Ther Adv Musculoskel Dis
(2013) 5(3) 127–139
DOI: 10.1177/1759720X13483187

A review on strontium ranelate long-term antifracture efficacy in the treatment of postmenopausal osteoporosis

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Abstract: Osteoporotic fractures are one of the major causes of increased morbidity and mortality in postmenopausal women and the overall aging population. One of the major issues in the management of postmenopausal osteoporosis is to find a safe and effective treatment in the long term (>3 years) to achieve and maintain a reduction in the risk of fracture. Strontium ranelate (PROTELOS®) is a relatively novel drug, currently approved in Europe for the treatment of postmenopausal osteoporosis. Strontium ranelate is the first agent of a new therapeutic class in osteoporosis, capable of both promoting bone formation and, to a lesser extent, inhibiting bone resorption. This uncoupling in bone turnover results in a net gain in bone mineral density (BMD), bone quality improvement and reduction in risk of vertebral and nonvertebral fractures, as initially demonstrated in the preplanned long-term registrative trials SOTI (Spinal Osteoporosis Therapeutic Intervention) and TROPOS (Treatment of Peripheral Osteoporosis) at 5 years. Recently, open-label extensions of the SOTI and TROPOS trials up to 8 and, recently, 10 years have confirmed the sustained efficacy of strontium ranelate in increasing BMD, the long-term safety profile and the high compliance to treatment, independently from baseline BMD or other risk factors for osteoporotic fractures. Recent economic impact analyses have proved that long-term treatment with strontium ranelate is highly cost effective, especially in women older than 70 years of age. Histomorphometric analyses in animals and humans participating in the phase III trials have proved that the quality of mineralization is preserved in the long term and bone microarchitecture is ameliorated, with increased bone strength. Thus, strontium ranelate has been confirmed to be an effective compound for the long-term, chronic treatment of postmenopausal osteoporosis.

Keywords: anabolic, antiresorptive, bone formation, bone mineral density, bone resorption, mineralization, safety, tolerability

Introduction

Postmenopausal osteoporosis is a chronic condition characterized by decreased bone mass, deterioration of bone microarchitecture compromising bone strength thus predisposing women to fragility fractures, a major cause of morbidity and mortality [Raisz, 2005]. The most prevalent type of fracture in postmenopausal osteoporosis is vertebral fracture, while nonvertebral fractures, including hip fractures, occurring at the level of cortical bone, account for 80% of all fractures. Trabecular bone loss has been classically linked to the development of osteoporosis. However, cortical trabecularization (i.e. cortical porosity) is now considered one of the major mechanisms through which bone strength is reduced, because of the greater impact on bone strength [Zebaze *et al.* 2010]. During the very first years after menopause bone loss is mainly due to an acceleration of bone turnover with prevailing of bone resorption over bone formation [Khosla *et al.* 2012]. The decrease in bone mineral density (BMD) is associated with a progressively increased fracture risk. This very short phase is followed by a sustained and prolonged period of defective bone formation, which is the main reason for the uncoupling of bone turnover during menopause and aging. However, the process of resorption is

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necessary for microfracture repair. Thus, an ideal treatment for this chronic and progressive condition should mainly provide a long-lasting enhancement of bone formation with relative inhibition of bone resorption, while being safe in the long term [Seeman, 2003]. In addition, mineralization, which is the completion process of each remodeling cycle, should be maintained in the physiological range to preserve optimal biomechanical properties. Current available and worldwide approved treatments for osteoporosis are antiresorptive medications, which include bisphosphonates, selective estrogen-receptor modulators and calcitonin, and bone-forming agents, such as teriparatide (PTH1-34) and parathyroid hormone (PTH1-84). Strontium ranelate (PROTELOS®, Les Laboratoires Servier, Neuilly-Sur-Seine, France) is a bone-forming agent with antiresorptive capacity, currently approved in Europe for the treatment of postmenopausal osteoporosis. This review discusses the long-term, sustained antifracture efficacy and safety profile of strontium ranelate, which has been proved in the results of the preplanned phase III registrative trials at 5 years and recently confirmed in open-label extension studies of the initial trials, starting from the basic *in vitro* and *in vivo* pharmacologic properties of this compound.

Rational for long-term treatment with strontium ranelate: *in vitro* and *in vivo* analyses

Bone turnover is a physiological process in which osteoclast-mediated bone resorption is constantly coupled to osteoblast-mediated bone formation to provide minerals to extracellular fluids, adapt to stress and strain, and constantly repair microfractures.

Since osteoclasts secrete factors that stimulate osteoblasts, drugs inhibiting bone resorption will constantly lead to a proportional inhibition of bone formation. Conversely, since osteoblasts are necessary for osteoclast activation, agents that stimulate only bone formation will subsequently elicit bone resorption. The net recovery in BMD during therapy with anabolic agents is obtained mainly during the so-called 'anabolic window', a period during which bone formation is uncoupled from resorption.

Mineralization is the completion stage of every cycle of bone turnover at the level of a single basic multicellular unit, after old bone is removed by osteoclasts and new bone is formed by osteoblasts. During primary mineralization the bone matrix is rapidly mineralized, while secondary mineralization is a slow process characterized by a gradual maturation of the mineral component. It is believed that the heterogeneity index of mineralization, and not the degree of mineralization itself, influences bone strength [Boivin *et al.* 2009]. Long-term inhibition of bone remodeling preserves structure but affects bone composition by increasing the mean degree of mineralization but decreasing the heterogeneity index. This is likely able to compromise bone quality and micromechanical properties in the long term.

The rational for the long-term treatment of osteoporosis with strontium ranelate {5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-3-thiophenacetic acid distrontium salt} comes from *in vitro* and *in vivo* studies, and in particular from histomorphometric analyses showing that bone quality, the major determinant of bone strength, is enhanced and preserved.

Determinants at the cellular and molecular level: in vitro evidence

Preliminary *in vitro* studies showed that strontium ranelate mediates an uncoupling in bone turnover since it enhances osteoblastogenesis and osteoblast activity while decreasing osteoclast differentiation and function [Bonnelye *et al.* 2008; Marie *et al.* 2011] (Figure 1).

Osteoblasts are considered the major direct target of this compound [Brennan *et al.* 2009]. Strontium induces preosteobast proliferation and enhances osteoblast activity, as demonstrated by the increase in the expression of several early and late osteoblastic markers, such as type I collagen, alkaline phosphatase, bone sialoprotein, osteocalcin and, ultimately, bone matrix mineralization and nodule formation in bone marrow stromal cell cultures and immature osteoblasts [Canalis *et al.* 1996; Barbara *et al.* 2004; Choudhary *et al.* 2007; Caversazio, 2008, Brennan *et al.* 2009]. Moreover, strontium inhibits osteoblast apoptosis and induces terminal differentiation of osteoblasts into osteocytes, as demonstrated by the increase in sclerostin expression [Atkins *et al.* 2009]. This latter effect could play a pivotal role in the uncoupling of bone turnover induced by strontium ranelate, since osteocytes can influence both osteoblasts and osteoclast function by producing paracrine signals to these cells. Recent

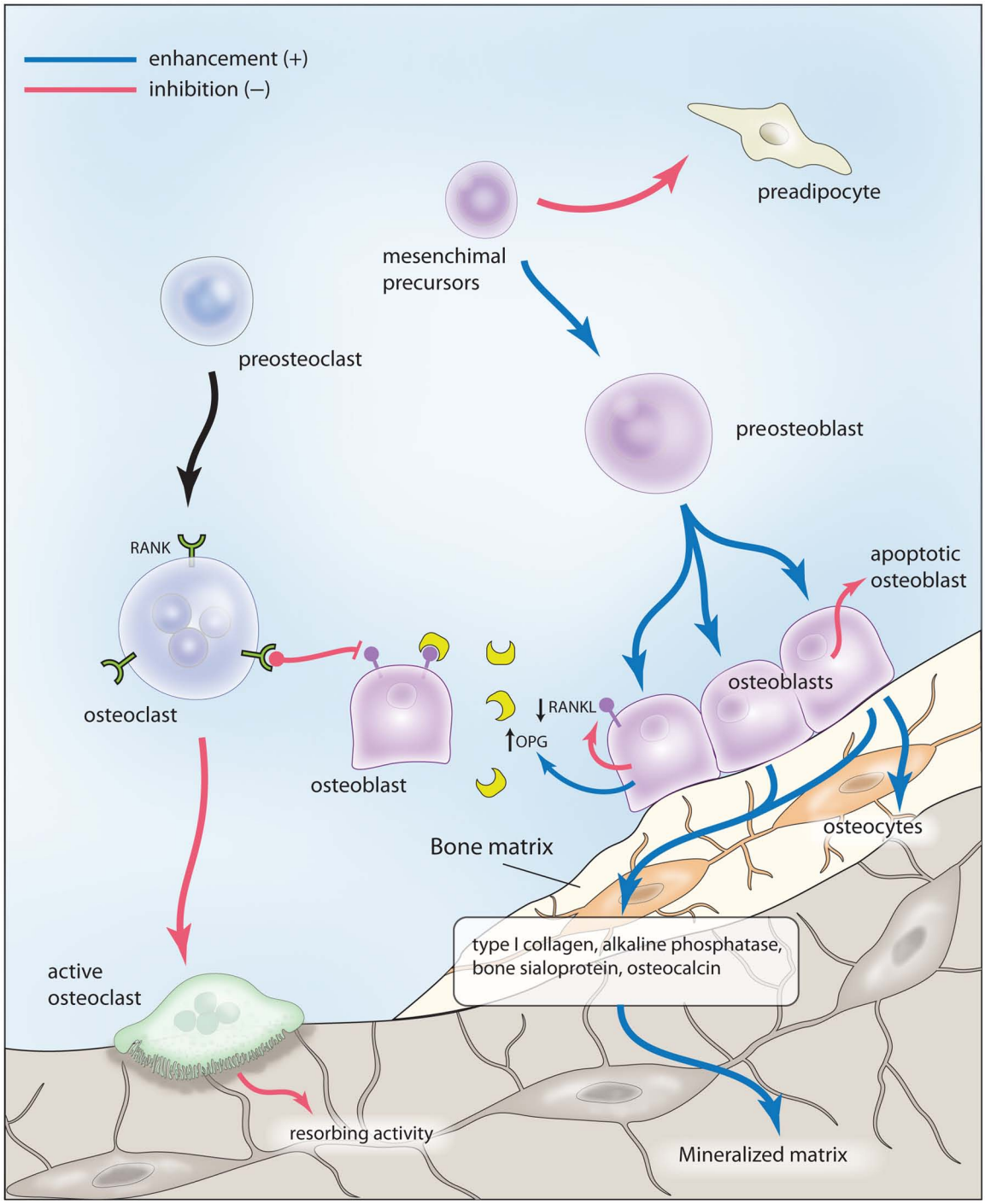

Figure 1. Proformative and antiresorptive effects of strontium ranelate. See text for details. OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κB ligand. Illustration courtesy of Alessandro Baliani © (2013).

studies have shown that strontium is also able to inhibit adipogenesis while enhancing osteogenesis both in bone marrow stromal cells and in multipotent C3H10T1/2 cells by selective peroxisome proliferator-activated receptor γ2 repression [Fournier *et al.* 2012; Li *et al.* 2012]. Considering that an increase in adiposity in bone marrow stroma sustained by an increase in adipogenesis may occur in patients with osteoporosis [Meunier *et al.* 1971], this novel mechanism could explain

at least in part the long-term efficacy of strontium ranelate in preventing fractures.

Strontium ranelate is able to decrease osteoclast differentiation and activity *in vitro*, as demonstrated by the reduction in the expression of markers of osteoclast function and the disruption of osteoclast cytoskeleton, essential for resorbing activity [Takahashi *et al.* 2003]. The principal mechanism by which strontium inhibits osteoclast activity *in vitro* is by enhancing the secretion of osteoprotegerin (OPG) and by reducing the expression of the receptor activator of nuclear factor κB ligand (RANKL) in osteoblasts [Atkins *et al.* 2009; Brennann *et al.* 2009]. Indeed, the OPG/RANKL system plays a key role in osteoclast differentiation. The increase in OPG is considered to be the main mediator of the strontium ranelate uncoupling effect on bone metabolism, as demonstrated by *in vitro* and subsequently *in vivo* studies [Peng *et al.* 2011a]. Moreover, the effect of strontium ranelate on bone formation and resorption is blunted in mice devoid of OPG [Peng *et al.* 2011b]. Thus, enhancement of OPG expression and inhibition of RANKL production by osteoblasts at various differentiation stages impairs osteoclast differentiation and function and would explain, at least in part, the uncoupling of bone turnover generated by strontium through a rebalance of this system. According to these *in vitro* findings, it has recently been reported that OPG is increased in postmenopausal women receiving strontium ranelate, as early as 3 months after treatment initiation and up to 3 years [Reginster *et al.* 2012].

Bone cells (osteoblasts, osteoclasts and osteocytes) harbor the calcium-sensing receptor (CaSR), a G-protein coupled receptor that is activated by extracellular divalent cations such as calcium and, with lower affinity, strontium. CaSR has been shown to mediate, at least in part, strontium-induced osteoblast proliferation [Chattopadhyay *et al.* 2007; Caudrillier *et al.* 2010], and osteoclast apoptosis [Hurtel-Lemaire *et al.* 2009]. CaSR signaling has been shown to play a key role in mediating the modulation of the OPG/RANKL system by strontium. However, since osteoblasts devoid of CaSR can still respond to strontium in terms of proliferation and apoptosis, other cation-sensing molecules and different mechanisms can be involved in mediating the effects of strontium on bone cells [Fromigue *et al.* 2009]. In this respect, it has been recently shown that the strontium-mediated activation of calcineurin/nuclear factor of activated Tc pathway induces osteoblastogenesis via stimulation of both canonical and noncanonical Wnt signaling pathways [Fromigue *et al.* 2010].

Determinants at the tissue level: in vivo evidence

Studies in rats, nonhuman primates, ovariectomized rodents and animal models of immobility-induced osteoporosis showed that strontium ranelate is able to increase bone mass, mineral content and strength while improving skeletal microarchitecture *in vivo*. Preliminary histomorphometric studies demonstrated that bone formation and mineral apposition rate are enhanced, while bone resorption indices are blunted by strontium ranelate over the first 6 months of treatment. This confirms *in vivo* the dissociating effect of strontium ranelate on bone turnover observed *in vitro*, indicating that this agent harbors the potential of a novel drug for the treatment of osteoporosis. In mice, this is reflected in an increase in vertebral bone mass. Studies in rats have demonstrated that in addition to the increase in bone mass, there is an increase in cortical thickness and an improvement in trabecular and cortical microarchitecture, leading to an increased bone quality and strength [Ammann *et al.* 2004, 2007]. In ovariectomized rats, an established animal model for postmenopausal osteoporosis, strontium ranelate was able to prevent bone loss by decreasing bone resorption while maintaining bone formation not only in the short term [Marie *et al.* 1993], but also in the long term [Bain *et al.* 2009]. In this latter study, the ovariectomy-induced decline in bone mass, volume and strength was prevented by achieving a plasma concentration of strontium ranelate similar to that obtained in women with osteoporosis treated with the therapeutic daily dose of 2 g.

In mice overexpressing *Runx2*, leading to an increased RANKL expression and accelerated bone loss and spontaneous fractures, strontium ranelate has been proved to be effective in increasing bone volume, cortical thickness and trabecular number, decreasing trabecular separation, with an amelioration of bone microarchitecture leading to improved bone strength and reduced vertebral fracture risk [Geoffroy *et al.* 2011]. This is the first study demonstrating in an experimental animal model the antifracture efficacy of strontium ranelate in the relative long term (9 weeks).

In rodents as well as in humans only a small fraction of strontium incorporates into the bone matrix and associates with hydroxyapatite crystals in the place of calcium, thus not directly influencing mineralization [Dahl *et al.* 2001]. Maintenance of the degree of bone mineralization and bone minerals at the crystal level was confirmed in monkeys after long-term administration of strontium ranelate, confirming the absence of deleterious effects of prolonged therapy with this agent on the quality of mineralization [Farlay *et al.* 2005]. It has recently been demonstrated in human bone biopsies from postmenopausal women with osteoporosis treated with strontium ranelate for up to 3 years that strontium accumulated only in newly formed bone during treatment, reaching a plateau in global strontium bone content after 3 years, with preservation of mineralization and focal strontium bone content [Li *et al.* 2010; Boivin *et al.* 2010].

This issue has been further analyzed in a recent study on bone biopsies from postmenopausal women treated with strontium ranelate for up to 5 years [Doublier *et al.* 2011]. This analysis shows that even after long-term treatment with strontium ranelate and independently of the distribution of the mineral at different bone sites, the quality of bone mineralization and the heterogeneity index, which reflects secondary mineralization, are maintained. Preservation of bone matrix quality in terms of mineralization has the great potential of maintaining bone strength over the long term, as discussed above.

It is also likely that the properties of the bone matrix are improved by treatment with strontium ranelate as demonstrated by nanoindentation analyses in ovariectomized rats [Bain *et al.* 2009; Ammann *et al.* 2007]. However, further studies are necessary on this subject since a small study on bone biopsies from postmenopausal women has not shown changes in nanoindentation parameters in a small group treated with strontium ranelate [Roschger *et al.* 2010].

Nonetheless, the consequences of the dissociating effect of strontium ranelate on bone turnover and modifications of bone matrix quality can at least in part explain the improved skeletal microarchitecture in patients treated with strontium ranelate, which can contribute to increased bone strength and resistance to fractures. Histomorphometry studies on unpaired human bone biopsies in women with osteoporosis participating in the Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS) trials, performed in the long term (after 1–5 years of treatment; see below for study details in terms of antifracture efficacy), have demonstrated an increased mineral apposition rate and osteoblast surface. A three-dimensional analysis by means of microcomputed tomography documented significant improvements in microarchitecture, such as increased cortical thickness and trabecular number and decreased trabecular separation compared with the placebo group, without changes in cortical porosity [Arlot *et al.* 2008]. These changes can reflect the enhanced bone formation and decreased bone resorption observed in *in vitro* and *in vivo* preclinical experiments. The modifications of bone microarchitecture seem to be particularly evident in the long term, since short-term studies on human bone biopsies obtained after 6 months of treatment with strontium ranelate do not display any change in histomorphometric indices [Recker *et al.* 2009]. However, a randomized study comparing the effects on bone microstructure (distal tibia) of therapy with strontium ranelate and alendronate for 1 year (*versus* double placebo) in women with osteoporosis by means of high-resolution peripheral quantitative computed tomography have confirmed increased cortical thickness and increased bone volume/total volume fraction (BV/TV) at 1 year in patients receiving strontium ranelate, while no modifications were observed in the bones of the alendronate-treated or placebo-treated subjects [Rizzoli *et al.* 2010]. This could explain the early protection against fracture obtained with strontium ranelate (within 1 year of treatment). In the analysis on distal tibia and radius at 2 years, cortical thickness and density and overall cancellous BV/TV increased by 6.3%, 2.4% and 2.5% respectively with strontium ranelate [Rizzoli *et al.* 2012]. Moreover, the quantification of bone strength and biomechanical properties of cortical and trabecular bone by means of finite element analysis shows that the estimated failure load increased, while cortical and trabecular stress decreased with strontium ranelate [Rizzoli *et al.* 2012].

Regarding secondary osteoporosis, strontium ranelate (900 mg/kg) has proven to be more effective than alendronate (1 mg/kg) in preventing glucocorticoid-induced osteopenia in rats, according to BMD and histomorphometric analysis [Sun *et al.* 2010]. Indeed, in a 2-year observational study strontium ranelate was more effective than risedronate in increasing BMD and decreasing back pain in patients with glucocorticoid-induced

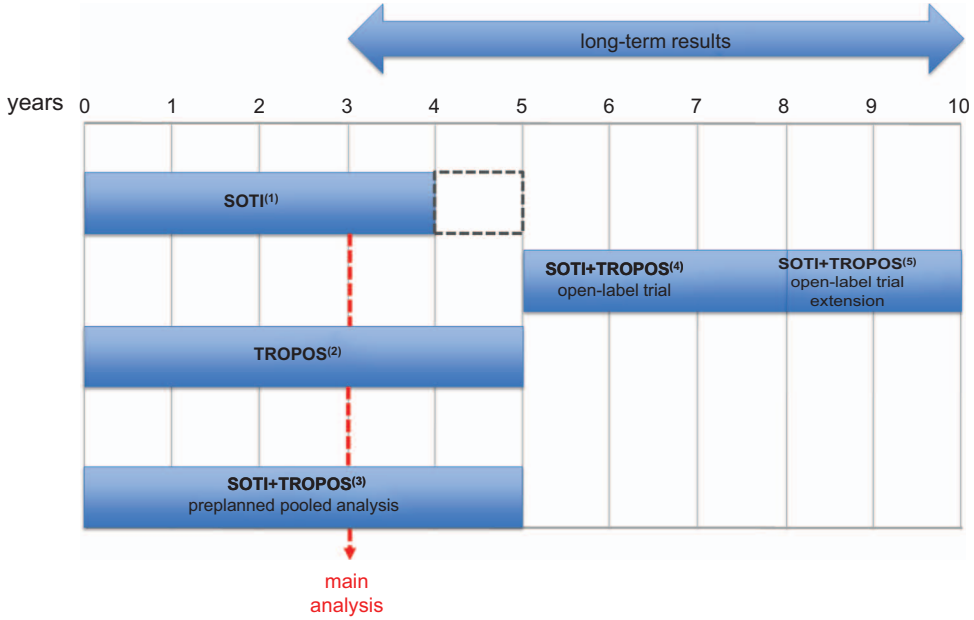

Figure 2. Randomized controlled trials and open-label extension studies designed to assess the antifracture efficacy of strontium ranelate 2 g/day in the long term. The dotted rectangle in the Spinal Osteoporosis Therapeutic Intervention (SOTI) study indicates the interruption of the study against placebo and the subsequent new randomization (see text). TROPOS, Treatment of Peripheral Osteoporosis.
[1]Meunier *et al.* [2004, 2009], Marquis *et al.* [2008].
[2]Reginster *et al.* [2005, 2008].
[3]Roux *et al.* [2006], Seeman *et al.* [2006, 2008, 2010].
[4]Reginster *et al.* [2009].
[5]Reginster *et al.* [2012].

osteoporosis, although the number of patients with new fractures did not differ between the two treatment groups [Ringe *et al.* 2009]. However, to date, this drug is not indicated in secondary osteoporosis since the phase III trials have not included such patients.

Additional evidence of improved bone strength during strontium ranelate treatment comes from animal and human studies on implant osseointegration and fracture healing (Maimoun *et al.* 2010). Indeed, in rats receiving strontium ranelate for 8 weeks, the resistance to pullout bone implants was increased. In ovariectomized rats, 4–8 weeks of treatment with strontium ranelate enhanced screw fixation in osteoporotic bone and improved fracture healing, by amelioration of microstructure, callus volume and biomechanical properties [Li *et al.* 2010], suggesting potential novel clinical applications for this drug *in vivo* [Goldhahn *et al.* 2012].

Long-term efficacy: intervention trials

The final endpoint of an antiosteoporosis therapy is to reduce fracture risk, by improving BMD, bone quality and strength.

Phase III randomized controlled trials (RCTs) for the clinical development of strontium ranelate in women with postmenopausal osteoporosis have been specifically designed to test the antifracture efficacy of this drug in the long term (5 years) with the main statistical analysis after 3 years of treatment (Figure 2).

These RCTs, together with open-label extension studies, have clearly demonstrated that the *in vitro* and *in vivo* effects of strontium ranelate translate into a long-term vertebral and nonvertebral antifracture efficacy and improvement in bone strength in postmenopausal osteoporosis. Open-label extensions of these trials have confirmed the increased BMD and safety of strontium ranelate up to 10 years of treatment. The limitations of these studies are comparable to those of any long-term trial. The observed reduction in fracture rates was not evaluated against a proper placebo group, which was unethical to pursue given the beneficial effects of strontium ranelate in a selected osteoporotic population at increased risk of fracture. Moreover, patients enrolled in the long-term studies were not randomized but they autonomously decided whether to continue or

not with the medication. In general, patients with higher compliance and those who responded to therapy were enrolled in the open-label RCT extensions. These issues have to be considered in the interpretation of the study results, which can lead to overestimation of the beneficial long-term effect of a given drug [Cooper *et al.* 2012].

The SOTI trial [Meunier *et al.* 2004] and the TROPOS trial [Reginster *et al.* 2005, 2008] are the first extensive international, prospective, double-blind RCTs which have been designed to test strontium ranelate (2 g/day) efficacy against placebo (calcium + vitamin D) in the prevention of vertebral and nonvertebral fractures respectively in postmenopausal women. In the SOTI trial, 1649 postmenopausal women with at least one osteoporotic vertebral fracture (age > 50 years and had been postmenopausal for at least 5 years), all receiving calcium and vitamin D, were randomized to receive 2 g/day of strontium ranelate or placebo for 4 years, followed by a 1-year period in which subjects receiving strontium ranelate were switched to placebo or continued on the active treatment, while all patients who had been treated with placebo were switched to strontium ranelate. In the main analysis at 3 years, the SOTI trial demonstrated that strontium ranelate is able to reduce the risk of new vertebral fractures by 41% [relative risk (RR) 0.59; 95% confidence interval (CI) 0.48–0.73; $p < 0.001$ *versus* placebo-treated group]. A significant reduction in fracture risk was observed after just 1 year of treatment (49%; RR 0.51; 95% CI 0.36–0.74; $p < 0.001$) [Meunier *et al.* 2004]. Subsequent analyses of the preplanned study demonstrated that the decrease in vertebral fracture risk is maintained after 4 and 5 years of treatment [Meunier *et al.* 2009]. In particular, the reduction in fracture risk was 33% after 4 years (RR 0.67; 95% CI 0.55–0.81; $p < 0.001$ *versus* placebo), with a concomitant improvement in quality of life ($p = 0.025$), especially in terms of absence of back pain ($p = 0.005$). In this study, the rise in BMD continued up to 5 years in the group that continued strontium ranelate, while it decreased in the group that was switched to placebo after 4 years.

The TROPOS study is the first RCT specifically designed to assess the efficacy of strontium ranelate on nonvertebral (peripheral) fractures in the long term (5 years) [Reginster *et al.* 2005, 2008], with the evaluation of vertebral fracture risk reduction as a secondary endpoint. In this study 5091 postmenopausal women with osteoporosis aged over 74 years (or aged 70–74 years with one additional fracture risk factor) were enrolled. The study was completed by 2714 subjects. A preliminary analysis of the results at 3 years showed that the RR reduction for all nonvertebral fractures was reduced by 16% (RR 0.84; 95% CI 0.702–0.995; $p = 0.04$), while the risk for major nonvertebral fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle and humerus) and new vertebral fractures was reduced by 19% (RR 0.81; 95% CI 0.66–0.98; $p < 0.001$) and by 39% (RR 0.61; 95% CI 0.51–0.73; $p < 0.001$) respectively in the group receiving strontium ranelate compared with placebo [Reginster *et al.* 2005]. In addition, therapy with strontium ranelate provided significant improvement in quality of life, analyzed as a secondary endpoint [Marquis *et al.* 2008]. In a *post hoc* analysis, the reduction in the relative risk of hip fracture, the type of fracture associated with greatest morbidity and mortality, was assessed in a group at higher risk for this type of fracture (age > 74 years, *T* score < –3) [Reginster *et al.* 2005]. In these high-risk women, strontium ranelate treatment decreased the relative risk of hip fracture by 36% (RR 0.64; 95% CI 0.412–0.997; $p = 0.046$). The complete analysis at 5 years confirmed the sustained antifracture efficacy of strontium ranelate, with a decrease in the risk of experiencing a nonvertebral, hip or vertebral fracture of 15% (RR 0.85; 95% CI 0.73–0.99), 43% (RR 0.57; 95% CI 0.33–0.97) or 24% (RR 0.76; 95% CI 0.65–0.88) respectively [Reginster *et al.* 2008].

The preplanned analysis of the pooled data from the SOTI and TROPOS studies at 3 years showed that the efficacy of strontium ranelate in reducing vertebral and nonvertebral fracture risk was independent of individual risk factors for osteoporotic fractures, such as baseline BMD, family history of osteoporosis, baseline body mass index and addiction to smoking [Roux *et al.* 2006]. This study also demonstrated that strontium ranelate was able to decrease the risk of first, second or third (or more) new vertebral fractures by 48%, 45% and 33% respectively. Strontium ranelate also displayed antifracture efficacy in the group with osteopenia at moderate risk of fracture [Seeman *et al.* 2008]. An additional preplanned analysis at 3 and 5 years of the two RCTs explored the specific antifracture efficacy of strontium ranelate in preventing either vertebral or nonvertebral fractures in the subgroup of 1488 women aged at least 80 years. In the intention-to-treat analysis the reduction in the risk of vertebral and

nonvertebral fractures was reduced by 32% and 31% at 3 years [Seeman *et al.* 2006], and 32% and 27% at 5 years [Seeman *et al.* 2010] respectively, with a long-term enhancement of quality of life.

Other surrogate markers for efficacy include BMD and bone turnover markers [Cooper *et al.* 2012]. Despite BMD being overestimated during treatment with strontium ranelate because of the uptake of strontium in bone, there is a strong correlation between the positive change in BMD and the decrease in fracture risk. It has been demonstrated that for each 1% increase in femoral neck BMD there is a 3% reduction in the risk of a new vertebral fracture within 3 years [Bruyere *et al.* 2007]. In a group of older women (≥74 years, with low femoral neck BMD) for each 1% increase in femoral neck BMD there was a 7% reduction in the risk of experiencing a hip fracture within 3 years [Bruyere *et al.* 2007].

Regarding markers of bone remodeling, the early dissociation of markers of bone remodeling (significant increase in bone formation markers and decrease in bone resorption markers as early as 3 months after treatment initiation) correlates with the increase in vertebral and femoral neck BMD at 3 years [Bruyere *et al.* 2010]. Thus, the early positive balance in bone remodeling reflecting the uncoupling of the two different processes could offer at least one rational for the anabolic effect of strontium ranelate documented since preclinical studies [Marie *et al.* 2011].

Open-label extension studies of the SOTI and TROPOS trials, specifically designed to directly assess the long-term change in BMD, tolerability and safety and, indirectly, the antifracture efficacy, were carried out in a group of 879 subjects for up to 8 years [Reginster *et al.* 2009] and extended in a group of 233 subjects for up to 10 years [Reginster *et al.* 2012]. The great limitation of these studies, as stated above, is the absence of a placebo group, which does not let us draw any definitive conclusion on the antifracture efficacy of strontium ranelate in this prolonged time period. Nevertheless, the characteristics of the final population enrolled in the 8- and 10-year study were representative of the whole SOTI and TROPOS population (mean age 72 ± 5.5 years, mean lumbar spine and femoral neck BMD *T* score of −3.3 ± 1.38 and −2.95 ± 0.57, respectively). Postmenopausal women who had participated in the phase III RCTs for 5 years in the treatment arm were invited to be enrolled in a 3-year open-label extension to continue to receive strontium ranelate 2 g/day [Reginster *et al.* 2009]. The initial 3-year extension was then increased to 10 years in a subset of patients [Reginster *et al.* 2012]. These studies clearly demonstrated that the rise in lumbar spine BMD was significant and sustained over the 10 years of treatment (up to 34.5 ± 20.2% *versus* baseline), while neck and total hip BMD reached a plateau after 7 years of treatment (10.7 ± 12.% and 11.7 ± 13.6% respectively). These studies also provide indirect evidence of maintained antifracture efficacy since the cumulative incidence of new vertebral and nonvertebral fractures in the 5-year extension (20.6% and 13.7% respectively) did not significantly differ from the cumulative incidences relative to the first 5 years of the original RCTs (18.5% and 12.9% respectively). To obtain an estimate of the antifracture efficacy, the authors selected a control group from the initial placebo group of the TROPOS study by means of the 10-year probability of major osteoporotic fracture derived from the FRAX algorithm (developed by World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK). In the group receiving strontium ranelate for 10 years a RR reduction of 35% and 38% for vertebral and nonvertebral fractures was then calculated [Reginster *et al.* 2012].

Recently, the results of a 2-year double-blind, placebo-controlled study to test the efficacy and safety of strontium ranelate in 243 men (intention-to-treat population, 161 patients received strontium ranelate) with osteoporosis have been reported (MALEO, i.e. MALE Osteoporosis, study) [Kaufman *et al.* 2013]. Statistically significant increases in BMD were observed as early as 6 months following initiation of strontium ranelate treatment *versus* placebo. The increase in BMD in men treated with strontium ranelate was similar to that observed in women in the same time period. In addition, bone resorption markers were significantly reduced in the first 3 months of treatment. The incidence of vertebral and nonvertebral fractures was lower in the treated men (5.8% and 3.5% *versus* 7.8% and 4.6% in the strontium and placebo groups respectively). Quality of life, as reflected by some of the QUALIOST (Quality of Life Questionnaire in Osteoporosis) scores [Marquis *et al.* 2001], improved in the strontium ranelate treated group *versus* placebo. The treatment was well tolerated. This study demonstrates that strontium ranelate offers a valid therapeutic option in men with osteoporosis.

A recent analysis on the economic impact of this therapy has assessed the cost effectiveness of strontium ranelate compared with no treatment over the long term in the target populations for routine use of the product [Hiligsmann *et al.* 2010a]. This study has used data from the TROPOS trial over 5 years of treatment in women aged 70 or older with a *T* score of −2.5 or lower or prevalent vertebral fractures (i.e. criteria for reimbursability in Belgium and other European countries) by means of a validated Markov simulation model with a Belgian healthcare cost perspective. Strontium ranelate was cost saving at the age of 80 years in both groups. Indeed, the cost per quality-adjusted life year gained of strontium ranelate compared with no treatment, when assuming adherence similar to bisphosphonate therapy, was inferior to the cutoffs established in other countries (i.e. the UK, Sweden) at all ages, in both groups. In particular, the cost-saving benefit of strontium ranelate was proved to be very sensitive to the risk of hip fracture during treatment.

A recent meta-analysis of cost-effectiveness studies in different settings (Belgium, the UK and Sweden) confirmed that treatment with strontium ranelate is cost saving in women with osteoporosis aged 80 years and older [Hiligsmann *et al.* 2010b]. Moreover it showed that strontium ranelate is cost effective compared with no treatment in women aged 70 years and older and in younger women with clinical risk factors for fragility fractures.

Other widely used osteoporotic therapies, such as bisphosphonates, have been proven to be cost effective compared with no treatment in the long term, but their long-term efficacy in terms of cost-saving benefit can be compromised by a poor adherence to treatment. Unfortunately, no head-to-head clinical trials are available. However, when strontium ranelate was indirectly compared with a branded risedronate it is cost effective in women older than 75 years. In another study strontium ranelate was proven to be less cost effective than a generic alendronate, but the authors have assumed a low antifracture efficacy of strontium ranelate at the hip [Hiligsmann *et al.* 2010b].

Further analyses are necessary to establish the cost effectiveness, adherence and persistence of strontium ranelate in other countries and in different settings other than clinical trials.

Long-term tolerability and safety issues

Strontium ranelate has a good tolerability and safety profile in long-term studies (RCTs at 5 years and open-label extension studies) and in the general population after 7 years of postapproval surveillance [Reginster *et al.* 2012; Rizzoli *et al.* 2011; Cooper *et al.* 2012]. The high tolerability leads to increased compliance, as demonstrated in a *post hoc* analysis of pooled data from the SOTI and TROPOS trials at 5 years [Rabenda and Reginster, 2010]. The medication possession ratio was high (82.6% in the active treatment group *versus* 86.8% in the placebo group) and influenced the risk of hip and nonvertebral fractures, since women with higher compliance displayed a greater reduction in this risk.

In the SOTI and TROPOS trials, adverse events, serious adverse events and withdrawals relative to adverse events were comparable in the active treatment group *versus* placebo and their incidence did not differ in women older than 80 years [Meunier *et al.* 2004, 2009; Reginster *et al.* 2005, 2008]. Nausea in the SOTI trial and nausea, diarrhea, headache, skin alterations (dermatitis) in the TROPOS trial were associated with strontium ranelate therapy, but only at the beginning of treatment and not after 3 months.

Uncommon side effects associated with a certain therapy are more likely to emerge in larger populations than in those included in the initial registrative trials. Thus, information on the long-term safety comes from postmarketing analyses, pharmacovigilance, case reports and after prolonged treatment, such as data from open-label studies [Cooper *et al.* 2012].

The rate of venous thromboembolism was not increased in the group of women receiving strontium ranelate *versus* placebo in the SOTI and TROPOS trials. However, when the data were pooled in a postmarketing analysis by the European Medicine Agency (EMA), the annual incidence of venous thromboembolism was 0.9% in the active treatment group *versus* 0.6% in the placebo group [EMA, 2009]. However, these rates of thromboembolism are similar in an age-matched general population and postmenopausal women *per se* are at increased risk of venous thromboembolism. A retrospective analysis using data from the British General Practice Research Database investigated this issue further by examining the rates of venous thromboembolism in women with osteoporosis treated with strontium

ranelate (2408), those treated with alendronate (20,084), and those who were untreated (11,546), and women without osteoporosis (115,009) [Breart *et al.* 2010]. There was an increase in the rate of venous thromboembolism in the untreated women with osteoporosis *versus* women without osteoporosis, but no difference was observed between treated and untreated women with osteoporosis or between different treatments. These observations were confirmed in two observational studies [Perrio *et al.* 2008; Breart *et al.* 2009]. However, in a recent recommendation by the EMA, since venous thromboembolism is more frequent in people with a positive history of thromboembolism, or temporarily or permanently immobilized, it is advised to avoid administration of strontium ranelate under these conditions. In addition, strontium ranelate should be used with caution in patients at risk of venous thromboembolism and discontinued as soon as possible in the event of an illness or a condition leading to immobilization and adequate preventive measures taken. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. Treatment is not contraindicated in patients aged 80 years and over in which the efficacy of strontium ranelate is well documented, but when treating patients over 80 years at risk of venous thromboembolism, the need for continued treatment should be re-evaluated [EMA, 2012].

DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is a rare hypersensitivity reaction. The highest risk usually occurs around 3–6 weeks after treatment initiation. The mortality rate can reach 8–10%. DRESS syndrome usually requires intensive care unit admission, with prompt drug withdrawal and proper management, sometimes including the administration of systemic glucocorticoids, which can improve the prognosis [Musette *et al.* 2011]. This syndrome is not unique to strontium ranelate since it has also been observed during other treatments (e.g. sulfonamides, aromatic antiepileptic agents, nonsteroidal anti-inflammatory drugs, neuroleptics, etc). This reaction is characterized by the development of a severe generalized eruption, facial edema, lymph node enlargement, high body temperature (>38.5°C) and multisystemic involvement (hepatitis, interstitial nephritis, interstitial pneumonia and hematological abnormalities). The macular then papular confluent exanthema begins on the upper trunk and face and descends to the lower extremities. Following the EMA recommendation, treatment with strontium ranelate should be discontinued in the case of rash, and should not be restarted [EMA, 2009, Musette *et al.* 2010].

Conclusion

Efficacy and safety have to be taken into account in the long-term treatment of any chronic condition such as osteoporosis. Long-term therapy with strontium ranelate has proven to be effective in reducing fracture risk, it is well tolerated and associated with a low incidence of side effects, making it a first-line treatment for postmenopausal women at high risk of fractures. Strontium ranelate is currently licensed in Europe for the treatment of postmenopausal osteoporosis and male osteoporosis.

More studies are needed to explore the mechanisms by which strontium ranelate promotes bone formation and inhibits bone resorption and how these effects reflect on amelioration of the biomechanical properties of skeletal tissue.

Funding

This work was supported through a grant from F.I.R.M.O. Fondazione Raffaella Becagli (to MLB).

Conflict of interest statement

MLB has received speaking honoraria and research funding from Amgen, Eli Lilly, MSD, Novartis, Roche and Servier. LC and FDA have no conflicts of interest to disclose.

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