Horák et al. J Rheum Dis Treat 2017, 3:050
DOI: 10.23937/2469-5726/1510050
Volume 3 | Issue 2

Journal of
Rheumatic Diseases and Treatment

ISSN: 2469-5726 Review Article: Open Access

Role of Strontium Ranelate in the Therapy of Osteoporosis

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Abstract

Strontium ranelate is a medicine used to treat postmenopausal osteoporosis in women and osteoporosis in men. Preclinical data suggest its dual effect consisting of the control of bone resorption and promotion of bone formation. Administration of strontium ranelate leads to significant increase in the bone mass. Changes in bone density can be used to evaluate the adherence of patients as well as, in case of strontium ranelate, to estimate the fracture risk reduction. Clinical studies demonstrated its effect on reducing the risk of both vertebral and non-vertebral fractures, including fractures of the proximal femur. Currently, it is a second-line treatment of osteoporosis administered in case of intolerance, failure or contraindication of other therapy. Recently its cardiovascular safety was discussed. Contraindications of strontium ranelate in patients with ischemic heart disease, peripheral arterial disease, cerebrovascular disease or uncontrolled hypertension were added in 2013 to the wording of the Summary of Product Characteristics (SPC). Cohort and observational studies, however, did not clearly confirm the cardiovascular risk associated with administration of strontium ranelate. It is still a medicine indicated for treatment of osteoporosis with a favourable risk and benefit ratio.

Keywords

Osteoporosis, Therapy, Strontium ranelate, Efficacy, Safety

Introduction

Postmenopausal osteoporosis is a condition associated with a significant increase in the risk of fractures. Fractures associated with postmenopausal osteoporosis have a profound and debilitating effect on the quality of life of patients and may significantly reduce years of life. This can have an economic impact. The main goal of osteoporosis treatment is primary and secondary prevention of fractures. Indications for therapeutic interventions in osteoporosis should be derived from the determination of the absolute risk of fracture [1], which takes into account the evaluation of selected risk factors and bone density. The European recommendations for the diagnosis and treatment of osteoporosis [2] propose a rational use of bone mineral density, fracture risk assessment for proper prevention and indication of pharmacotherapy for postmenopausal osteoporosis and therapy monitoring. Particular attention should be given to women and men with a recent history of fractures, including fractures of the femoral neck.

The most common cause of osteoporosis in women is the decrease of the oestrogen levels during menopause, leading to a significant increase in bone mass turnover and subsequent imbalance between bone formation and resorption with increased bone loss and deterioration of bone structure and strength. In therapy anti-catabolic agents (such as bisphosphonates, denosumab, selective oestrogen receptor modulators, oestrogens) can be used which reduce bone resorption while reducing bone formation. The final effect is to preserve the bone microarchitecture and strength and reduce the fracture incidence. An alternative to this option is intermittent administration of parathyroid hormone derivatives, which act as a very strong osteoanabolic product increasing the bone formation over bone resorption, which again leads to a positive bone balance, improvement of bone structure and reduction of the risk of fractures. The third therapeutic approach is the medicine, which simultaneously increases bone formation and decreases bone resorption. Currently, the only medicine in this category which can be considered is strontium ranelate, consisting of the organic component (ranelic acid) with

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Citation: Horák P, Skácelová M, Kazi A (2017) Role of Strontium Ranelate in the Therapy of Osteoporosis. J Rheum Dis Treat 3:050. doi.org/10.23937/2469-5726/1510050

Received: October 13, 2016: **Accepted:** February 27, 2017: **Published:** March 01, 2017

two strontium atoms attached to it. Preclinical studies demonstrated that strontium ranelate has the synergistic ability to increase bone forming osteoblastic activity whilst reducing bone resorbing osteoclastic activity. The article provides an overview of its mechanism of action, effects on bone mineral density, bone turnover markers, strength and bone mineralization as well as summarises the clinical effectiveness in reducing the risk of osteoporotic fractures. Finally, the article also focuses on the safety of the medicine.

Mechanism of Action

There is evidence for dual biological and pleiotropic mechanism of action of strontium ranelate-receptor-mediated effects on CaSR (calcium-sensing receptor) and apparently also on Cn/NFATc (calcineurin/nuclear factor of T cells) or GPRC6A receptor (G protein coupled receptor 6A) [3]. Calcium-sensing receptor (CaSR) is present in a variety of cells, including osteoclasts and osteoblasts. According to several studies, CaSR was shown to be of importance in osteoblast proliferation [4].

Anti-resorptive effect of the SrR indicates osteoclast cytoskeleton disruption, increased apoptosis, reduction of their activity or reduction of the levels of RANKL demonstrated in both cell models-animal [5-9] and human [10,11].

The research also demonstrated the regulatory mechanisms of SrR on osteoblasts, including an increase in proliferative activity, reduction in apoptosis and increase in the production of biochemical markers of bone formation. [3,12-14]. Furthermore, experimental tests on laboratory animals demonstrated formation of a normally mineralized, quality and strong bone [15-17] upon exposure to SrR.

Moreover, upon administration of Strontium ranelate in ovariectomized mice at a dose similar to the serum concentration in humans, a marked increase in bone strength and an influence on bone resistance was seen [18].

The dose administered has a close association with the effect on bone formation. For example, a study of Fuchs, et al. [19] illustrated that when using a dose with a six-fold decrease than the clinically effective level of SrR, no required bone forming effects were seen.

Effects on bone mineral density (BMD) in postmenopausal women and men with osteoporosis

Use of SrR in clinical studies consistently demonstrates a strong effect particularly on bone mineral density (BMD). When compared with a placebo, the three-year administration of SrR in postmenopausal women led to an increase in BMD in the lumbar spine by 14.4%, in the femoral neck by 8.3% [20,21]. Similar results were also obtained when the medicine was used for therapy of osteoporosis in men [22].

Strontium ranelate is deposited with high affinity in the predilection areas of new bone formation, where it replaces some of the calcium atoms in the molecules hydroxyapatite. With time, the concentration in bone stabilises at about 1.6 to 1.8% [23], wherein there is up to 20% increase in bone density at the lumbar spine after eight-year exposure [24]. Prolonged administration of SrR is associated with a continuously progressive effect on bone density without achieving a plateau trend [24]. High BMD changes enable effective use of DEXA measurements for monitoring treatment efficacy and patient adherence. There is an association between increase of uncorrected BMD and reduction of the risk of fractures [25]. Use of conversion coefficients for the content of strontium in the skeleton is problematic, has no practical significance, and currently it is not recommended [23,25].

Effect on remodelling markers associated with strontium ranelate therapy

Studies of indicators of bone mass also showed data suggesting a dual effect of the SrR on bone metabolism. The registration trials in large population of patients showed a significant effect of SrR administration on lowering the levels of the resorption marker C terminal telopeptide of collagen (CTX) as well as increasing the activity of bone specific fraction of the alkaline phosphatase (bALP) [20].

Another study indicated a proportional effect on other markers of bone turnover, including bone formation marker P1CP, and bone resorption marker N-terminal telopeptide of collagen (uNTX) [26,27], showing an increased rate of bone formation combined with a reduced rate of resorption.

The extent to which the dual effect of strontium ranelate is evident from preclinical studies on the medicine of the bone density, strength, microarchitecture and reduction of the risk of fractures may still be in question. Comparitively, a change of the bone indicators is noticeably less pronounced than in the case of anti-catabolic or osteoanabolic medicines, however it is significant and consistent and cumulative amplitude (about 20-25%) between indicators of resorption and formation is apparently sufficient to induce a positive balance of bone remodelling [11].

Bone microarchitecture and effect on biomechanics of bone

The effect of SrR on bone microarchitecture was studied in several studies using a variety of different methods. Histomorphometry and analysis using three-dimensional microCT of biopsy samples (μCT) in bone biopsies obtained under registration studies showed an improvement of bone microarchitecture on the level of the trabeculae by increasing their number (+14%), reducing the number of interruptions (-16%), improving the structural model index

of trabecular bone of 22% and ultimately increasing the cortical bone thickness (+18%) [28].

In a comparative study with alendronate using a non-invasive method of high-resolution peripheral computed tomography (HR-pQCT), administration of SrR resulted in a significant improvement of bone microarchitecture (increase in the thickness of cortical bone and volume of trabecular bone) and an increase in the burden necessary for failure (failure load) [29].

The biopsy comparative study with alendronate showed higher parameters of bone formation in the SrR after 6 and 12 months of treatment with preserved parameters of bone mineralization [30]. In another study, using nanoindentation, SrR significantly increased elastic modulus of cortical bone, hardness and work energy, leading to greater resistance of the bone [31].

Clinical efficacy

Two large five-year registration studies in different populations of postmenopausal women-Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS) were conducted. For five years, both studies were placebo controlled and blinded. The main analysis was carried out after three years. Both studies were followed by a five-year open extension study, allowing a 10-year data collection for the various clinical parameters. In both of these studies, the patients took 2 g of SrR or placebo along with the substitution of calcium and vitamin D [20,21].

Effectiveness in the reduction of the risk of vertebral fractures

SOTI study was aimed to confirm the efficacy and tolerability of strontium ranelate therapy. The primary endpoint was the reduction in the relative risk of new vertebral fractures. The study included a total of 1,659 women older than 50 years. All patients had a history of vertebral fractures and BMD of the lumbar spine ≤ 0.840 g/cm^2. In the first year the risk of new vertebral fractures decreased by 49%, after 3 years of treatment it decreased by 41%. The risk of new clinical manifesting vertebral fractures decreased after a year by 52%, within three years by 38% [20].

TROPOS study included 5,091 postmenopausal women over 74 years of age or between the ages of 70 and 74 years with one additional risk factor and femoral neck BMD ≤ 0.600 g/cm^2. The primary endpoint was to evaluate the reduction in the relative risk of peripheral fractures over 3 years; vertebral fractures were evaluated as a secondary parameter. The relative risk of vertebral fracture was reduced after a year of treatment by 45%, over 3 years by 39% [21].

Effectiveness in the reduction of the risk of non-vertebral fractures

Data on the effectiveness of the SrR in the reduction of the risk of non-vertebral fractures comes from the previously mentioned TROPOS trial, with emphasis on studying older-aged postmenopausal women with a high risk of fractures. The risk of non-vertebral fractures was reduced by 16%. Fractures of the proximal femur were analysed separately in a high-risk population of patients over 74 years with femoral neck T score ≤ 3.0SD. During three years of follow-up of this subgroup (n = 1.977), the incidence of proximal femur fractures versus placebo decreased by 36% [21].

Long-term efficacy

Efficacy of SrR to reduce the risk of vertebral, non-vertebral fractures and fractures of the proximal femur was evident even after five years of TROPOS study showing 24%, 15% and 43% reduction in risk, respectively [32].

The population treated with SrR for 10 years consisted of 237 women from an extension of the SOTI and TROPOS studies. The incidence of vertebral and non-vertebral fractures was comparable to that in the first five years and was significantly lower than in the placebo group with corresponding risk score at the baseline. The relative risk of vertebral and non-vertebral fractures was reduced by 35% and 38% respectively [33].

Efficacy in a broad spectrum of patients, including male population

Analysis of SOTI and TROPOS studies provided a range of complementary data that suggest the effect of SrR in a broad spectrum of postmenopausal women with osteoporosis [34]. Strontium ranelate was effective regardless of the number of previous vertebral fractures [35], and age, for patients younger and older than 80 years [36]. The medicine was also effective in the group with and without a frailty syndrome, which is a geriatric syndrome that explains a higher risk and general decline in health condition and function with age and was defined by Fried, et al. [37]. Data from SOTI also showed the positive effect on the pain associated with administration of SrR, which increased the number of patients without spinal pain in the first year of use [38] and limited the progression of thoracic kyphosis [35]. The Male Osteoporosis Study (MALEO) evaluated the effect of the two-year therapy with SrR in men with osteoporosis (n = 261) [22]. The primary outcome was the assessment of bone density, which increased significantly in the area of the lumbar spine and proximal femur similar to postmenopausal women. In terms of fracture incidence, a trend towards reduction of vertebral and non-vertebral fractures during the therapy with SrR was observed. Given the number of subjects and relatively low incidence of fractures, however, the study was underpowered to demonstrate a statistically significant association between the medicine and the fractures.

Use of strontium ranelate after previous therapy of osteoporosis

Currently, after 3-5 years of treatment with bisphos-

phonates it is recommended to consider the benefit risk ratio of the continued therapy especially in view of the possible negative impact of these products on bone turnover and the resulting risk of osteonecrosis of the jaw and atypical fractures. A study evaluating the effect of administration of the SrR after previous treatment with bisphosphonates showed a significant increase in bone density in the spine and proximal femur. This increase, however, is significantly lower than in patients without prior exposure to bisphosphonates [39,40]. After previous treatment with bisphosphonates, SrR administration leads to increased bone formation (increase of bALP); the bone resorption does not significantly decrease probably due to the long-term persistence of anti-resorption effect of the bisphosphonates. Paired bone biopsies from patients previously treated with bisphosphonates at baseline and after a year of therapy with SrR showed significant increase of bone volume (30.4%), increased thickness of the beams (10.4%), and their connectivity (48%) [41]. These changes were associated with an increase in the number of osteoblasts and increased surface area and volume of the osteoma suggestive of newly formed bone together with persistently low bone resorption. Trabecular bone architecture, significantly impaired in a patient after 89 months of treatment with bisphosphonates showed significant improvement after administration of the SrR [42] especially due to increased connectivity index and rebuilding of trabecular bone from the thin rod-like beams to more resistant plate-like beams. There are also data on the effect of SrR after previous treatment with teriparatide, which have not yet been published (personal communication).

Safety

The safety data were derived from studies of osteoporosis or osteoarthritis, from the post-marketing surveillance and from cohort and observational studies. Common side effects of SrR include gastrointestinal disorders (nausea, constipation, diarrhoea, flatulence) which are mostly minor. In connection with therapy of osteoporosis with strontium ranelate, a higher incidence of thromboembolic disease in some patient cohorts was observed. A history of an episode of venous thromboembolism, as well as temporary or permanent immobilisation of the patient is the contraindication to administration of the SrR. In post-marketing surveillance a very rare incidence of skin reactions was reported such as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Cardiovascular safety

In the last two years there has been considerable debate around the issue of cardiovascular safety. This was due to a report of the European Pharmacovigilance Committee of November 2012 [43], which drew attention to a numerically higher incidence of myocardial infarction associated with therapy with SrR. A subsequent analysis of clinical studies (two phase II studies and five phase III studies) involving over 7,000 women with postmenopausal osteoporosis showed a higher incidence of nonfatal myocardial infarction associated with the use of SrR (1.7% versus 1.1% for placebo). The study did not show higher cardiovascular mortality [44]. The only significant risk factor of myocardial infarction interfering with the administration of SrR was diastolic blood pressure (< 90/≥ 90 mmHg), $p = 0.014$, but not age, body mass index, diabetes mellitus, dyslipidemia, or history of smoking. Exclusion of patients diagnosed with coronary heart disease, cerebrovascular disease or peripheral atherosclerosis from the analysis showed a risk of MI associated with administration of SrR comparable to placebo. The incidence of ischemic events in this population was even numerically lower than in placebo (3.9 vs. 4.7) [44]. On the other hand, the 36-month cohort study in 12,046 patients treated with SrR did not show any increased risk of cardiovascular events, while 30% of participants had hypertension and 16% dyslipidemia [45]. Three large observational studies (1 in the UK, 2 in Denmark) were performed using an analysis of electronic records of health insurance companies. None of them, however, found an increased incidence of coronary heart disease in patients treated with SrR [46-48].

This discussion and partly contradictory findings led, from the safety point, to the introduction of new contraindications to the use of SrR, which included ischemic heart disease, peripheral arterial disease, cerebrovascular disease and untreated hypertension [49].

Conclusion

According to the current version of the Summary of Product Characteristics, strontium ranelate remains an effective and viable pharmacological option in the prevention of vertebral and femoral neck fractures in postmenopausal women and adult men with osteoporosis, in terms of indications, contraindications and careful evaluation of its effects and risks. It represents an alternative to anti-resorptive medicines in case of contraindication, intolerance or failure. It is also a therapeutic option after a long-term treatment with bisphosphonates, denosumab or teriparatide, when additional therapy with these agents is not possible or appropriate. Its remarkable and noticeable effects on bone density, bone strength, bone microarchitecture and reduction of the risk of fractures, together with the results of further research in osteoarthritis, fracture healing and dental implants could in the future lead to extending its indications both in therapy of osteoporosis as well as some other diagnoses.

Funding

Supported by grant IGA_LF_2016-014 and 2017_015.

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