Mechanism of action of strontium ranelate: what are the facts?

João Eurico Fonseca[1]
Maria Luisa Brandi[2]

[1] Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal
Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, Lisbon, Portugal
[2] Department of Internal Medicine, University of Florence, Florence, Italy

Address for correspondence:
João Eurico Fonseca
Rheumatology Research Unit, Instituto de Medicina Molecular, Edifício Egas Moniz,
Faculdade de Medicina da Universidade de Lisboa
Av. Professor Egas Moniz
1649-028 Lisboa, Portugal
Tel: +351-969049532, Fax: +351-217999412,
E-mail: jefonseca@netcabo.pt

Introduction

We read with great interest the commentary by Blake et al., *Could strontium ranelate have a synergistic role in the treatment of osteoporosis?* which appeared in Journal of Bone and Mineral Research in August 2009. These authors attribute the majority of the mode of action of strontium ranelate to the incorporation of strontium into bone. They go on to suggest that this mode of action could act in synergy with other antiosteoporotic treatments, mainly bisphosphonates, thus providing greater benefits for osteoporotic patients, particularly in the long term.

There is a substantial amount of evidence supporting the biological dual mode of action of strontium ranelate that has appeared in the medical literature in recent years. In fact, regarding bone-forming mechanisms, strontium ranelate is known to increase in vitro osteoblast differentiation from progenitors, as well as osteoblast activity and survival (1-4), and regulate osteoblast-induced osteoclastogenesis both in vitro (3, 4) and in vivo (5). Concerning bone-antiresorbing mechanisms, strontium ranelate decreases osteoclast differentiation and activity, while increasing their apoptosis (2, 6). In addition, the uncoupling of bone formation and resorption with strontium ranelate has also been studied in depth. In vivo studies in intact animals, immobilization-induced osteopenia, ovariectomy-induced osteoporosis, and spontaneously fractured mice strongly support the hypothesis that strontium ranelate maintains or increases bone formation while inhibiting bone resorption (7-13). Moreover, large-scale randomized trials with this drug have shown results which are in accordance with this experimental data: an increase in bone formation markers coupled with a decrease in bone resorption markers in treated osteoporotic women (14, 15). On the other hand, there is also evidence of the benefits of strontium ranelate on bone microarchitecture in different animal models. 2D and 3D histomorphometric analysis has demonstrated prevention in the deterioration of bone microarchitecture with strontium ranelate in ovariectomized rats, leading to a prevention of bone strength decrease (8). Of interest, in transgenic mice overexpressing Cbfa-1/Runx 2, a model of severe osteoporosis characterized by accelerated bone turnover resulting in spontaneous fractures, strontium ranelate significantly reduced the risk of new fractures. This reduction in fracture incidence was associated with increased bone mass due to improved trabecular microarchitecture and cortical bone geometry (13). The cited failure of Fuchs et al. to observe such benefits is most likely due to the use of inappropriate doses in that study [the plasmatic strontium exposure was sixfold lower than the one obtained after a therapeutic dose and than the one used in the Bain et al. study (8)] (16).

The influence of strontium ranelate on bone microarchitecture in osteoporotic women has been the subject of a number of studies using a variety of techniques by independent academic groups, with remarkably consistent results. Analysis of bone biopsies collected after 3 years' treatment with strontium ranelate shows improved bone microarchitecture in both cortical and trabecular bone, with no change in cortical porosity (17). Similarly, a recent analysis of hip geometry in patients treated over 5 years demonstrated improved bone structure and increased bone strength at the hip. The measurements were consistent across three different sites, particularly regarding the increase in cortical thickness associated with strontium ranelate. Moreover, this benefit remained significant after adjustment for bone mineral density, highlighting the influence of this agent on bone geometry in osteoporotic patients, independently of the presence of strontium in bone (18). Another recent study compared the efficacy of strontium ranelate and alendronate on bone microarchitecture after 1 year of treatment, and clearly showed that strontium ranelate increases the cortical thickness and bone volume (BV/TV) by comparison with baseline status and with alendronate-treated women (19). Lastly, it is also relevant to emphasize that bone mineral density continues to increase after strontium saturation is reached in bone and even after stopping the drug (20).

The study by Recker et al., on which the commentary is based, actually provides clear evidence that teriparatide and strontium ranelate have similar efficacy on bone formation after 6 months of treatment. The low power of the study cannot explain the non-significant differences in the histomorphometric parameters between the two treatments, as this power was sufficient enough to show a significant increase in a potential confounder of bone quality, cortical porosity, after only 6 months' treatment with teriparatide. Finally, increased formation does not necessarily mean "large increases", the fact that strontium decrease resorption without decreasing formation signifies per se that strontium stimulates formation. It is a semantic and quantitative problem.

Blake et al. discussed the interesting concept of a possible direct effect of strontium on bone strength. Although speculative this concept can be better understood after reviewing the observations performed by Ammann P et al., which have shown that strontium is mainly located in the bone hydrated layer and proposed that it could structurally modify the bone matrix in relation to the hydration state of the bony tissue. Such an effect on tissue organization could potentially decrease the propagation of microdamage or cracks and/or prevent the fusion of microcracks leading to fissures and fractures, and hence help to improve bone strength (21). In fact, this could be an additional exciting effect

of this drug in the line of the "medical vertebroplasty" referred by Blake et al.

In the commentary by Blake et al. a suggestion to combine strontium ranelate with another antiosteoporotic treatment was made. However, there is no evidence that combining two antiosteoporotic treatments would be beneficial for patients in terms of efficacy. The antiosteoporotic potency of strontium ranelate is clearly sufficient in monotherapy and there is plenty of evidence for the good tolerability of strontium ranelate over 8 years. Therefore, it would be unreasonable to expose patients to multiple antiosteoporotic treatments without solid evidence for that. On top of that, it should be emphasized that there is no pharmacoeconomic evidence of the cost-effectiveness (or indeed cost-saving) of a combination of two antiosteoporotic treatments.

To conclude, there is solid evidence for the dual mode of action of strontium ranelate from in vitro and in vivo animal studies, as well as from randomized controlled trials in postmenopausal osteoporotic women. Consistent results from independent studies, performed by independent teams with different techniques, have supplied ample proof that strontium ranelate has beneficial effects on bone microarchitecture in both cortical and trabecular bone. This leads to an increase in bone strength that might be potentiated by the actual presence of strontium in bone. This is reflected in the efficacy of strontium ranelate against vertebral, nonvertebral, and hip fracture in postmenopausal women with osteoporosis. In fact, uncoupling might be the ideal mechanism to control bone turnover, as strontium exerts a 360° action in preventing fragility fractures at any site and in the future it would be interesting to compare strontium ranelate with anti-sclerostin treatment.

References

1. Zhu LL, Zaidi S, Peng Y, Zhou H, Moonga BS, Blesius A, Dupin-Roger I, Zaidi M, Sun L 2007 Induction of a program gene expression during osteoblast differentiation with strontium ranelate. Biochem Biophys Res Commun 355:307-11.
2. Bonnelye E, Chabadel A, Saltel F, Jurdic P 2008 Dual effect of strontium ranelate: stimulation of osteoblast differentiation and inhibition of osteoclast formation and resorption in vitro. Bone 42:129-38.
3. Atkins GJ, Welldon KJ, Halbout P, Findlay DM 2009 Strontium ranelate treatment of human primary osteoblasts promotes an osteocyte-like phenotype while eliciting an osteoprotegerin response. Osteoporos Int 20:653-64.
4. Brennan T, Rybchyn M, Green W, Atwa S, Conigrave A, Mason R 2009 Osteoblasts play key roles in the mechanisms of action of strontium ranelate. Br J Pharmacol 157:1291-300.
5. Brennan T, Rizzoli R, Ammann P 2009 The mode of action of strontium ranelate involves the stimulation of IGF-I production and a decrease in signals for osteoclastogenesis in vivo. Abstract OP02. Bone 44:S236.
6. Hurtel-Lemaire AS Mentaverri R, Caudrillier A, Cournarie F, Wattel A, Kamel S, Terwilliger EF, Brown EM, Brazier M 2009 The calcium-sensing receptor is involved in strontium ranelate-induced osteoclast apoptosis. New insights into the associated signaling pathways J Biol Chem 284: 575-84.
7. Ammann P, Shen V, Robin B, Mauras Y, Bonjour JP, Rizzoli R 2004 Strontium ranelate improves bone resistance by increasing bone mass and improving architecture in intact female rats. J Bone Miner Res 19:2012-20.
8. Bain SD, Jerome C, Shen V, Dupin-Roger I, Ammann P 2009 Strontium ranelate improves bone strength in ovariectomized rat by positively influencing bone resistance determinants. Osteoporos Int 20:1417-28.
9. Marie PJ, Hott M, Modrowski D, De PC, Guillemain J, Deloffre P, Tsouderos Y 1993 An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats. J Bone Miner Res 8:607-15.
10. Hott M, Deloffre P, Tsouderos Y, Marie PJ 2003 S12911-2 reduces bone loss induced by short-term immobilization in rats. Bone 33:115-23.
11. Delannoy P, Bazot D, Marie PJ 2002 Long-term treatment with strontium ranelate increases vertebral bone mass without deleterious effect in mice. Metabolism 51:906-11.
12. Buehler J, Chappuis P, Saffar JL, Tsouderos Y, Vignery A 2001 Strontium ranelate inhibits bone resorption while maintaining bone formation in alveolar bone in monkeys (Macaca fascicularis). Bone 29:176-9.
13. Geoffroy V, Chappard D, Libouban H, Pascaretti C, Ostertag A, De Vernejoul MC 2007 Strontium ranelate counteracts the dramatic increase of endocortical resorption in mice with a severe osteoporosis. Abstract P020-M. Calcif Tissue Int 80(suppl 1):S42.
14. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, Cannata J, Balogh A, Lemmel EM, Pors-Nielsen S, Rizzoli R, Genant HK, Reginster JY 2004 The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 350:459-68.
15. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, Devogelaer JP, Curiel MD, Sawicki A, Goemaere S, Sorensen OH, Felsenberg D, Meunier PJ 2005 Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 90:2816-22.
16. Marie PJ 2008 Effective doses for strontium ranelate. Osteoporos Int 19:1813.
17. Arlot ME, Jiang Y, Genant HK, Zhao J, Burt-Pichat B, Roux JP, Delmas PD, Meunier PJ 2008 Histomorphometric and microCT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. J Bone Miner Res 23:215-22.
18. Briot K, Benhamou CL, Roux C 2009 Effect of strontium ranelate on hip structural geometry. Abstract SAT0375. Ann Rheum Dis 68(suppl 3):665.
19. Rizzoli R, Felsenberg D, Laroche M, Seeman E, Krieg MA, Frieling I, Thomas T, Delmas PD 2009 Superiority of strontium ranelate as compared to alendronate on microstructural determinants of bone strength at the distal tibia in women with postmenopausal osteoporosis. Abstract SAT0388. Ann Rheum Dis 68(suppl 3):669.
20. Blake GM, Fogelman I 2006 Theoretical model for the interpretation of BMD scans in patients stopping strontium ranelate treatment. J Bone Miner Res. 2006 Sep;21(9):1417-24.
21. Ammann P, Badoud I, Barraud S, Dayer D,Rizzoli R 2007 Strontium ranelate treatment improves trabecular and cortical intrinsic bone quality, a determinant of bone strength. J Bone Miner Res 22:1419-25.