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Long-term treatment of postmenopausal osteoporosis with strontium ranelate: Results at 8 years

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ABSTRACT

Objectives: Strontium ranelate 2 g/day has proven efficacy against vertebral and nonvertebral fracture over 5 years in postmenopausal osteoporosis, though many women require longer-term treatment. This article describes the efficacy, safety, and tolerability of this agent over 8 years.
Methods: Postmenopausal osteoporotic women having participated in the 5-year efficacy trials SOTI and TROPOS were invited to enter a 3-year open-label extension study. The results presented here focus on patients who received strontium ranelate for 8 years.
Results: At the extension baseline, the population treated for 8 years ($n = 879$; 79.1 ± 5.6 years) had femoral neck T-score of -2.61 ± 0.71. The cumulative incidences of new vertebral and nonvertebral fractures (13.7% and 12.0%, respectively) over years 6 to 8 were non-statistically different from the cumulative incidences in the first 3 years of the original studies (11.5% and 9.6%). Lumbar spine, femoral neck, and total hip bone mineral density (BMD) increased throughout the 8-year period. Annual relative change in BMD was significant at every visit, except the 8-year visit for femoral neck and total hip BMD. Strontium ranelate was safe and well tolerated over 8 years.
Conclusions: Long-term treatment with strontium ranelate 2 g/day in postmenopausal osteoporotic women leads to continued increases in BMD at all sites. The data also provide some evidence for a sustained antifracture efficacy.

Introduction

Postmenopausal osteoporosis is a chronic disease requiring long-term management. Most antiosteoporotic treatments have been tested in 3- to 5-year studies, though the optimal treatment duration may be much longer [1]. It is therefore vital to assess the long-term safety and efficacy of antiosteoporotic agents. To date, only three antiosteoporotic drugs have published long-term (beyond 5 years) follow-up data. The antifracture efficacy trials for the bisphosphonates risedronate [2] and alendronate [3] were extended to 7 and 10 years, respectively, while the selective estrogen receptor modulator raloxifene has been evaluated over 8 years [4]. These studies demonstrated continued gains in bone mineral density (BMD), and maintenance of safety profiles, but remained inconclusive regarding long-term antifracture efficacy. Additionally, a 5-year re-randomized double-blind trial (FLEX) conducted in patients assigned to alendronate in the FIT trial demonstrated that women who discontinued alendronate for 5 years showed a moderate decline in BMD but no higher fracture risk other than clinical vertebral fractures [5].

Strontium ranelate is an oral antiosteoporotic drug that has been shown to increase bone formation *in vitro*, enhancing pre-osteoblastic cell replication and osteoblastic differentiation and decreasing abilities of osteoblasts to induce osteoclastogenesis via the calcium sensing receptor and an increase in the OPG/RANKL ratio [6,7]. Independently from these effects on osteoblasts, strontium ranelate decreases bone resorption by inhibition of osteoclast resorbing activity and osteoclastic differentiation [8]. This dual mode of action of strontium ranelate [9,10] results in a rebalance in bone turnover, and therefore in an improvement of bone microarchitecture and strength [11]. Results on iliac crest bone biopsies in postmenopausal osteoporotic women from a phase III study have demonstrated some improvement of both trabecular and cortical bone microstructure after 3 years of treatment [12]. Oral administration of strontium ranelate 2 g/day to postmenopausal osteoporotic women significantly reduces the risk of new vertebral fracture as demonstrated in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial [13]. In the

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TReatment Of Peripheral Osteoporosis Study (TROPOS), strontium ranelate significantly reduced the risk of vertebral, nonvertebral, and hip fracture in patients at risk with parallel increases in BMD [14–16]. The populations of SOTI and TROPOS having completed the 5-year double-blind phase were invited to enter a 3-year, open-label, extension phase to analyze the long-term effect of the drug on fracture risk, BMD, and safety. Results described here focus on the subgroup of patients treated with strontium ranelate from the beginning of the initial trials.

Materials and methods

Study design and population

The population for this open-label extension study was pooled from the treatment arms of SOTI and TROPOS (study design in Fig. 1) [13,14,17].

Main analyses of SOTI and TROPOS were performed over 3 years [13,14]. Data for patients in the treatment arms at 3 years are presented here for the purposes of comparison. Details of this population have been described elsewhere [18]. The double-blind, placebo-controlled phases of both trials lasted for 5 years. Patients were thus invited to participate in a 3-year, open-label extension, in which they were to receive treatment with strontium ranelate 2 g/day (Fig. 1). The criteria for entering the extension study was participation in SOTI or TROPOS for 5 years, or interruption of study treatment or withdrawal within the 6-month period preceding the 5-year visit. Only results in patients continuously treated with strontium ranelate over the whole follow-up period will be presented here.

Incidence of fracture

Procedures used to measure fracture are described in the original reports [13,14]. Clinical peripheral fractures were assessed throughout the study according to radiological evaluation and written documentation (radiological report, hospitalization report) [14]. Fractures of skull, jaw, coccyx, phalanx (fingers and toes), ankle, cervical and thoracic vertebrae (C1 to T4), and of posterior arches of the vertebra were not considered as osteoporosis-related fractures and were excluded from the analysis.

Spinal X-rays were recorded at inclusion and then yearly in all patients recruited from SOTI and TROPOS, according to standardized procedures enabling proper visualization of vertebrae from T4 to L5 [13]. Spinal X-rays were read centrally and incident vertebral fracture detected by semi-quantitative assessment and grading, according to the method of Genant [19]. During the extension study, new fracture was defined as the occurrence of a new vertebral, nonvertebral, or hip fracture during the 3-year extension, regardless of the occurrence of fracture during the main analyses of SOTI and TROPOS.

Bone mineral density

BMD was measured by dual energy X-ray absorptiometry (DXA, Hologic) at lumbar spine, femoral neck, and total hip at entry to the extension study and yearly thereafter. Acquisition and quality control programs were the same as those applied during the original studies [13,14,20].

Safety, tolerability, and compliance

Adverse events were recorded at each 6-month visit. Compliance was also assessed every 6 months by counting the number of sachets returned by the patient.

Statistical analysis

The full analysis set (FAS) was defined as patients having taken ≥ 1 sachet of strontium ranelate after inclusion into the extension study, having at least one baseline and one post baseline lumbar spine L2–L4 BMD measurement, and at least one evaluation of fracture incidence. The efficacy and safety results presented here focus on the subgroup of patients continuously treated with strontium ranelate for up to 8 years.

The Kaplan–Meier method was used to estimate the cumulative incidences of patients with at least one new vertebral, nonvertebral, or any osteoporotic fracture over the first 3 years of SOTI and TROPOS and the 3 years of the extension study in the subgroup of patients treated with strontium ranelate for up to 8 years.

BMD values are expressed as change and relative change from baseline to each visit and to the last value under treatment. Student *t* test for paired samples was used for within-group comparison of the progression of BMD with the previous year's value. *P* value ≤ 0.05 was considered significant.

The association between changes in BMD and fracture incidence in women treated with strontium ranelate was assessed through a logistic regression analysis after adjusting for covariates. Mann–Whitney test was used to compare changes in BMD after strontium ranelate in patients with and without new fractures.

Statistical analysis was performed using SAS/PC software version 8.2.

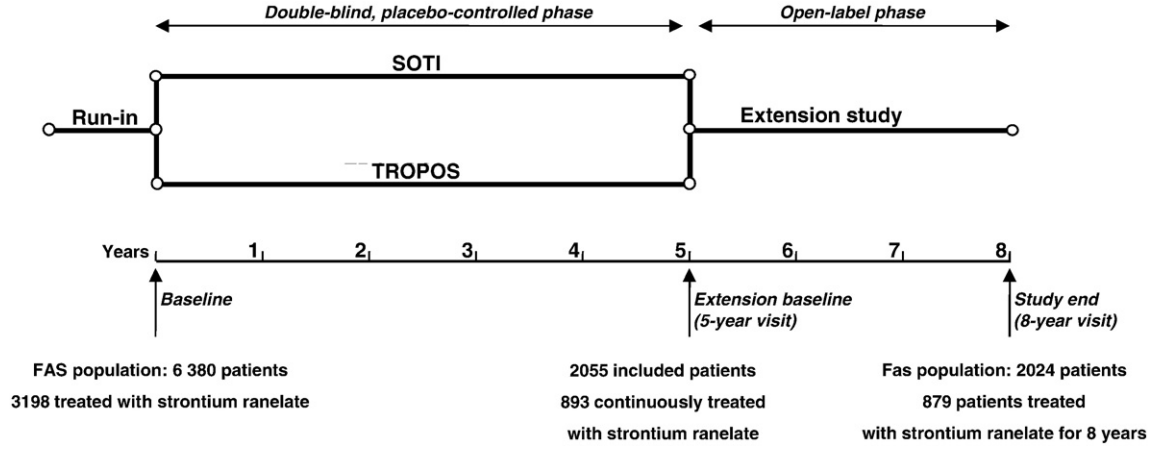

Fig. 1. Study design. Description of the pooled 8-year population from the SOTI and TROPOS studies receiving strontium ranelate 2 g/day. SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, TReatment Of Peripheral Osteoporosis Study.