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Review Article

A Review of Strontium Ranelate and Its Effect on DXA Scans

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Abstract

Strontium ranelate is a new orally administered agent for the treatment of women with postmenopausal osteoporosis that reduces the risk of vertebral and nonvertebral fractures. This review article examines the evidence for the antifracture efficacy and safety of strontium ranelate treatment and discusses the effect of DXA scans, biochemical markers of bone turnover, and bone histology. In the SOTI trial, three years treatment with strontium ranelate led to a 41% reduction in vertebral fracture risk (relative risk [RR] = 0.59; 95% CI: 0.48−0.73; $p < 0.001$), while in the TROPOS study there was a 16% reduction in nonvertebral fractures (RR = 0.84; 95% CI 0.702−0.995; p = 0.04). Compared with alternative osteoporosis therapies, strontium ranelate treated patients show large increases in BMD coupled with comparatively modest changes in biochemical markers of bone turnover and bone histology. While the large BMD changes provide a useful way of monitoring patients' response to treatment, it is important to appreciate that much of the increase is a purely physical effect due to the increased attenuation of X-ray when some of the calcium in bone is replaced by strontium. Strontium ranelate is a useful addition to the range of antifracture treatments available for treating postmenopausal women with osteoporosis and is the only treatment proven to be effective at preventing both vertebral and nonvertebral fractures in women aged 80 yr and older.

Key Words: Bone mineral density; fracture risk; osteoporosis; strontium ranelate; treatment.

Introduction

Strontium ranelate is a new orally administered agent for the treatment of osteoporosis licensed for use in Europe and several other countries, but not yet in the United States. Evidence for its antifracture efficacy comes from 2 large trials, the Spinal Osteoporosis Therapeutic Intervention (SOTI) *(1)* and Treatment of Peripheral Osteoporosis (TROPOS) *(2)* studies, which were designed to study vertebral and nonvertebral fractures, respectively. Additional clinical data about strontium ranelate, including its effect on bone mineral density (BMD) and biochemical markers of bone turnover, are provided by 2 smaller trials, the Strontium Ranelate for Treatment of Osteoporosis (STRATOS) *(3)* and Prevention of Osteoporosis (PREVOS) *(4)* studies. A number of patients from the SOTI, TROPOS, and STRATOS studies consented to have transiliac bone biopsies, and these have provided information on the effect of strontium ranelate on bone histology *(5)* and direct measurements of bone strontium content (BSC) *(6)*.

A new strontium compound, strontium malonate, is under development in Europe and is currently being studied in a phase 2 clinical trial *(7)*. In addition, the success of strontium ranelate as an osteoporosis treatment has encouraged a number of manufacturers of health supplements to offer products containing other forms of strontium (e.g., citrate or carbonate). However, these latter compounds are not subject to the stringent regulatory processes assessing efficacy, safety, tolerability, and bioavailability applicable to licensed medicines. Due to these uncertainties, the clinical use of unlicensed strontium compounds should be discouraged.

In this review, we examine the evidence for the antifracture efficacy of strontium ranelate and discuss its effect on dual-energy X-ray absorptiometry (DXA) scans, biochemical markers of bone turnover, and bone histology. As will be described below, compared with alternative osteoporosis

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treatments such as bisphosphonates (BPs) and selective estrogen-receptor modulators (SERMs), strontium ranelate–treated patients show large increases in BMD coupled with comparatively modest changes in biochemical markers and bone histology. Much of the BMD increase is due to the higher atomic number of strontium (Z = 38) compared with calcium (Z = 20). DXA scanners measure BMD through the increased attenuation of X-rays by the photoelectric effect, which varies as the third power of the atomic number ($\sim Z^3$). If 1% of calcium atoms in hydroxyapatite are replaced by strontium, BMD measurements are increased by 10% although the net mass of bone mineral increases by only 0.5% *(8,9)*. Therefore, if sufficient strontium is present in bone it can cause a clinically significant overestimation of BMD compared with the true mass of bone mineral that would be found by the conventional gold standard of bone densitometry, a bone ashing study *(10)*. There are no data presently available for the effects of strontium malonate or the strontium-containing health supplements on BMD.

Strontium has long been known to have strong affinity to bone with potential pharmacologic properties *(11,12)*. Strontium ranelate was chosen from among 20 different strontium compounds based on the bioavailability of strontium, gastric tolerability, and physicochemical characteristics *(13)*. Fig. 1 shows its chemical structure, which is composed of 2 atoms of stable strontium combined with organic ranelic acid. Strontium is the bone-active component and makes up 34% by weight of the whole molecule *(13)*, so each 2 g dose of strontium ranelate delivers 680 mg of elemental strontium. The daily dose comes as granules in a sachet that are suspended in water and taken at bedtime. The summary of product characteristics (SPC) *(14)* gives the gut absorption of strontium as 25%, a figure consistent with the findings of a recent meta-analysis *(15)*. As the absorption of strontium ranelate is competitive with calcium, calcium supplements should be taken at a different time of day to avoid reducing strontium absorption. Similarly, absorption is affected by food, milk, and milk derivatives, so that strontium ranelate should be taken at least 2 h after these products. The gut absorption of the ranelate anion is poor (2.5%), with the absorbed ranelic acid quickly excreted by glomerular filtration *(13,14)*.

Vertebral Fracture Efficacy

The 2 most important requirements of any osteoporosis treatment are its antifracture efficacy and safety. For strontium ranelate, these data come from the SOTI and TROPOS studies.

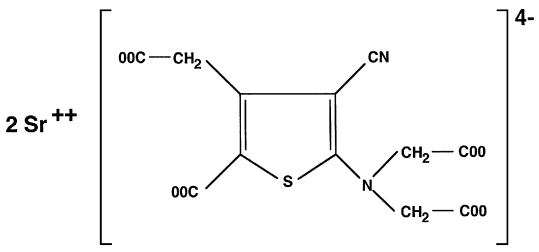

Fig. 1. Chemical structure of strontium ranelate.

The SOTI trial enrolled a total of 1649 women (mean age: 69 yr) who were randomized to receive either strontium ranelate 2 g/d or placebo *(1)*. All subjects were also given calcium and vitamin D supplements. The women were aged 50 yr and older, at least 5 yr postmenopausal, had at least 1 previous vertebral fracture and a Hologic spine BMD less than 0.840 g/cm^2 (equivalent to a T-score less than −1.9 on the Hologic reference range). Lateral spinal radiographs were performed annually and evaluated using the Genant semi-quantitative method *(16)*. At the end of the first year, there was a 49% lower risk of a new radiographic vertebral fracture in the strontium ranelate group compared with placebo (relative risk [RR] = 0.51; 95% confidence interval [CI]: 0.36–0.74; $p < 0.001$). The risk of a clinically symptomatic vertebral fracture was 52% lower (RR = 0.48; 95% CI: 0.29–0.80; $p = 0.003$). After 3 yr, the strontium group had a 41% lower risk of a new radiographic fracture (RR = 0.59; 95% CI: 0.48–0.73; $p < 0.001$), whereas the incidence of clinically symptomatic vertebral fractures was 38% lower (RR = 0.62; 95% CI: 0.47–0.83; $p < 0.001$). Recently the 4-yr data were reported and show a 33% reduction in radiographic vertebral fractures (RR = 0.67; 95% CI: 0.55–0.81; $p < 0.001$) *(17)*. The 1-, 3-, and 4-yr SOTI fracture data are summarized in Fig. 2A.

Further data on vertebral fracture prevention by strontium ranelate were provided by the TROPOS study *(2)*. Although not primarily intended to study vertebral fractures, 71% of the women in the TROPOS study had annual spinal radiographs, of which two thirds had no prevalent vertebral fracture at enrollment. Over 3 yr, the reduction in vertebral fracture risk was 39% (RR = 0.61; 95% CI: 0.51–0.73; $p < 0.001$; Fig. 2A) and was similar for patients with and without vertebral fractures at baseline. The recently reported 5-yr data showed a 24% reduction in vertebral fracture risk (RR = 0.76; 95% CI: 0.65–0.87; $p < 0.001$) *(17)*. Although both trials show an apparent decline in antifracture efficacy with longer durations of treatment (Fig. 2A), such a trend is expected because in Kaplan-Meier analyses *(18)*, patients are censored after their first fracture and with time, the remaining subjects become less well matched.

One interesting aspect of the SOTI and TROPOS studies was the advanced age of many of the subjects compared with many previous osteoporosis trials *(19)*. Taken together, 23% of the combined study populations were aged 80 yr or older at enrollment *(14)*. The pooled analysis for vertebral fracture risk showed no evidence of a treatment-by-age interaction ($p = 0.652$) *(20)*. In women older than 80 yr, strontium ranelate demonstrated a significant reduction of the RR of vertebral fractures by 59% ($p = 0.002$) over the first year of treatment and 32% ($p = 0.013$) over 3 yr *(19)*.

Nonvertebral Fracture Efficacy and Safety

The effectiveness of strontium ranelate in preventing nonvertebral fractures was studied in the TROPOS trial, a study