Strontium ranelate normalizes bone mineral density in osteopenic patients

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ABSTRACT. ***Aims:*** *To assess the capacity of strontium ranelate to restore normal bone mineral density (WHO definition: T-score ≥-1) in post-menopausal osteopenic women (T-score between -1 and -2.5) at baseline.* ***Methods:*** *Post-hoc analysis from SOTI and TROPOS studies of 1428 patients randomly assigned to receive either 2 g of strontium ranelate a day or placebo for three years. Bone mineral density was measured at baseline and each year for three years. Results were analyzed on an intention-to-treat basis.* ***Results:*** *At lumbar spine, after one, two and three years of treatment with strontium ranelate, 26.4, 42.1 and 58.2% respectively of osteopenic patients normalized their bone mineral density, compared with 6.6, 8.9 and 11.9% in the placebo group (all p<0.001). At total hip, the percentage of patients normalizing their bone mineral density was 5.4, 10.0 and 19.6% in the strontium ranelate group and 1.8, 1.4 and 1.6% in the placebo one (all p<0.001).* ***Conclusion:*** *Strontium ranelate is able to normalize bone mineral density in a significant proportion of osteopenic patients after one, two and three years of treatment. The clinical relevance of these results should be confirmed by direct demonstration of the anti-fracture efficacy of strontium ranelate in osteopenic patients.*
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INTRODUCTION

Osteoporosis is "a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (1). The operational definition of osteoporosis, proposed by the World Health Organisation, is based on a value of bone mineral density (BMD) 2.5 standard deviations (SD) or more below the young adult mean value (T-score). Osteopenia is defined by a BMD between 1 and 2.5 SD below the young adult mean value (2). In the USA, 16.8 million (54%) post-menopausal white women are osteopenic, 9.4 million (30%) are osteoporotic (3), and the prevalence of osteoporosis is continuing to escalate with the increasingly elderly population (4). Recent epidemiological studies have shown that a substantial number of fractures occurs in patients with osteopenia (5, 6) and many researchers and clinicians believe that osteopenia does warrant treatment and that it is essential to begin therapy as soon as diagnosis is made (7).

In post-menopausal women, osteoporosis results from both a reduction in bone formation and an increase in bone resorption at the cellular level (8). Whereas its molecular mechanisms of action are not totally elucidated, strontium ranelate, a new drug for post-menopausal osteoporosis, has been suggested, in preclinical models, concomitantly to reduce resorption and increase formation. In two large, international, randomized, double-blind, placebo-controlled phase III studies, SOTI (Spinal Osteoporosis Therapeutic Intervention) (9) and TROPOS (TReatment Of Peripheral OSteoporosis) (8), a 3-year treatment with 2 g per day of strontium ranelate orally was shown to reduce the risk of vertebral and non-vertebral fractures by 41% over 3 years (9) and 16% (8) respectively, with a 36% reduction of the risk of hip fracture in the subgroup of high-risk women (8).

Significant increases in lumbar spine and femoral neck BMD have been consistently reported in all populations exposed to strontium ranelate (at 3 years +12.7% and 9.8% at lumbar spine and +7.2% and 8.2% at femoral neck in the SOTI and TROPOS studies, respectively) (8-10).

Based on some of the SOTI and TROPOS population samples, the objective of this study was to assess the capacity of strontium ranelate to restore normal BMD (T-score ≥-1) in patients who were osteopenic (T-scores between -1 and -2.5) at baseline.

Key words: Bone mineral density, osteopenia, strontium ranelate.

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SUBJECTS AND METHODS

Study population

Seventy-five centers in eleven European countries and Australia recruited ambulatory post-menopausal women with osteoporosis in both the SOTI and TROPOS studies. The protocols and methods of these two studies are fully developed in their respective original reports (8, 9).

From the osteoporotic subjects included in the SOTI and TROPOS studies, for the current *post-hoc* analysis, we selected 1428 women with osteopenia at the non-osteoporotic site at baseline (i.e., patients having T-scores between -2.5 and -1 SD at lumbar spine or total hip) and without any prevalent vertebral or peripheral fracture.

Treatment protocol and follow-up

Patients were randomly assigned to receive either a day of strontium ranelate 2 g (2 sachets daily of drug powder mixed with water), or placebo for 5 years. Calcium and vitamin D supplementation was prescribed throughout the studies, the dosage being determined during the run-in period.

Bone densitometry

BMD was measured by dual-energy X-ray absorptiometry at baseline and at 6-month intervals, at the lumbar spine (region of interest L2-L4) and proximal femur (Hologic Inc., Bedford, MS). All scans were analyzed centrally, and hip and spine BMD T-scores were calculated according to the centralized European normative data (D.O. Slosman, Geneva, Switzerland) references available during phase II and at the beginning of phase III development programs of strontium ranelate (homogeneity of data). A quality control program, including serial measurements of a spine phantom and daily quality controls, was conducted throughout the studies (11).

Statistical analysis

Results were analyzed on an intention-to-treat (ITT) basis, and analysis included patients who underwent randomization, who had taken at least one packet of treatment, and for whom at least one measure of the BMD was obtained after baseline.

The Mann-Whitney U-test was used to compare the baseline characteristics of the placebo and strontium ranelate groups, among patients presenting osteopenia at the lumbar spine or total hip. Differences in the proportion of osteopenic patients, whose BMD returned to normal values, were assessed by a χ^2 test. Relative risk was calculated as the ratio between probabilities of normalizing BMD in patients treated with strontium ranelate and those treated with placebo.

Patients were considered normal if their T-score was ≥-1, and osteopenic if they had a T-score between -1 and -2.5 (2).

RESULTS

From the whole osteoporotic population included in the SOTI and TROPOS trials, among patients without any prevalent vertebral or peripheral fracture, spinal and total hip BMD values between -1 and -2.5 were identified in 562 and 866 patients respectively. No differences in baseline characteristics were observed between patients randomized to the strontium ranelate or placebo groups (Table 1).

At all time-points, the proportion of previously osteopenic patients who normalized their BMD was significantly higher in the strontium group than in the placebo one (all $p<0.001$) (Table 2).

Compared with patients receiving placebo, after three years of treatment with strontium ranelate, the relative risk of patients of restoring their BMD to normality (T-score >-1) was 4.87 (95% CI: 3.13-7.57) and 12.38 (95% CI: 5.04-30.45) for lumbar spine and total hip respectively (Figure 1).

DISCUSSION

The present study demonstrates the ability of strontium ranelate to normalize BMD in osteopenic patients after one, two and three years. Treated with 2 g of strontium ranelate a day, 26.4% of the patients, who were osteopenic at the lumbar spine, had normal values after one

Table 1 - *Baseline characteristics.*

	Lumbar spine						Total hip					
	Placebo			Strontium ranelate			Placebo			Strontium ranelate		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Age (years)	278	75.92	4.99	284	76.05	5.13	444	74.77	5.28	422	75.06	5.03
BMI (kg/cm^2)	271	25.90	4.06	281	26.26	4.02	435	26.22	3.73	413	26.29	3.91
Lumbar spine BMD (g/cm^2)	278	0.89	0.04	284	0.89	0.04	444	0.85	0.15	421	0.85	0.15
Total hip BMD (g/cm^2)	240	0.70	0.08	231	0.71	0.08	444	0.73	0.04	422	0.73	0.04
T-score at lumbar spine	278	–1.89	0.41	284	–1.86	0.42	444	–2.24	1.54	421	–2.32	1.52
T-score at total hip	240	–2.20	0.81	231	–2.15	0.81	444	–1.92	0.39	422	–1.95	0.38

Table 2 - *Percentage of baseline osteopenic patients who normalized their BMD.*

	Lumbar spine			Total hip		
	Placebo %	Strontium ranelate %	*p*-value	Placebo %	Strontium ranelate %	*p*-value
After 1 year	6.6	26.4	<0.001	1.8	5.4	<0.001
After 2 years	8.9	42.1	<0.001	1.4	10.0	<0.001
After 3 years	11.9	58.2	<0.001	1.6	19.6	<0.001

year, i.e., a 5.01-fold increase compared with the placebo group. After three years, the percentage was 58.2 in the strontium ranelate group. Significant results were also obtained for the total hip values: 19.6% of osteopenic patients were normalized after three years.

Strontium ranelate is a new drug that has been shown to increase bone mineral density and to reduce the incidence of vertebral (9) and non-vertebral (8) fractures, including hip fractures. This treatment is the first anti-osteoporotic treatment shown, in animal models, concomitantly to increase bone formation (by enhancing pre-osteoblastic cell replication) and to reduce bone resorption (by inhibiting pre-osteoclast differentiation and suppressing the bone-resorbing activity of osteoclasts) (12).

It has been shown in animals and humans that strontium is present in the bone mineral substance (13). The uptake of strontium ranelate by the crystals of bone mineral substance is possible either by ion exchange and adsorption at the surface of crystals, or by the substitution of calcium ion for strontium ion in the only cells of crystals forming during the administration of strontium ranelate (14). Most of the strontium linked to the bone mineral substance is probably adsorbed or exchanged onto the surface of the crystals, and only one out of ten calcium ions are replaced by strontium in hydroxyapatite crystals, easily exchangeable in bone mineral, as strontium is weakly linked to crystals by ion substitution, indicating that strontium uptake is minimal and does not alter calcium uptake or distribution, in either old or young bone (14). It should be noted that, as shown in animal studies (14), strontium ranelate uptake decreases by 50% ten weeks after treatment withdrawal; the decrease occurs almost exclusively in new bone. Since strontium is a heavier element than calcium, it may be expected to influence and overestimate BMD measurements by dual-photon X-ray absorptiometry (DXA), expressed in grams of equivalent calcium hydroxyapatite (15). However, preclinical studies in animal models have shown a robust correlation between the increase in BMD during strontium ranelate treatment and the improvement of the biomechanical properties of the vertebral and upper femoral extremities (16). Therefore, an increase in BMD occurring during treatment with strontium ranelate in humans, may be seen as an interesting predictor of further decrease in fracture risk. This is supported by the fact that the risk of experiencing a new vertebral fracture has been shown to be lower in patients treated with strontium ranelate with a higher measured BMD (17). Moreover, based on the SOTI and TROPOS trials, it has been recently shown that an increase in femoral neck or total hip BMD is associated with a reduction in the incidence of vertebral fracture (18).

Although the long-term uptake of strontium ranelate by the crystal of bone mineral is responsible for overestimation of BMD values during strontium ranelate treatment (19), recent studies have shown that long-term strontium ranelate administration (52 weeks) in a primate model preserves the main parameters reflecting the degree of mineralization of bone, crystallinity, and the characteristics of crystal unit cells. These results fit with previous data, showing the absence of impairment of bone mineralization in women treated for three years with strontium ranelate (9) and other studies reporting an improvement in the biomechanical properties of bone in animals, reflecting the increase in BMD observed during strontium ranelate treatment (16).

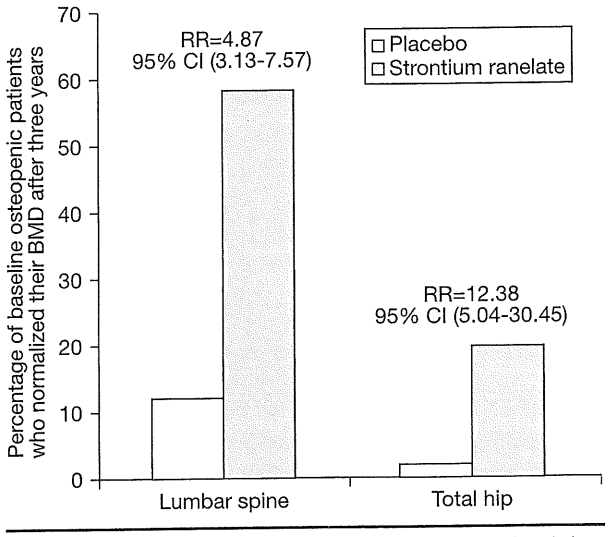

Fig. 1 - *Percentage of osteopenic patients who normalized their BMD at lumbar spine and total hip after three years.*

Therefore, an increase in BMD in osteopenic patients, leading to the observation of normal values in a substantial proportion of subjects after three years of therapy, indirectly suggests the beneficial effect of strontium ranelate on both the axial and appendicular skeleton in this particular population.

Recent epidemiological data has shown that a substantial number of osteoporotic fractures does occur in patients with osteopenia and associated clinical risk factors (5, 6). Therefore, assessment of anti-osteoporotic medications in patients with osteopenia becomes a first priority, as recommended by scientific societies and regulatory authorities (20). Whereas the anti-fracture efficacy of strontium ranelate is well documented in patients with osteoporosis, analysis of results, when considering only women with osteopenia, are still pending. Few medications used for the management of osteoporosis have been investigated in patients with osteopenia (21, 22). If the present results, based on changes in BMD observed at the lumbar spine and total hip, are confirmed by reductions in the numbers of fractures, strontium ranelate may be considered an interesting option for managing this particular population.

In summary, our study demonstrates that strontium ranelate is able to normalize BMD in a large proportion of patients with osteopenia. The clinical importance of these results should be confirmed by direct demonstration of the anti-fracture efficacy of strontium ranelate in osteopenic patients.

REFERENCES

1. Anonymous. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. Am J Med 1993; 94: 646-50.
2. Report of a WHO Study Group. Assessment of fracture risk and its implication to screening for postmenopausal osteoporosis. World Health Organ Technical Report Ser 1994; 843: 1-129.
3. Jordan KM, Cooper C. Epidemiology of osteoporosis. Best Pract Res Clin Rheumatol 2002; 16: 795-806.
4. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone 2006; 38 (2 Suppl 1): S4-9.
5. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 2001; 286: 2815-22.
6. Schuit S, Van Der Klift M, Weel A, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 2004; 34: 195-202.
7. Simon JA. Does osteopenia warrant treatment? Menopause 2005; 12: 639-48.
8. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) Study. J Clin Endocrinol Metab 2005; 90: 2816-22.
9. Meunier P, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350: 459-68.
10. Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis. J Clin Endocrinol Metab 2002; 87: 2060-6.
11. Slosman D, Provvedini DM, Meunier PJ, et al. The use of different dual X-ray absorptiometry brands in a multicenter clinical trial. J Clin Densitom 1999; 2: 37-44.
12. Reginster JY, Devogelaer JP. Traitement de l'ostéoporose postménopausique en 2004. Rev Med Liège 2004; 59: 633-47.
13. Dahl SG, Allain P, Marie PJ, et al. Incorporation and distribution of strontium in bone. Bone 2001; 28: 446-53.
14. Farlay D, Boivin G, Panczer G, Lalande A, Meunier PJ. Long-term strontium ranelate administration in monkeys preserves characteristics of bone mineral crystals and degree of mineralization of bone. J Bone Miner Res 2005; 20: 1569-78.
15. Nielsen SP, Slosman D, Sorensen OH, et al. Influence of strontium on bone mineral density and bone mineral content measurements by dual X-ray absorptiometry. J Clin Densitom 1999; 2: 371-9.
16. Ammann P, Shen V, Robin B, Mauras Y, Bonjour JP, Rizzoli R. Strontium ranelate improves bone resistance by increasing bone mass and improving architecture in intact female rats. J Bone Miner Res 2004. 19: 2012-20.
17. Roux C, Reginster JY, Fechtenbuam J, et al. Vertebral fracture risk reduction with strontium ranelate in women with post-baseline osteoporosis is independent of baseline risk factors. J Bone Miner Res 2006; 21: 536-42.
18. Bruyere O, Roux C, Cannata JB, et al. Associations between increase in bone mineral density and decrease in clinical vertebral fracture incidence during a treatment with strontium ranelate. Osteoporosis Int 2006; 17 (Suppl 1): S8.
19. Blake GM, Fogelman I. Long-term effect of strontium ranelate on BMD. JBMR 2005; 20: 1901-4
20. Reginster JY, Abadie E, Delmas P, et al. Recommendation for an update of the current (2001) regulatory requirements for registration of drugs to be used in the treatment of osteoporosis in postmenopausal women and in men. Osteoporos Int 2006; 17: 1-7.
21. Boonen S, Body JJ, Boutsen Y, et al. Evidence-based guidelines for the treatment of postmenopausal osteoporosis: a consensus document of the Belgian Bone Club. Osteoporosis Int 2005; 16: 239-54.
22. Makita K, Nozawa S. Osteopenia. Clin. Calcium 2002; 12: 1301-5.