, of whom 2,315 followed the treatment for at least 36 months. The adverse effects detected in these patients were no different from those observed in the group treated with placebos, and in general, were moderate and transitory. The most frequent were related to the digestive system: nausea (6.6% and 4.3% respectively) and diarrhoea (6.5% and 4.6 % respectively). Both adverse effects diminished after the first 3 months of treatment. In terms of the biochemistry, a small reduction in the concentration of blood calcium and an increase in blood phosphate was observed, neither clinically significant[1,2]. Table 1 includes the adverse effects most frequently detected in these two trials. In patients older than 80 years the most frequent adverse effect was headache, 3.3% in the group with ranelate as opposed to 1.7% in the control group with a confidence interval of 95%: 0.01-3.3 followed by the adverse effects of the digestive system[6].

One of the controversial problems is venous thrombosis. Although taken separately, in each of the studies no increase in thromboembolic disease was found, in a subsequent analysis of aggregated data, and increase was found. A meta-analysis of the two reference studies in phase 3 found that after 5 years of treatment with strontium ranelate the annual incidence of cases of thromboembolic disease was 0.9%, as opposed to 0.6% in the placebo group, with a relative risk (RR) or 1.4, CI 95%; 1.0-2.0[7]. The cause of this effect is unknown and does not have a reasonable scientific explanation. As a consequence, the technical information for the product includes the recommendation that precautions should be taken with patients with increased risk of thromboembolic disease, especially in cases with previous history of venous thromboembolism. Recently, this effect has been investigated using the classic general medicine

research database of the United Kingdom (General Practice Research Database), which includes 1,754 patients being treated with strontium ranelate, and the authors found that there had been a significant increase in episodes of deep vein thrombosis[8]. In another study with the same GPRD database, an increase in risk of suffering deep vein thrombosis was observed in women with osteoporosis as opposed to non-osteoporotic women. The annual incidence was 5.6 in the first group of women as opposed to 3.2 per 1,000 in the second (RR 1.75; 95% CI 1.09-1.84). In the osteoporotic women there were no differences between those treated with alendronate or ranelate, and those not treated[9].

Notable was the description of the few cases of DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) in patients in treatment with strontium ranelate. This is a reaction of hypersensitivity which is very infrequent and which appears after 3-6 weeks of treatment, consisting of fever, exanthema, eosinophilia and systemic affectation such as adenopathy, hepatitis, nephritis, etc[10,11]. The EMEA has assessed the data and recommends that patients should be informed that they should cease treatment when exanthema appears and seek medical attention. Exanthema is an adverse reaction described both in treated patients and in those in the placebo group, and it should be taken into account that not all exanthemas have sufficient manifestations, or are sufficiently serious to be considered as symptoms of DRESS.

Although there are no data of patients with renal insufficiency, it is thought that strontium ranelate can increase its concentration in cases of reduced renal function and the consequent decrease in its elimination by the kidney. In this situation the strontium may accumulate to excess when the clearance of creatinin is lower than 30 mL/min. Its effect is not known during pregnancy, lactation or in children, due to lack of information.

Results of using strontium ranelate

There is much data related to the treatment of osteoporosis with strontium ranelate. That the treatment is considered efficacious is due to its capacity to reduce the frequency of osteoporotic fractures. The known data are related to vertebral and non-vertebral factures. In addition, there are data concerning surrogates of fractures, such as BMD and histomorphometry. We will present a summary of these results, given that these data are commented on in greater detail in another chapter of this monograph.

Prevention of vertebral fractures

The first great reference study, called, in its abbreviated form, SOTI, included 1,649 women over 50 years of age, whose average age was 69 years, having been postmenopausal for a period of at least 5 years. They were randomly selected into two groups, one treated with 2 mg of strontium ranelate and the other with a placebo. In addition both groups received calcium and vitamin D supplements to guarantee the provision of the recommended daily dose. All the women had at least one earlier vertebral fracture due to their fragility, and a lumbar bone mineral density (BMD) below 0.840 g per cm^2 measured by a Hologic densitometer, equivalent to a T-score of -1.9. The assessment of the vertebral fractures was made through Genant's quantitative morphometric method in lateral X-rays of the lumbar and thoracic spinal column, taken at their inclusion in the trial and annually during the follow up.

A decrease in the frequency of radiographical vertebral fractures was observed of 49% (6.4% as opposed to 12.2% RR 0.51; CI 95%: 0.36-0.74) in the group treated with strontium ranelate at the end of the first year of follow up. In the same period, the risk of symptomatic vertebral fractures was reduced by 52% (3.1% as opposed to 6.4%; RR= 0.48; CI 95%: 0.29-0.80). At the end of the three years of treatment the results were similar. The radiological vertebral fractures were reduced by 41% (20.9% as opposed to 32.8%; RR= 0.59; CI 95%; 0.48-0.73) and the symptomatic fractures by 38% (11.3% as opposed to 17.4%; RR= 0.62; CI 95%: 0.47-0.83). At the end of the fourth year the reduction in risk of radiological fracture was 33% (RR= 0.67; CI 95%: 0.55-0.81; $p<0.001$)[12].

The TROPOS study was designed to assess the efficacy of strontium ranelate in the prevention of non-vertebral fractures, but results were also obtained for vertebral fractures. In 71% of the 5091 women included in this study, x-rays of the spinal column were taken and it was observed that 66.4% of them had earlier fractures, which was a criterion for inclusion in the SOTI study. After 3 years of treatment, a reduction in risk of vertebral fractures of 39% (RR= 0.61; CI 95%: 0.51-0.73) was observed in those women who had been incorporated in the group having treatment with strontium ranelate, there already having been observed after the first year, a reduction of 45% in the risk of fracture (RR= 0.55; CI 95%:0.39-0.77; $p<0.001$). This reduction affected both those women with an earlier vertebral fracture and those who did not have previous fractures.

A joint analysis was carried out of the results of the third year of both the SOTI and TROPOS studies. 5082 women were evaluated, in whom the risk of vertebral fracture was reduced to 40% (RR= 0.60; CI 95%: 0.65-0.87). The anti-fractural result observed during the first three years was maintained during the extension phase up to the fifth year. In these two last years, a tendency to a reduction in efficacy was observed. However, this fact was not interpreted as a reduction in the anti-fractural effect of the drug, but to the fact of the patients remaining in the study brings with it a loss of randomness in distribution, since those patients remaining in the placebo group are those who have a lower risk of fracture[3].

One of the characteristics of the population included in the SOTI and TROPOS studies is the large group of women over 80 years of age who made up over 20% of the total. In a sub-analysis

of the results of this group a reduction in risk of fracture of 32% was observed. But the anti-fractural effect is not very different in the remaining age groups, since in the youngest (less than 70 years of age) the reduction was 37%, and 42% in those women between the ages of 70 and 80[13]. The number of patients it is necessary to treat (NNT) to avoid a vertebral fracture at three years is 13[14].

With the objective of seeing if the effect was independent of the risk of fracture in the patients, a sub-analysis was carried out, analysing the efficacy according to the number of earlier vertebral fractures. The main risk to these women was verified in the placebo group, since the incidence of new vertebral fractures increased according to the number of previous fractures, being 40.3% higher in the group with two or more fractures. In the group of patients treated there was a reduction in the risk of new fractures independent of the number of fractures they had before the start of treatment, 25.2% in patients with only one fracture and 40.3% in those who had two or more fractures. The risk of experiencing a first fracture, a second, or more than two fractures was reduced by 48%, 45% and 33% respectively[13].

The drug was also efficacious in women with osteopenia, both in those who had a previous fracture, of 41% (RR 0.59; CI 95%: 0.43-0.82), as well as those who did not, of 38% (RR 0.62; CI 95%: 0.44-0.88)[6].

Prevention of non-vertebral fracture

The efficacy of treatment with strontium ranelate in the prevention of non-vertebral fractures was investigated in the TROPOS trial, which included, as we have already stated, 5091 women with an average age of 77 years. The criteria for inclusion were to have a BMD in the femoral neck lower than 0.600 g/cm^2, which is the equivalent to a T-score of -2.2, and to be older than 74 years or between 70 and 74 years old with at least one of the following risk factors: previous history of fracture, or maternal history of fracture. The patients were randomly chosen to receive 2 g of strontium ranelate or placebo, and received calcium and vitamin D supplements.

All non-vertebral fractures were recorded, with the exception of those not related to osteoporosis: coccyx, cranium, jaw, face, phalangeal and ankle. In the 3 year follow up period, there was a reduction of 16% in all non-vertebral fractures (11.2% as opposed to 12.9%; RR= 0.84; IC 95%: 0.702-0.995: NNT to avoid one fracture was 49). The principal non-vertebral fractures considered were of the hip, wrist, pelvis, sacrum, ribs, sternum, clavicle and humerus. There was a reduction of 19% (8.7% as opposed to 10.4%; RR= 0.81; IC 95%: 0.66-0.98; NNT= 59). The global risk of fracture of the hip was reduced by 15%, but the difference was not significant since the study was not designed with sufficient power to investigate this anti-fractural effect. However, in a sub-group of high risk patients, aged over 74 years and BMD with a T-score lower than -2.3, there was a reduction of 36% in hip fractures (4.3% as opposed to 6.4%; RR= 0.64; IC 95%:0.412-0.997; NNT= 48).

Table 1. Adverse effects described in the clinical trials SOTI and TROPOS

Adverse effect	Strontium ranelate	Placebo
	(%)	(%)
Nausea	6.6	4.3
Diarrhoea	6.5	4.6
Loose faeces	1.1	0.2
Headache	3.0	2.4
Dermatitis	2.1	1.6
Eczema	1.5	1.2
Allergic dermatitis	1.0	0.5

In the period of extension to 5 years, the TROPOS study the efficacy was maintained, with a reduction of 15% in the reduction of non-vertebral fractures (RR= 0.85; IC 95%: 0.73-0.99). The SOTI study was not powerful enough to assess the efficacy in relation to non-vertebral fractures. However, the fractures in 234 women after 3 years were recorded (with an incidence of 15.5% as opposed to 16.8%; RR= 0.90; IC95%: 0.69-1.17). In the study of the aggregated data from the two studies – SOTI and TROPOS – the global reduction in non-vertebral fractures was 15% (11.6% as opposed to 13.1%; RR= 0.85; IC 95%: 0.74-0.99)[15]. In the SOTI and TROPOS cohort of over 80 years, the reduction in the risk of non-vertebral fracture was 1% (14.2% as opposed to 19.7%; RR= 0.69; IC 95%: 0.52-0.92)[6].

As with other chronic diseases, the effect of treatment is related to compliance. In those patient with good compliance with the treatment the risk of fracture reduces to 38% in relation to those patients who are non-compliant[16]. Compliance in those patients in the TROPOS study was very high at the end of 5 years of follow up, higher than 80%.

Bone mineral density and makers for bone remodelling

Treatment with strontium ranelate increases BMD considerably. After 3 years of treatment the SOTI study noted an increase of 14.4% in the lumbar spinal column and 9.8% in total hip with respect to that observed in the placebo group[1]. The period of extension of the TROPOS study showed an increased BMD in the lumbar spinal column of 4.9%, 1.8% in the femoral neck, and 2% in the total hip[3].

However, this major increase in BMD measured by double energy X-ray absorptiometry

(DXA) requires an interpretation due to the physical characteristics of strontium. Its high atomic number attenuates the X-rays more than calcium, which produces an overestimation of the values of BMD. Blake has studied this phenomenon quantitatively and calculates that the artificial component of the density could approximate to 50%[17].

The SOTI study studied the modifications produces in the markers for bone formation and resorption. These biochemical markers are an indirect measure of bone metabolism. They are useful as indicators of the therapeutic response and are an indirect measure of compliance. The SOTI study observed that the bone iso-enzyme alkaline phosphatase increased by 8.1% more in patients treated than in those in the placebo group from the first three months of treatment[1]. In the case of the markers for resorption, the C-terminal with bridges fragment (CTX) diminished 12.2% in the first few months. This behaviour is different from the increase which the anabolics produce and the significant decrease produced by the most commonly used anti-resorptives. The results observed in the STRATOS and PREVOS studies had a similar profile[4,5]. These modifications are compatible with the action mechanism proposed or strontium ranelate which is that it stimulates the formation and reduces the resorption of bone.

Histology

There are biopsy data from the iliac crest which come from the STRATOS, SOTI and TROPOS studies, obtained over 5 years of treatment[1,3,4]. The positive effect on bone formation is confirmed by the finding of an increase in the osteoblastic surface area and in the rate of mineral apposition in the trabecular and cortical bone. No changes were seen in the frequency of activation. The effect on the parameters of bone resorption indicate its reduction, although not statistically significant. Neither were any changes in primary bone mineralisation found. Recently, the results of a 3D using micro-TAC study were published, observing that treatment with strontium ranelate improves the indices which contribute to an increase in the biomechanical competence of bone and which explain the anti-fractural effect of strontium ranelate[18].

Conclusions

The available evidence indicates that strontium ranelate is a safe drug, with a preventative effect on vertebral and non-vertebral fractures. This effect is maintained for at least 5 years and is independent of age, including in women over 80 years of age. Prevention is seen in women with osteopenia, with non-established osteoporosis and with fractures. The biochemical markers for bone turnover and data from biopsies confirm for us its dual action mechanism, moderately stimulating bone formation and inhibiting resorption.

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