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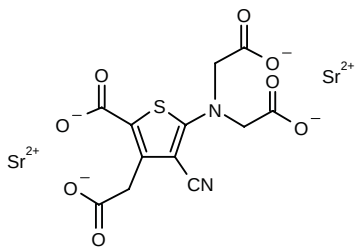
Strontium Ranelate

Treatment and Prevention of Osteoporosis
Bone Resorption Inhibitor
Bone Formation Stimulant

Ranelic Acid Distrontium Salt (Prop INNM)
S-12911-2
Protos®

2-[2-Carboxy-4-cyano-5-[*N*,*N*-di(carboxymethyl)amino]thiophen-3-yl]acetic acid distrontium salt



$C_{12}H_6N_2O_8SSr_2$
Mol wt: 513.4914
CAS: 135459-87-9
CAS: 135459-90-4 (as free acid)
EN: 170934

Abstract

Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and an increased risk for fractures. The majority of the agents currently available for the treatment of osteoporosis decrease bone resorption (*e.g.*, estrogens, selective estrogen modulators, calcitonin and bisphosphonates) although some agents increase bone formation (*e.g.*, fluoride and parathyroid hormone). In contrast, strontium ranelate was found to simultaneously decrease bone resorption and stimulate bone formation. It was also shown to increase bone volume and improve the mechanical properties of bone *in vivo* and was chosen for further development. Strontium ranelate has shown efficacy in preventing early postmenopausal bone loss and reducing the risk of hip fracture in women with postmenopausal osteoporosis. The agent is in phase III development for the prevention and treatment of osteoporosis.

Synthesis

Condensation of the substituted aminothiophene (I) with ethyl bromoacetate (II) by means of K_2CO_3 in refluxing acetone gives the corresponding ethyl tetraester (III) (1), which is converted into the desired strontium salt by treatment with NaOH in refluxing EtOH/H_2O, followed by reaction with strontium hydroxide or strontium chloride in H_2O. Alternatively, this transformation can also be achieved by direct treatment of (III) with strontium hydroxide in H_2O/EtOH (2). Scheme 1.

Introduction

Osteoporosis is a skeletal disorder that is the most common type of metabolic disease affecting an estimated 10 million Americans and 200 million women worldwide. An estimated 18 million Americans suffer from low bone mass and therefore are at an increased risk for the disease. The disease is characterized by low bone mass and structural deterioration of bone tissue resulting in bone fragility and increased susceptibility to fractures. Osteoporosis develops when the rate of bone resorption is accelerated or new bone formation is too slow. The process of modeling and remodeling of the skeleton is a finely balanced and specialized process involving new bone formation and resorption of old bone so that the entire adult skeletal is renewed about every 10 years. The rate of bone resorption gradually begins to exceed that of new bone formation by age 30 and, by age 50, 1-3% of bone mass of both men and women is lost (3, 4).

Osteoporosis is classified into two types which are both considered primary disorders related to decreased gonadal function or aging. Osteoporosis associated with normal aging in both women and men is referred to as

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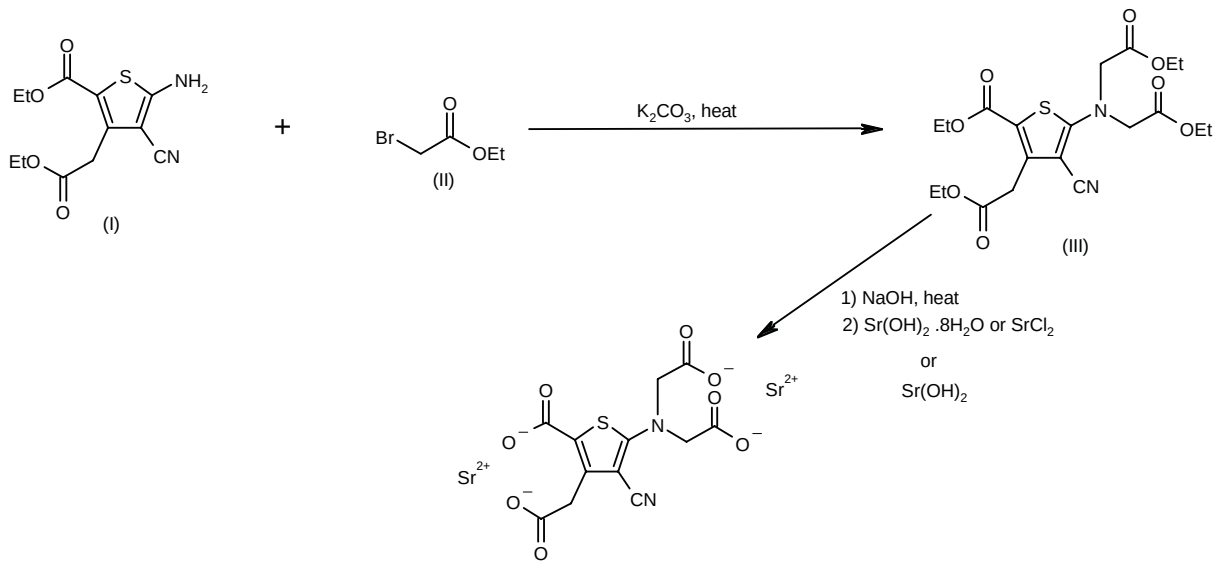
Scheme 1: Synthesis of Ranelic Acid Distrontium Salt



type II (senile) osteoporosis. In older women, bone loss is evident throughout the entire postmenopausal period although it can become extremely accelerated in some individuals during the first 5-10 years after menopause. This accelerated and severe bone loss is classified as type I (postmenopausal). Osteoporosis can also be a secondary disorder, occurring in patients administered glucocorticoids or other chemotherapeutic agents and in individuals suffering from other conditions such as malignancies, inflammatory bowel disease, hypothyroidism and cystic fibrosis (3-5).

Osteoporosis is routinely prevented with calcium and vitamin D supplementation combined with good nutrition, weight-bearing exercise and reductions in tobacco, alcohol and caffeine intake. However, restoration of bone loss in those patients with established osteoporosis is much more difficult. The majority of the agents currently available for the treatment of osteoporosis decrease bone resorption (*e.g.*, estrogens, selective estrogen modulators, calcitonin and bisphosphonates), although a few agents have been shown to increase bone formation (*e.g.*, fluoride and parathyroid hormone). Antiresorptive therapies have been shown to be particularly effective in the treatment of osteoporosis but they generally do not induce formation of new bone. Moreover, to date, there is no treatment available that can prevent new vertebral or peripheral osteoporotic fractures. Thus, the search for new therapies continues, with particular emphasis on discovering agents which optimize the risk/benefit ratios of osteoporosis treatment (3).

One agent to emerge from research efforts is strontium ranelate (S-12911, Protos®). The agent has a unique mechanism whereby it simultaneously decreases bone resorption and stimulates bone formation. Due to its excellent activity *in vitro* and *in vivo* and its good bioavailability and gastric tolerance, strontium ranelate was chosen for further development for the treatment and prevention of osteoporosis (3, 6).

Pharmacological Actions

Strontium ranelate was shown to enhance bone cell replication and bone formation *in vitro*. In experiments using newborn rat calvaria labeled with [^{3}H]-thymidine or [^{3}H]-proline, strontium ranelate (1 mM) increased preosteoblast cell replication by 30-50% at 24 h and by 60% at 96 h without affecting osteoblasts or periosteal cells; bone formation rates were increased by 20-35%. Further experiments using [^{3}H]-thymidine or [^{3}H]-proline labeled cell populations enriched with fibroblasts and preosteoblastic cells or with mature osteoblasts isolated from 22-day old fetal rat calvaria showed that treatment with strontium ranelate increased DNA synthesis by 3- to 4-fold at 24 h in those cultures enriched with fibroblasts and preosteoblastic cells. The agent had less marked or inconsistent effects on DNA synthesis in populations enriched with osteoblasts. However, collagen and non-collagen protein production was increased in osteoblasts by 35%, an effect absent in fibroblasts and preosteoblastic enriched cells (7).

The effects of strontium ranelate on osteoclast activity and bone resorption were examined *in vitro* in tissue and cell cultures. Strontium ranelate (0.05-1 mM for 48 h) dose-dependently inhibited [^{45}Ca] release (maximum of 28% at 1 mM) in cultured mouse calvariae. The agent had no effect on [^{45}Ca] release when calvariae were heated before treatment at 80 °C for 5 min, thus indicating that

the inhibitory effects of the agent on bone resorption were cell-mediated (8).

In vitro analysis of the effects of the agent on osteoclast activity showed that strontium ranelate at 0.1-1 mM significantly and dose-dependently inhibited 1,25$(OH)_2$-vitamin D_3-induced expression of osteoclastic markers in chicken bone marrow cultures, *i.e.*, carbonic anhydrase II (30-46%) and the α_v subunit of the vitronectin receptor (30.7-40%). Thus, the inhibitory effects of the agent on bone resorption are via direct and/or matrix-mediated inhibition of osteoclast activity (9).

Strontium ranelate may be an agonist at the G-protein-coupled, extracellular cation-sensing receptor (CaSR). CaSRs are present on osteoblasts and putative osteoclast precursors where they appear to mediate the stimulatory and inhibitory actions of Ca^{2+} on osteoblast function and osteoclastogenesis, respectively. The CaSR binds Ca^{2+} in addition to other cations. Experiments conducted using CHO cells transfected with cloned rat brain CaSR, mouse anterior pituitary (AtT20) cells constitutively expressing mouse CaSR or HEK293 cells transfected with bovine CaSR, showed that strontium can act as an agonist at CaSR. In CHO and AtT20 cells expressing CaSR, strontium ranelate (0.4-15 mM) stimulated Ca^{2+} (0.3 or 2 mM)-induced [^{3}H]-inositol phosphate (IP) production, with more pronounced effects seen in the presence of 2 mM Ca^{2+}. At a dose of 5.4 mM, strontium ranelate caused a 15-fold increase in IP production. The effects of strontium were found to be 80-100% of the maximal effects observed with Ca^{2+}. Sodium ranelate had no effect on Ca^{2+}-induced IP production in CHO cells expressing the CaSR. Similarly, strontium increased cytosolic Ca^{2+}, increased IP production and activated a Ca^{2+}-permeable, nonselective cation channel (NCC) in HEK293 cells expressing the bovine CaSR. The EC_{50} values for these effects were between 2 and 3 mM which are approximately 0.5 mM higher than values obtained for Ca^{2+}. Strontium resulted in responses that were 70-100% of those of Ca^{2+} (10-12).

Results from an *in vitro* study using human cartilage chondrocytes isolated from normal or osteoarthritic cadavers showed that strontium ranelate (0.1-1 mM for 24-72 h) markedly stimulated cartilage matrix formation. The agent had no effect on stromelysin synthesis although it markedly stimulated proteoglycan synthesis. In addition, the agent (1 mM) increased IGF-I (1 nM)-stimulated proteoglycan production but had no effect on the inhibitory action of IL-1β. It was concluded that stimulation of matrix formation by strontium ranelate occurred via direct ionic effects without altering chondroresorption activity (13).

Strontium ranelate optimized bone metabolism *in vivo* by increasing bone formation and reducing bone resorption in several normal and osteoporotic animal models.

Long-term treatment of normal intact female and male rats (7 weeks old) with strontium ranelate (225, 450, 625 or 900 mg/kg/day p.o. for 104 weeks) resulted in dose-dependent increases in bone strength as assessed by tests for vertebral body compression and femur bending. In females, the increase in bone strength was associated with alterations in bone mineral density and microarchitecture and an increase in vertebral volume. Significant and dose-dependent increases in cancellous bone volume (27 ± 41%) were observed and significant decreases in trabecular separation; osteoid volume and thickness were not affected by treatment indicating no changes in bone mineralization. Comparable alterations in bone strength and bone mineral density (BMD) were noted in the femur of females and in the vertebrae and midshaft femur of males. Males also exhibited histomorphometric modifications in the tibia as well as increases in bone formation markers and plasma IGF-1 levels. Thus, strontium ranelate increased bone mass and strength without impairing mineralization (14, 15).

Long-term treatment with strontium ranelate (200, 600 or 1800 mg/kg/day p.o. for 104 weeks) was also safe and effective in increasing vertebral bone mass and decreasing bone resorption in adult male and female mice. Plasma strontium and AUC values dose-dependently increased in both males and females treated with the agent. Females treated with the 600 and 1800 mg/kg doses displayed 25% and 59% increases in trabecular bone volume, respectively, and 27% and 62% increases in mineralized bone volume, respectively. Treated females also exhibited a 52% decrease in osteoclast surface and a 30-47% dose-dependent reduction in osteoclast number. Male mice treated with 200 and 1800 mg/kg showed increases in bone mass of 17% and 38%, respectively, and an increase in osteoblastic surface of 131% was noted in all treated males. Strontium ranelate did not impair bone mineralization (*i.e.*, unaltered osteoid thickness) even at the highest dose tested (16, 17).

The safety and efficacy of long-term strontium ranelate (100, 275 or 750 mg/kg/day p.o. for 13 weeks and 200, 500 and 1250 mg/kg/day p.o. for 52 weeks) treatment was demonstrated *in vivo* in studies conducted in normal adult monkeys (*Macaca fascicularis*). Bone resorption was reduced by 20-60% depending on the duration of treatment and bone volume at the iliac increased (22% after 13 weeks). Strontium was dose-dependently taken up in compact and cancellous bone, with 3-4 times (at 13 weeks) and 1.7-2 times (at 52 weeks) higher uptake observed in new as compared to old bone. Marked reductions in strontium levels to almost one-half were observed in new bone at the end of a 6- or a 10-week recovery period. Treatment did not alter mineral crystal characteristics or the degree of bone mineralization (18-21).

A study using ovariectomized (OVX) rats as a model for osteoporosis examined the efficacy of strontium ranelate (77, 154 or 308 mg/kg/day p.o. for 60 days) as compared to 17β-estradiol injection (E2; 10 μg/kg/day for 60 days) in reducing bone resorption and maintaining bone formation. Untreated OVX rats displayed a significant loss of bone associated with high bone turnover (*e.g.*, 46% decrease in trabecular bone volume in the tibial metaphysis). Strontium ranelate-treated OVX rats exhibiting dose-dependent increases in plasma, urine

and bone strontium concentrations, had a significant increase in femoral bone mineral content and a 30-36% increase in trabecular bone volume as compared to untreated OVX rats. E_2 treatment corrected the OVX-induced decrease in trabecular bone. Strontium ranelate was also found to reduce histomorphometric indices of bone resorption (*i.e.*, osteoclast surface and number) to the levels of sham animals while osteoid surface, osteoblast surface, mineral apposition rate and bone formation rates were similar in untreated and treated OVX animals; osteocalcin and alkaline phosphatase levels remained elevated or were higher in treated OVX rats. In contrast, E_2 treatment decreased both bone resorption and formation and plasma osteocalcin and alkaline phosphatase to the levels observed in sham rats. Thus, strontium ranelate prevented femoral osteopenia and partially prevented trabecular bone loss in E_2-deficient rats through inhibition of bone resorption without decreasing bone formation (22).

Strontium ranelate (200 mg/kg p.o. pretreatment followed by 50, 200 or 800 mg/kg/day for 10 days) was also effective in another rat model of osteoporosis involving immobilization-induced (unilateral hind-limb immobilization for 10 days) bone loss in male rats. Treatment resulted in dose-dependent increases in bone ash weight and bone mineral content (48% with 800 mg/kg) of the immobilized limb as compared to untreated controls (23).

Distribution and Pharmacokinetics

The skeletal distribution of strontium was examined in rats, monkeys and humans following repeated administration of strontium ranelate. The strontium/calcium ratio was found to peak at about 4 weeks in rats and was higher in males than in females due to differences in absorption. Steady-state strontium plasma levels were achieved more quickly (about 10 days in rats). Plasma strontium levels highly correlated with bone strontium content. Differential distribution of strontium in bone was observed according to anatomical site, bone structure and type of bone (*e.g.*, higher content in cancellous and newly formed bone *vs.* cortical and old bone). In monkeys, lumbar vertebral strontium levels could be estimated from iliac crest bone biopsies. At the end of treatment, bone strontium levels decreased rapidly in monkeys. Incorporation of strontium in bone was found to be due to exchange onto the crystal surface and was dependent on duration of treatment, dose, gender and skeletal site (24).

The pharmacokinetics of strontium ranelate were examined in humans. The absolute bioavailability after an oral dose of 2 g was determined to be 27% (2.5% for ranelate acid). Gastrointestinal absorption appeared to involve two mechanisms: active absorption at low doses (less than 1 g) and passive absorption that is nonsaturable at higher doses. The bioavailability of strontium was reduced with concomitant calcium administration and with food intake. Thus, it was recommended that strontium ranelate be administered once daily at bedtime without concomitant calcium or food intake (6).

After repeated dosing with strontium ranelate (0.5-4 g/day p.o. for 25 days), steady-state levels for strontium and ranelic acid were achieved after 15 days. The accumulation ratios were 9.2 ± 3.9 and 5.1 ± 3.4, respectively. The C_{max} and C_{min} of strontium were 20 ± 2.3 and 16.2 ± 3 (in the AM) mg/l, respectively, after 25 days of treatment with 2 g b.i.d strontium ranelate; C_{max} and C_{min} values for ranelic acid were 0.79 ± 0.36 and 0.65 ± 0.42 mg/l, respectively. Renal clearance was responsible for 57% of the total clearance of strontium (12 ml/min) and 80% of the total clearance of ranelic acid (78 ml/min). In postmenopausal women, chronic administration of strontium ranelate resulted in stable plasma levels of strontium at 3-24 months and dose-dependent bone strontium/calcium ratios. The $t_{1/2}$ values for strontium and ranelic acid were 6.3 ± 2.7 and 3.3 ± 2.3 days, respectively, in postmenopausal women (6).

Clinical Studies

Strontium ranelate (0.125, 0.5 or 1 g/day p.o. for 2 years) prevented early postmenopausal bone loss in the randomized, double-blind, placebo-controlled, dose-ranging Prevention of Osteoporosis (PREVOS) trial involving 160 healthy early postmenopausal women (lumbar BMD = 0.91 ± 0.14 g/cm^2) who also received calcium (500 mg/day) supplementation. Treatment was well tolerated. Significant increases in adjusted lumbar BMD (0.66% *vs.* –0.5% annual increase; overall benefit with 1 g = 2.4% increase) and in femoral neck (2.46%) and total hip BMD (3.21%) were observed at 24 months in the 1 g strontium ranelate group as compared to placebo. In addition, the group receiving 1 g strontium ranelate exhibited significant increases in serum bone alkaline phosphatase throughout the treatment period, with significant increases observed at 18 months as compared to placebo. No changes in bone resorption markers (*i.e.*, urinary cross-linked N- or C-terminal telopeptide of type I collagen [NTX and CTX, respectively]) were observed. It was concluded that a 1 g/day dose of strontium ranelate is the minimum dose required to prevent bone loss in this subject population (25). The results of this clinical study and those that follow are summarized in Table I.

The safety and efficacy of strontium ranelate (0.5, 1 or 2 g/day p.o. for 2 years) were demonstrated in the Strontium Ranelate for Treatment of Osteoporosis (STRATOS) trial, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-year phase II trial involving 353 osteoporotic postmenopausal women (66 ± 7 years; lumbar BMD = 0.699 ± 0.10 g/cm^2) with at least 1 previous vertebral fracture and a lumbar T-score of less than –2.4. Patients received supplementary calcium (500 mg/day) and vitamin D_3 (800 IU/day). Treatment was well tolerated. The majority of adverse events reported were mild or moderate, with no differences in incidence seen between placebo and treated groups. No significant

Table I: Clinical studies of strontium ranelate in postmenopausal osteoporosis (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Randomized, double-blind	Strontium ranelate, 125 mg po od + Calcium, 500 mg po od x 2 y (n=40) Strontium ranelate, 500 mg po od + Calcium, 500 mg po od x 2 y (n=40) Strontium ranelate, 1000 mg po od + Calcium, 500 mg po od x 2 y (n=40) Placebo + Calcium, 500 mg po od x 2 y (n=40)	160	An oral daily dose of 1 g of strontium ranelate was well tolerated and more effective than placebo in increasing bone mineral density in early postmenopausal women	25
Randomized, double-blind, multicenter	Strontium ranelate, 250 mg po bid + Calcium, 500 mg po od + Vitamin D, 800 IU od x 2 y (n=85) Strontium ranelate, 500 mg po bid + Calcium, 500 mg po od + Vitamin D, 800 IU od x 2 y (n=90) Strontium ranelate, 1000 mg po bid + Calcium, 500 mg po od + Vitamin D, 800 IU od x 2 y (n=87) Placebo + Calcium, 500 mg po od + Vitamin D, 800 IU od x 2 y (n=91)	353	Strontium ranelate increased vertebral bone mineral density and reduced the incidence of vertebral fractures. All the tested doses were well tolerated, although the 2-g daily dose offered the best efficacy	26
	Strontium ranelate, 0.5 g/d po x 2 y + Calcium-Vitamin D supplements (n=6) Strontium ranelate, 1 g/d po x 2 y + Calcium-Vitamin D supplements (n=6) Strontium ranelate, 2 g/d po x 2 y + Calcium-Vitamin D supplements (n=8) Placebo + Calcium-Vitamin D supplements (n=7)	27	Strontium ranelate was dose-dependently incorporated into new bone without altering bone mineralization in postmenopausal women with osteoporosis	27
Open, multicenter	Strontium ranelate x 101 d [mean]	9196	Conducting a short-term study with strontium ranelate in osteoporosis optimized the inclusion/exclusion criteria and avoided the inclusion of patients most likely to withdraw prematurely, therefore increasing the quality of future long-term clinical trials	28
Randomized, double-blind, multicenter	Strontiu ranelate, 2 g po od + Calcium od + Vitamin D od x 3 y Placebo + Calcium od + Vitamin D od x 3 y	1649	Strontium ranelate administered once daily was well tolerated and reduced the risk of vertebral fractures in postmenopausal women with osteoporosis	29
Randomized, double-blind, multicenter	Strontium ranelate, 2 g po od + Calcium od + Vitamin D od x 3 y Placebo + Calcium od + Vitamin D od x 3 y	1240	Daily administration of strontium ranelate was effective in preventing a reduction in health-related quality of life associated with incidental vertebral fractures in postmenopausal women	30
Randomized, double-blind, multicenter	Strontium ranelate, 2 g po od + Calcium od + Vitamin D od x 3 y Placebo + Calcium od + Vitamin D od x 3 y	5091	Strontium ranelate administered once daily for 3 years was well tolerated and effective in reducing the risk of hip fractures in postmenopausal women with osteoporosis	31

changes in laboratory parameters were observed, with the exception of significantly increased musculoskeletal creatinine phosphokinase activity in patients treated with the 1 and 2 g doses of strontium ranelate. However, the increase was moderate and transient A dose-dependent increase in lumbar BMD (adjusted for strontium content) was observed in the intent-to-treat population; the mean annual slope was significantly increased over placebo, from 1.4% with 0.5 g to 3% with 2 g strontium ranelate. In the second year of treatment, significantly fewer patients treated with 2 g strontium ranelate experienced new vertebral deformities as compared to placebo and other treatment groups. A significant increase in serum bone alkaline phosphatase and a significant reduction in urinary NTX were seen in patients treated with the 2 g dose of strontium ranelate. Analysis of transiliac bone biopsies revealed that strontium ranelate was dose-dependently incorporated into compact and cancellous bone with a significantly higher content found in new bone. The degree of bone mineralization was similar in placebo and all treatment groups. From the results of this trial, it was concluded that 2 g of strontium ranelate was safe and the most effective dose (26, 27).

Phase III development has also shown the efficacy and safety of oral strontium ranelate as a treatment for osteoporosis in postmenopausal women. Two multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III trials (Spinal Osteoporosis Therapeutic Intervention [SOTI] and Treatment of Peripheral Osteoporosis [TROPOS] trials) have been conducted. The subjects involved in these trials first participated in the Fracture International Run-in Strontium Trials (FIRST) in which calcium and vitamin D supplementation was normalized and noneligible patients or those likely to discontinue prematurely (for compliance or adverse events) were excluded (28).

The 3-year SOTI trial involved 1,649 postmenopausal women (69.7 ± 7.3 years) with vertebral osteoporosis (lumbar BMD = 0.73 ± 0.12 g/cm^2) of whom 27.5% had vertebral prevalent fracture. Patients were randomized to receive either placebo or 2 g/day strontium ranelate p.o. and daily calcium and vitamin D supplementation. Treatment was well tolerated with no significant adverse events observed. A significant 41% reduction in the relative risk of vertebral fracture was observed over the entire experimental period in the intent-to-treat population as compared to placebo (139 *vs.* 222 patients with new fractures); this effect was rapid since a significant 49% reduction was observed after the first year. Significant increases in bone specific alkaline phosphatase, reductions in CTX and increases in lumbar BMD (11.4% *vs.* –1.3%) were observed in the strontium ranelate-treated group. The SF36 questionnaire and a specific module QUALIOST were completed every 6 months by a subset of patients (n=1,240) involved in this trial. Analysis of scores indicated a significant improvement in health-related quality of life in patients who had not experienced a new fracture as compared to patients who had, regardless of whether the patient was treated with placebo or the agent. Further analysis indicated that treatment with strontium ranelate prevented additional reductions in health-related quality of life associated with vertebral fractures (29, 30).

The TROPOS trial involving 5,091 women with postmenopausal osteoporosis also given calcium and vitamin D supplementation examined the efficacy and safety of strontium ranelate (2 g/day p.o. for 3 years) in preventing nonvetebral fractures. Treatment was well tolerated with no significant adverse events observed. A significant reduction in the relative risk of experiencing a first nonvetebral fracture was observed in the strontium ranelate-treated group throughout the 3 years as compared to placebo. Moreover, a 41% reduction in the relative risk of experiencing a hip fracture was seen at 18 months (31).

Strontium ranelate continues to undergo phase III development as a treatment for osteoporosis (32).

Source

Servier Laboratoires (FR).

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