Strontium ranelate: a new alternative treatment for postmenopausal osteoporosis

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Osteoporosis results from an increase in bone remodeling, which leads to bone loss and deterioration in the microarchitecture of bone tissue. It increases susceptibility to bone fractures, particularly of the vertebrae, hip and wrist, and is a major cause of morbidity and mortality in the elderly population. With an aging world population, early prevention of bone loss is essential for adequate control of this condition. The majority of pharmaceutical agents currently approved for the treatment of osteoporosis effectively inhibit bone resorption, but this benefit is offset by reduced bone formation due to the normal coupling between bone resorption and bone formation in the adult skeleton. In contrast, some therapies with an anabolic effect are associated with both an increase in bone formation and bone resorption. Strontium ranelate, a new treatment for osteoporosis, is unique in its action as an antiresorptive agent without negative effects on bone formation. Thus, it rebalances bone turnover in favor of bone formation. Its antifracture efficacy against vertebral, nonvertebral and hip fractures, as well as its safety have been demonstrated in two large clinical trials; Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS).

Remodeling and turnover of the organic and mineral contents of bone matrix are parts of normal bone maintenance, and involve the activities of osteoblasts and osteoclasts. In the systemic skeletal disorder osteoporosis, there is an increase in both bone formation and bone resorption. Bone resorption usually supersedes bone formation, which continuously results in loss of bone mass and strength. Bone loss is exacerbated by an increase in bone remodeling and deterioration in the microarchitecture of bone tissue [1]. Osteoporosis results in an increased susceptibility to bone fracture, with vertebral fractures being the most common. The first fracture is associated with a marked increase in the risk of subsequent vertebral fractures [2]. The next most common fractures are of the hip and wrist, and the pain, disability and loss of independence associated with these fractures can substantially reduce quality of life and are a major cause of mortality in the elderly population. Thus, diagnosis of osteopathist and early prevention of bone loss are essential for adequate control of this condition.

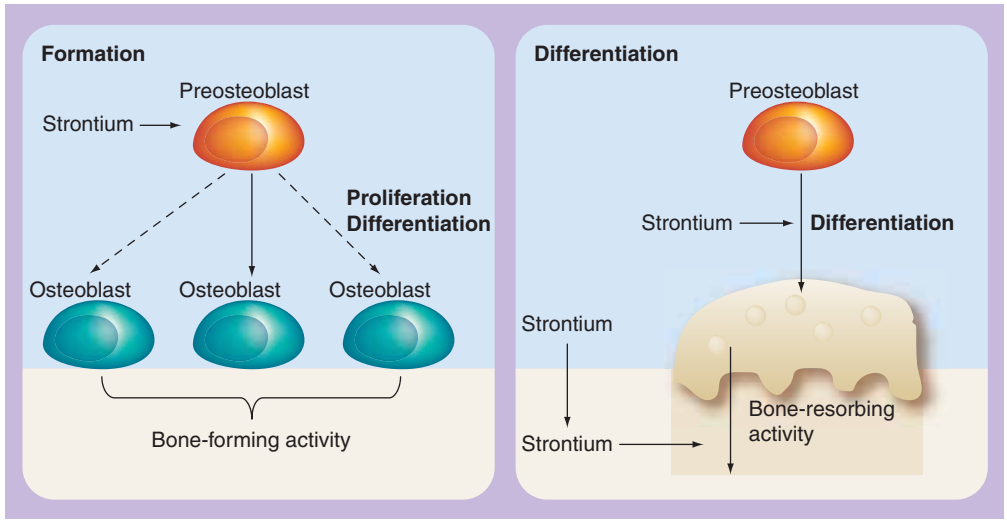
Strontium ranelate (Protelos®) is a new oral drug for the treatment of postmenopausal osteoporosis. In this review, our current understanding of the cellular components of bone turnover and the response to strontium ranelate, including its effect on both osteoblasts and osteoclasts, are discussed. The majority of pharmaceutical agents that are currently approved for the treatment of osteoporosis, including the bisphosphonates (alendronate and risedronate) and selective estrogen receptor modulators (SERM; raloxifene), effectively inhibit bone resorption. However, due to the tight coupling between bone resorption and bone formation in the adult skeleton, a secondary decrease in bone formation is observed [3]. Other therapies such as teriparatide (parathyroid hormone 1-34) induce bone formation by osteoblasts, which may be paralleled by an increase in bone resorption, following the initial treatment period [4]. Strontium ranelate demonstrates a different mode of action whereby bone resorption is inhibited without negatively affecting bone formation [4,5] and, thus, it rebalances bone turnover in favor of bone formation. Although more research is still needed to elucidate the definitive mode of action of strontium ranelate, direct effects on both the osteoblasts and osteoclasts have been presented. A representative model of the effects of strontium ranelate on bone formation and resorption at the cellular level is given in Figure 1.

In this review, the efficacy of strontium ranelate on bone integrity and improved health as well as possible cellular mechanisms for its action are presented. The results of a dose-ranging Phase II study, the 3-year data (planned principal analysis), the recently available 4- and 5-year data from two multinational 5-year Phase III clinical trials using strontium ranelate for treatment of postmenopausal osteoporosis and prevention of fractures, and the rationale for the consideration of strontium ranelate as a first-line therapy for osteoporosis are discussed.

Keywords: osteoporosis, Protelos®, strontium ranelate, treatment

future medicine

Figure 1. Potential mechanisms of action of strontium at the cellular level.



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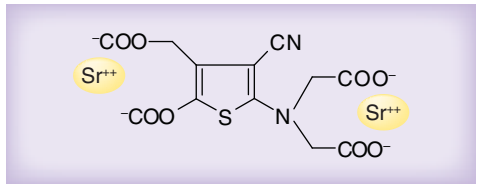
Chemical aspects of strontium ranelate

Strontium ranelate (5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-3-thiophenacetic acid distrontium salt) is a compound containing two atoms of stable strontium and, ranelic acid an organic moiety, that permits an optimal compromise in terms of molecular weight, pharmacokinetics and acceptability of the medicinal product (Figure 2). The strontium (Sr^{2+}) content of strontium ranelate is 34.1% for a relative molecular weight (anhydrous) of 513.49 [6].

Stimulation of bone formation

Some *in vitro* studies have indicated a direct effect of strontium ranelate on osteoblasts, whereas some *in vivo* studies have provided evidence for an uncoupling of bone resorption and bone formation, as bone resorption was inhibited without a secondary decrease in bone formation. Bone formation is among other important events characterized by increased mineralized bone volume. After oral intake of strontium ranelate (intestinal absorption), the distribution of Sr^{2+} is characterized by its high affinity for calcified tissues, where it is predominantly located. Sr^{2+} has a number of physical properties that are similar to those of calcium (Ca^{2+}); it appears to adsorb or exchange on the surface of the bone matrix crystals, and only a few Sr^{2+} atoms are incorporated into the crystal. The incorporation of Sr^{2+} into bone is dependent on the dose, gender and skeletal site [7], and it is rapidly eliminated from the bone on treatment withdrawal [13]. Following a 1-year study whereby strontium ranelate was administered to 2-year-old monkeys, dose-dependent strontium uptake occurred in cortical and cancellous bone, with a higher content (×1.6) of new bone synthesized during treatment than in old bone [13]. Similar results have been found in humans. In postmenopausal osteoporotic women treated with strontium ranelate, Sr^{2+} is deposited dose-dependently in bone, with significantly higher content in newly formed bone structure units (BSUs) than in old BSUs, which are constantly devoid of Sr^{2+}, even after 3 years of treatment [34].

Figure 2. Strontium ranelate.



In bone formed under treatment, Sr^{2+} uptake is mainly on the mineral surface (adsorption and exchange) and slightly incorporated into the crystals (heteroionic substitutions). A total of 10 weeks after strontium ranelate treatment withdrawal, bone Sr^{2+} content greatly decreased (approximately twofold), and this affected almost exclusively new cortical and cancellous tissue formed under treatment, while no variations were observed in old bone, where Sr^{2+} uptake was lower [13].

In female rats treated with strontium ranelate at doses of 225, 450 and 900 mg/kg/day for 2 years, dose-dependent increases in bone

strength and bone mass of the vertebral body and midshaft femur were observed, without change in bone stiffness [8]. Similar effects were seen at the vertebra level in male rats treated with strontium ranelate 625 mg/kg/day. In mice, microarchitecture, as assessed by increases of trabecular and cortical bone volumes, and trabecular number and thickness, was improved and normal bone mineralization observed.

Animal studies in which mice were given strontium ranelate for their entire lifespan, (1800 mg/kg/day for 104 weeks), had significant increases in trabecular bone volume (59%) that was associated with in mineralized bone volume (62%) [9]. The high bone formation level observed in intact animals following strontium ranelate treatment was also apparent in two animal models of osteoporosis; namely ovariectomized rats and limb immobilization. In a pivotal rat study, which was performed to resemble the bone physiology of postmenopausal women, strontium ranelate was able to inhibit bone resorption without affecting bone formation. Bone formation measured by state-of-the-art methods demonstrated that osteoid and osteoblast surfaces, mineral apposition rate and bone formation in ovariectomized rats treated with strontium ranelate were similar to those observed in control animals, paralleled with a decrease in bone resorption as compared with control animals [10]. Thus, bone formation and bone resorption were uncoupled by strontium ranelate treatment. Similar positive effects were observed in the limb immobilization model, where strontium ranelate (800 mg/kg/day) increased bone mineral density (BMD; 4%) and trabecular bone volume (19%) compared with placebo [11].

Evidence of bone maintenance by strontium ranelate has also been demonstrated in non-human primates (cynomolgus monkeys), where a trend towards an increased volume of the organic bone matrix was observed without any defects in bone mineralization. Bone formation indices, such as mineral apposition rates and bone formation rates, remained stable after 6 months of strontium ranelate treatment [12]. The incorporation of Sr^{2+} was 1.6-times higher in new bone compared with old bone, and following treatment withdrawal for 10 weeks, the decrease in Sr^{2+} was largely due to release from the new bone.

At the cellular level, the changes in mass of rat bone induced by strontium ranelate treatment were accompanied by an increase in plasma markers of bone forming activity (total alkaline phosphatase activity and insulin-like grwoth factor [IGF]-I), which have been shown to be associated with bone formation [8]. New bone matrix arises from mononuclear osteoclast progenitor cells that divide to produce preosteoblasts, which then differentiate into osteoblasts. An increase in bone-forming osteoblast cell number observed in female mice was confirmed in studies of rat calvariae organ cultures, where replication of preosteoblast cells was enhanced after incubation with strontium ranelate [14]. These findings were consistent with the three- to fourfold increase in DNA synthesis in fibroblast- and preosteoblast-enriched cell cultures, which was less pronounced in mature osteoblast populations. The changes were specific for strontium ranelate as calcium and sodium ranelate salts were not effective [15]. Consistent with the animal studies, long-term incubation of osteoblast cell cultures with strontium ranelate increased collagenous matrix formation without any deleterious effect on matrix mineralization [16]. Thus, the effects of strontium ranelate on bone-forming cells involve induction of precursors, which results in increased matrix formation without disruption of bone mineralization.

Decrease in bone resorption

With regards to its effect on bone resorption, strontium ranelate appears to be unique in its dual action of preventing bone resorption without affecting bone formation, thus, rebalancing bone turnover towards an increase in bone formation. In studies using animal osteoporosis models, strontium ranelate prevented trabecular bone loss and reduced histomorphometric indices (osteoclast surface and number) of bone resorption in ovariectomized rats and immobilized rat limbs [10,11]. The histomorphometric indices of bone resorption were also significantly reduced with strontium ranelate treatment in cynomolgus monkeys [12].

Strontium ranelate appears to directly inhibit the bone-resorbing activity of osteoclasts, the giant multinucleated cells derived from monocytes. *In vitro*, pit formation in bone slices by rat osteoclasts was inhibited in a dose-dependent fashion by strontium ranelate (32% at 0.1 mM Sr^{2+} and 66% at 1 mM Sr^{2+}; $p < 0.05$ for each) [17]. Similarly, pit formation in dentine slices by osteoclast-like cells, produced by co-culture of mouse bone marrow cells and osteoclasts, was significantly inhibited by 1 mM Sr^{2+} [18]. In cultures of fetal mouse long bones, the release of pre-incorporated $^{45}Ca^{2+}$ was reduced in the presence of strontium ranelate, thereby indicating reduced bone resorption.

Electron microscopy of these bones treated with strontium ranelate showed osteoclasts with clear zones facing the bone surface, but without the well-developed ruffled borders evident on untreated bones, which suggests that strontium ranelate inhibits pre-existing osteoclast activity [18]. Strontium ranelate also inhibited the production of new osteoclasts in a dose-dependent manner in mice [13]. *In vitro*, strontium ranelate (0.1–1 mM) significantly inhibited osteoclast differentiation in chicken marrow macrophage cell cultures, as evidenced from markers such as carbonic anhydrase II (46% reduction) and vitronectin (40% reduction) induced by 1,25-dihydroxyvitamin D. The differentiation was not inhibited by either calcium ranelate or sodium ranelate [17].

Mechanisms of action

The molecular mechanisms by which strontium ranelate uncouples the normally tightly linked bone resorption and formation in adult bone remodeling is under investigation. It is likely that this uncoupling is achieved through a combination of direct effects of Sr^{2+} on bone cells and indirect systemic effects.

Strontium ranelate induces an increase in osteoblast numbers and inhibits the activity of pre-existing mature osteoclasts and the recruitment of new osteoclasts that are responsible for bone resorption. High levels of Ca^{2+} promote chemotaxis, proliferation of pre-osteoblasts and osteoclast activity, and these actions may be mediated by the extracellular calcium-sensing receptor (CaSR) [35]. It is established that this sensor influences systemic mineral ion homeostasis, hormonal secretion, various ion channels and longer term control of gene expression, apoptosis and cellular proliferation in various cell lines [19]. Strontium ranelate was shown to be an agonist of the rat CaSR cloned in Chinese hamster ovary (CHO) and constitutively expressed in AtT-20 cells [20]. During strontium ranelate therapy, the plasma levels of Sr^{2+} may be sufficient to activate CaSR in bone as it is present at high levels in this tissue. Although some of the molecular mechanisms through which strontium ranelate exerts its influence might be mediated by the CaSR, the difference in the response of bone cells to Ca^{2+} and Sr^{2+} suggests that other currently unidentified mechanisms are important.

Therapeutic aspects

A 2-year, dose-ranging, multicenter European Phase II trial of 353 women with postmenopausal osteoporosis, and at least one prevalent fracture, established strontium ranelate at 2 g/day to be an effective and well-tolerated therapy, (STrontium RAnelate for Treatment of OSteoporosis [STRATOS]). Lumbar BMD, assessed by dual-energy x-ray absorptiometry and adjusted for bone Sr^{2+} content, increased in a dose-dependent manner from 1.4% in patients receiving strontium ranelate 0.5 g/day to 3.0% in those receiving 2 g/day. The BMD calculations are complicated by the increased molecular weight of strontium compared with that of Ca^{2+}; however, they may be used by clinicians as an indicator of compliance. The number of patients experiencing new vertebral deformities was significantly reduced in the second year of treatment with strontium ranelate 2 g/day (relative risk [RR]: 0.56; 95% confidence interval [CI]:[0.35;0.89], $p < 0.01$) [21].

Two 5-year studies aiming at demonstrating the efficacy of strontium ranelate against vertebral fractures; Spinal Osteoporosis Therapeutic Intervention (SOTI) [22], and against nonvertebral fractures; TReatment Of Peripheral Osteoporosis (TROPOS) [23], were designed. These international, multicenter, double-blind trials with strontium ranelate versus placebo were conducted with Caucasian women on individually titrated Ca^{2+} and vitamin D supplementation, who were identified during a common run-in, trial; Fracture International Run-in for Strontium Ranelate Trial (FIRST). In the SOTI study, 1649 postmenopausal women aged at least 50 years, with low lumbarspine BMD (≤0.840 g/cm^2 as measured with Hologic) and with at least one prevalent spinal fracture, were enrolled, randomized and treated with either strontium ranelate or placebo [22]. In the TROPOS study, 5091 women were recruited with the following inclusion criteria: postmenopausal, aged either over 74 years or between 70 and 74 years, one additional risk factor (i.e., history of osteoporotic fracture after menopause, residence in a retirement home, frequent falls or a maternal history of osteoporotic fractures of the hip, spine or wrist), and low femoral neck BMD (≤0.600 g/cm^2, as measured with Hologic) [23].

Prevention of fracture in osteoporosis

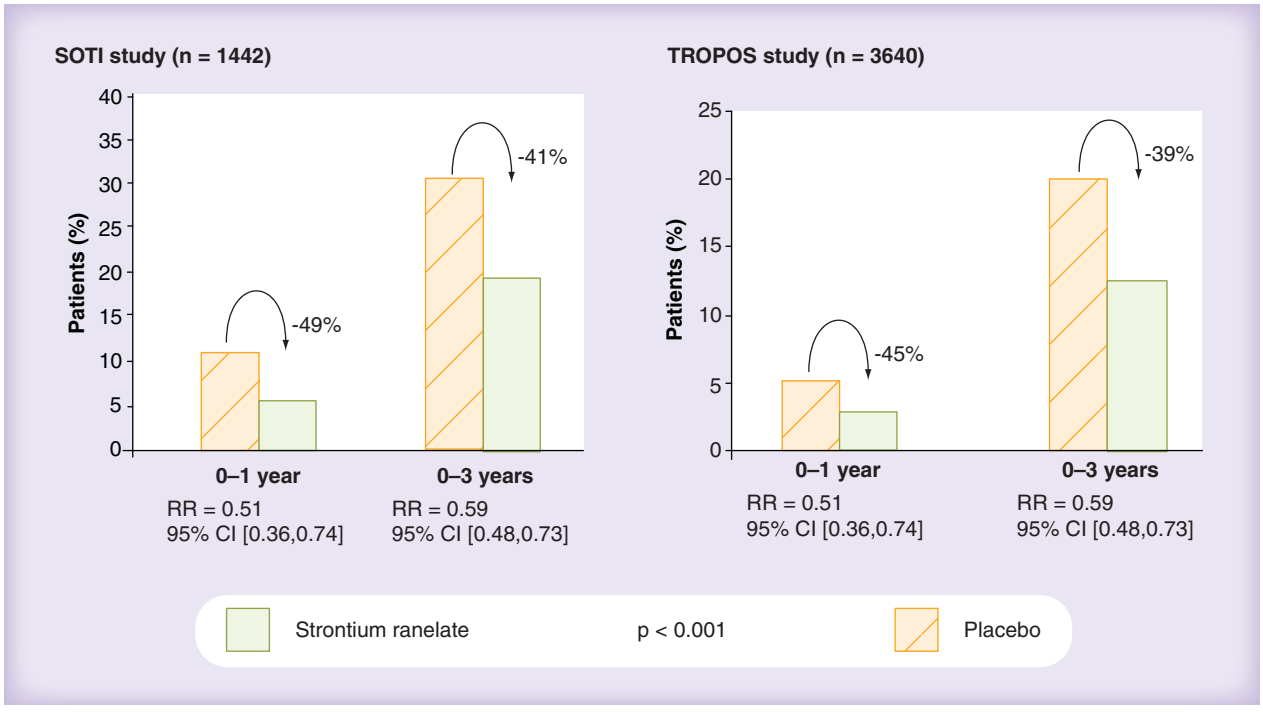
Most studies with antiosteoporotic agents have addressed the risk of vertebral fracture and, to a lesser extent, nonvertebral fractures. Risk factors differ between vertebral and nonvertebral fractures, and overall risk of fractures varies widely in different geographic regions and according to ethnicity/race. In the SOTI study, the risk of

new vertebral fracture was decreased by 49% over the first year of treatment with strontium ranelate, and 41% over the 3-year study period (RR: 0.59; 95% CI[0.48;0.73]; $p < 0.001$ Figure 3) [22]. On this basis, nine patients would need to be treated for 3 years in order to prevent one patient from having a vertebral fracture. This was consistent with the TROPOS study, where the RR of vertebral fracture was reduced by 39% (RR: 0.61; 95% CI[0.51;0.73]; $p < 0.001$) after 3 years, and by 45% (RR: 0.55; 95% CI[0.39;0.77]; $p < 0.001$) over the first year in patients treated with strontium ranelate compared with those treated with placebo (Figure 3). In the TROPOS study, the reduction in risk of fracture was even more marked in patients without prevalent fracture, where the risk reduction was 45% (RR: 0.55; 95% CI[0.42;0.72]; $p < 0.001$) [23]. Interestingly, the vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis was shown to be independent of baseline risk factors (age, family history of osteoporosis, initial BMD, prevalent vertebral fractures and addiction to smoking) after the pooled analysis of both the SOTI and TROPOS trials, which included a population of 5082 postmenopausal women [30].

The 5-year data of these studies were recently obtained, confirming that strontium ranelate provides sustained long-term efficacy over 5 years against vertebral fractures [36].

The effects of pharmacotherapy on nonvertebral fractures are less well studied, even though hip fractures are the most disabling fracture type. Between 10 and 20% of women die earlier than expected for their age within the first year of sustaining a hip fracture; after 1 year there is a 20% mortality rate and approximately 50% of patients are unable to live independently [28,29]. Although trauma has a greater contribution towards nonvertebral than vertebral fractures, bone fragility is still a major component in the occurrence of nonvertebral fracture. TROPOS was designed to assess the effectiveness of strontium ranelate on nonvertebral fracture in postmenopausal women with osteoporosis. Over 3 years of treatment, the RR of all nonvertebral fractures was reduced by 16% (RR: 0.84; 95% CI[0.702;0.995]; $p = 0.04$), and by 19%

Figure 3. Proportion of patients (strontium ranelate and placebo group) with risk reduction of new vertebral fractures, after 1 and 3 years of treatment.



CI: Confidence interval; RR: Relative risk; SOTI: Spinal Osteoporosis Therapeutic Intervention; TROPOS: TReatment Of Peripheral Osteoporosis Study.

(RR: 0.81; 95% CI[0.66;0.98]; p = 0.031) for major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle and humerus) [23].

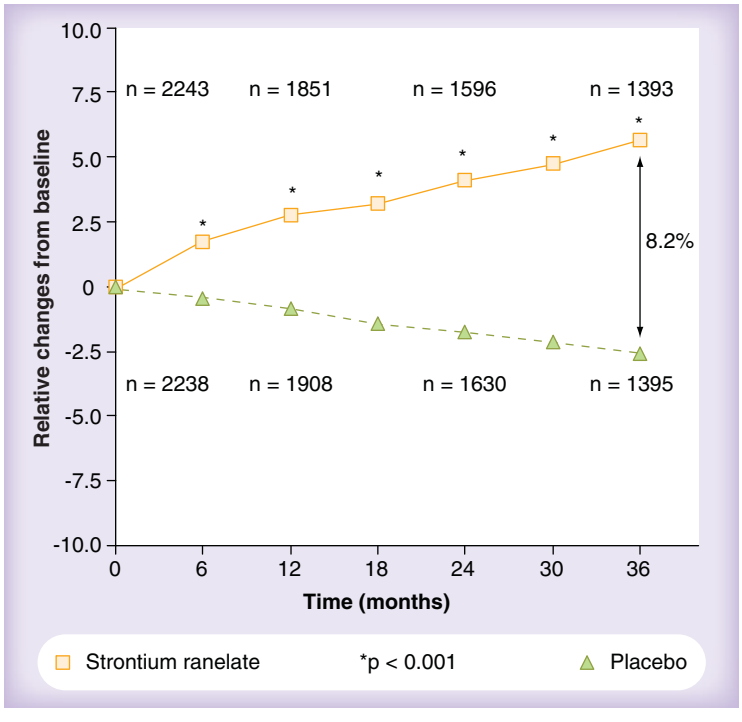
Although the TROPOS study was not specifically powered to demonstrate a reduction in risk of hip fracture, patients (n = 1977) aged 74 years or more and with a femoral neck BMD T-score less than -2.4 according to NHANES reference, were analyzed *post hoc*. The RR reduction for hip fracture was 36% (RR: 0.64; 95% CI[0.412;0.997]; p = 0.046) [23].

Similar to vertebral fractures, the long-term efficacy of strontium ranelate against nonvertebral fractures was confirmed over 5 years in the TROPOS study [36].

In addition to these results, strontium ranelate was shown to reduce the risk of vertebral and nonvertebral fractures over 3 years in elderly women with osteoporosis aged 80 years and over, with a good safety profile [37]. As demonstrated in the general study population, this antifracture efficacy appears early from the first year and is sustained over 5 years in this aged population [38,39].

In conclusion, as a consequence of these results, strontium ranelate demonstrates a very wide range of efficacy against vertebral and nonvertebral fractures (including hip) with an early and sustained long-term effect, irrespective of the existing risk factors at baseline (including age of the patients).

Figure 4. Relative mean difference between changes from baseline for femoral neck bone mineral density between strontium ranelate and placebo.



Effects on bone turnover

In animal models, the increase in bone density following strontium ranelate treatment closely correlated with increases in biomechanical bone strength and bone quality [31]. Thus, strontium ranelate exhibited the potential for a new long-term therapeutic agent in the prevention of osteoporotic fracture.

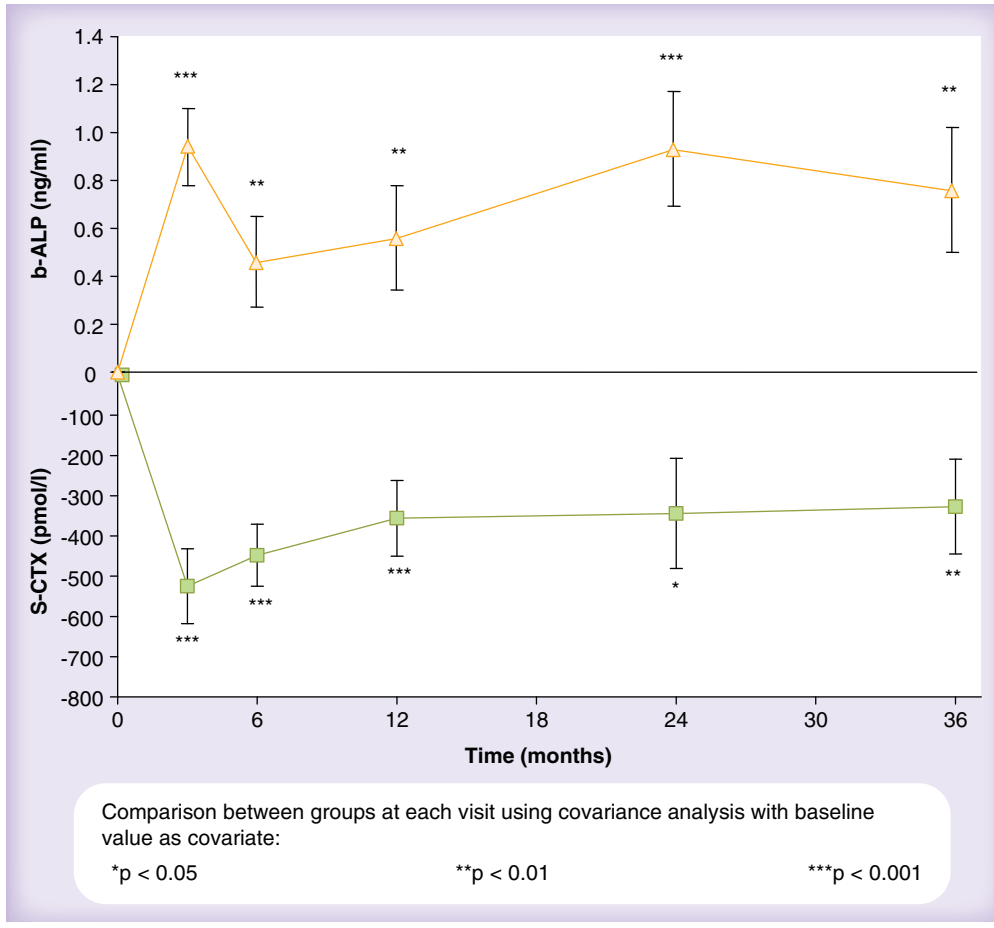
In the SOTI study, there was a continuous increase in BMD at the spine, femoral neck and total hip in strontium ranelate-treated patients compared with placebo over the 3-year period and with no trend towards a plateau [22]. A similar trend was observed in the TROPOS study at the total hip and femoral neck, where the difference in strontium ranelate treated patients from placebo in BMD was 8.2% at the femoral neck and 9.8% for total hip after 3 years (Figure 4) [23]. The presented uncorrected BMD gain is most likely higher than the real BMD gain, due to the molecular weight ratios of calcium and Sr^{2+}.

Increased levels of serum bone-specific alkaline phosphatase and decreased levels of serum C-telopeptide crosslinks in the strontium ranelate group compared with the placebo group provided evidence of bone formation, and a reduction in bone resorption. In many studies and under various conditions, these biochemical markers have been shown to be accurate markers of bone turnover [32]. Changes were observed from the third month of treatment and the difference between the two treatment groups were maintained over 3 years ($p < 0.001$, Figure 5) [22].

Safety & treatment compliance

Osteoporosis is a chronic disease that requires long-term treatment, and compliance with current treatment regimes is often suboptimal. Thus, there is a need to continue the search for new medications for postmenopausal osteoporosis that are effective, safe and tolerable. Treatment compliance over 3 years in the SOTI study was 83% for the strontium ranelate patients and 85% for placebo. The incidence of adverse events, serious adverse events and withdrawals related to adverse events was similar in the strontium ranelate and placebo groups in both the SOTI and TROPOS studies. During the first 3 months of treatment in the TROPOS study, nausea (7.2% strontium ranelate vs 4.4% placebo), diarrhoea (6.7 vs

Figure 5. Differences over time between strontium ranelate and placebo in serum biochemical markers of bone metabolism.



Absolute changes data adapted from Meunier *et al. N. Engl. J. Med.* 350, 459–468 2004 [22].
b-ALP: Bone-specific alkaline phosphatase; S-CTX-1: Serum C-terminal telopeptide fragments of type I collagen.

5.0%), headache (3.4 vs 2.4%) and dermatitis and eczema (5.5 vs 4.1%) were more frequently associated with strontium ranelate treatment compared with placebo but, thereafter, no difference was observed between the incidence of nausea and diarrhoea in the treated and placebo groups [23].

With regard to bone safety, as with animal studies, bone integrity was maintained in patients treated with strontium ranelate. There was no evidence of osteomalacia or primary mineralization defects in biopsies of lamellar bone [23].

Conclusions

The aims of osteoporosis therapy are to prevent initial and subsequent fracture by ensuring patients at most risk are appropriately advised and treated. The ideal therapy for osteoporosis should prevent the loss of bone tissue and maintain the apatite, mineral content and architecture of bone. Strontium ranelate decreases bone resorption and activates bone formation without any deleterious effect on bone mineral content. It increases mechanical strength of bone, thereby protecting against new fractures. Sr^{2+} is closely related to Ca^{2+} in its chemistry and is likely to affect bone formation and resorption through direct and indirect effects on bone cells and mineral content. The mechanisms by which strontium ranelate contributes towards bone formation include adsorption of Sr^{2+} onto the surface of bone, activation of replication of pre-osteoblasts, and an increase in collagenous protein formation. The observed decrease in bone resorption is characterized by a decrease in osteoclast differentiation and a decrease in the activity of existing mature osteoclasts. These actions on both pre- and mature osteoclasts may, partly, explain the ability of strontium ranelate to prevent bone loss in osteoporosis.

The dual action of strontium ranelate is unique in osteoporosis therapy, and the effectiveness and safety of this drug has been demonstrated over a 5-year period in two large clinical trials involving 6740 patients. In these trials, the incidence of vertebral, nonvertebral and hip fractures decreased and BMD increased. This wide range of antifracture efficacy appears early and is sustained over 5 years in the entire population as well as in the elderly subset. The efficacy that is demonstrated regardless of the baseline risk factor for osteoporosis, and the safety profile observed in these trials support strontium ranelate use as a first-line therapy for postmenopausal osteoporosis.

Future perspective

The effect of strontium ranelate is very different compared with other antiresorptive treatments. Whereas some antiresorptive treatments, such as bisphosphonates, inhibit bone resorption to below premenopausal levels [33], strontium ranelate shifts the balance between bone resorption and bone formation, with a rebalance in favor of bone formation.

In the normal adult skeleton, bone resorption by osteoclasts is important for maintaining the quality of bone. It is not currently known whether excessive inhibition of bone resorption is optimal for bone health, although emerging evidence from case studies suggests that severely suppressed bone remodeling by pharmacological intervention may be unfavorable for bone quality [40]. In contrast to excessive inhibition of bone remodeling, strontium ranelate shifts the balance by inhibition of bone resorption to normal and healthy levels, and at the same time enables continuous or even increased bone formation.

This uncoupling between bone resorption and bone formation, with sufficient activity of osteoclast to enable the maintenance of bone quality, may be one new path for developing new and even more potent modulators of bone health.

Author disclosure

Morten A Karsdal is a full-time employee at Nordic Bioscience, Denmark. Claus Christiansen is the Chief Executive Officer of Clinical and Basic Research, an organization involved with performing clinical Phase II, III and post-marketing trials for the pharmaceutical industry. Claus Christiansen has worked with most sponsors involved in the area of osteoporosis and postmenopausal complaints, including most pharmaceutical companies involved in the field of osteoporosis. The list includes Roche, Wyeth-Ayerst, Eli Lilly & Co, Novartis, Novo Nordisk, Proctor and Gamble, Groupe Fournier, Besins EscoVesco, MSD, Chiesi, Boehringer Mannheim and Pfizer.

Executive summary

Osteoporosis

- Osteoporosis is a systemic skeletal disorder that arises from a mismatch between bone resorption by osteoclasts and bone formation by osteoblasts.
- Osteoporosis affects approximately 30% of postmenopausal women and results in an increased susceptibility to bone fracture, particularly of the vertebrae, hip and wrist.
- Pain, disability and loss of independence associated with osteoporosis can substantially reduce the quality of life.

Strontium ranelate

- Strontium ranelate is a compound containing two atoms of stable strontium and ranelic acid, an organic moiety.
- It is administered orally at 2 g/day as therapy for postmenopausal osteoporosis.

Bone formation

- Strontium ranelate maintains or even enhances bone formation.
- It increased bone mineral density (BMD) and trabecular bone volume in a limb-immobilization model of osteoporosis in rats. In monkeys, the volume of the organic matrix of bone was increased, which was not associated with defects in bone mineralization.
- *In vitro*, incubation with strontium ranelate enhanced replication of preosteoblast cells.

Bone resorption

- Strontium ranelate reduced histomorphometric indices of bone resorption in the limb-immobilization model and cynomolgus monkeys.
- Strontium ranelate decreased pit formation by osteoclasts co-cultured with bone or dentine slices.
- Strontium ranelate decreases bone resorption in ovariectomized rats.

Bone mass & microarchitecture

- Strontium ranelate increases bone mass and bone microarchitecture in ovariectomized rats.

Executive summary

Mechanisms of action

- Strontium (Sr^{2+}) appears to adsorb or exchange on the surface of the matrix crystals, and there is little exchange between Sr^{2+} and calcium (Ca^{2+}).
- The incorporation into bone varies with the dose of strontium ranelate, gender and skeletal site. The incorporation was 1.6-times higher in new bone compared to old bone.
- Some molecular mechanisms though which strontium ranelate exerts its influence might be mediated by the Ca^{2+}-sensing receptor, but the difference in the response of bone cells to Ca^{2+} and Sr^{2+} suggests that other currently unidentified mechanisms are also important.

Therapeutic aspects

- The effective and safe dose of strontium ranelate therapy to increase lumbar BMD was established in the STrontium RAnelate for Treatment of OSteoporosis (STRATOS) trial.
- The 4- and 5-year data are available from two ongoing 5-year studies; Spinal Osteoporosis Therapeutic Intervention (SOTI), with vertebral fracture as a primary end point; and TReatment Of Peripheral Osteoporosis (TROPOS), with nonvertebral fracture as a primary end point.
- The relative risk of new vertebral fracture was reduced by 41% after 3 years in the SOTI study (risk of new vertebral fracture was 20.9% in the strontium ranelate group vs 32.8% in the placebo group).
- In the TROPOS study, the relative risk of all nonvertebral fractures were reduced by 16%, and major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, and clavicle and humerus) by 19%. The relative risk reduction for hip fracture was 36% in a subpopulation at particular risk for this type of fracture.
- A continuous increase in BMD at the spine, femoral neck and total hip occurred over the 3-year period in both trials with no trend towards a plateau. Bone integrity was maintained.
- Treatment compliance was high and the incidence of adverse events, serious adverse events and withdrawals related to adverse events were similar in the strontium ranelate and placebo groups.

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