Continuous broad protection against osteoporotic fractures with strontium ranelate

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Among the available agents for osteoporosis, anti-resorptive drugs do not increase bone formation, whereas anabolic agents do not reduce bone resorption. Strontium ranelate (SR) uniquely does both, rebalancing bone turnover in favour of bone formation. In the Spinal Osteoporosis Therapeutic Intervention (SOTI) study, a 4-year trial, SR treatment reduced vertebral fracture risk by 33% ($P < 0.001$), and symptomatic vertebral fracture risk by 36% ($P < 0.001$). SR also significantly improved quality of life as assessed by the Quality-of-Life Questionnaire in Osteoporosis (QUALIOST) instrument. In the Treatment of Peripheral Osteoporosis Study (TROPOS) study, a 5-year trial, SR significantly reduced total fracture risk by 20% (29.1 *vs* 33.9%; $P < 0.001$), total non-vertebral fracture risk by 15% (18.6 *vs* 20.9%; $P = 0.032$) and hip fracture risk by 43% (7.2 *vs* 10.2%; $P = 0.036$) in the subgroup that is at high risk for hip fracture. Analysis of pooled data from these two studies found that SR is also safe and effective in patients aged ⩾80 years, reducing the risk of vertebral fracture over 5 years by 31% ($P = 0.010$) and non-vertebral fracture by 26% ($P = 0.019$). Adherence to treatment in the trials exceeded 80%, and the adverse event profile of SR was similar to that of placebo. Taken together, these long-term findings clearly demonstrate that SR is safe and effective in reducing both vertebral and non-vertebral (particularly hip) fracture risks for at least 5 years of pre-planned follow-up.

KEY WORDS: Vertebral fracture, Non-vertebral fracture, Hip fracture, Strontium ranelate, Bone.

Introduction

Osteoporosis, whose worldwide incidence is on the increase, is a disease with potentially devastating consequences. Approximately 1.6 million hip fractures occur every year, and this number is expected to reach 4.5–6.3 million in 2050. Mortality rates of 20–24% have been reported in the first year after a hip fracture, and 33% of these individuals are totally dependent or in a nursing home in the year following a hip fracture [1–3]. It is therefore essential that safe and effective treatments for osteoporosis are available. Menopause [4] is characterized by an increase in osteoclast activity, which markedly outweighs osteoblast activity [5], leading to an imbalance of bone remodelling in the direction of bone resorption. A range of therapies are available with proven reduction of vertebral fracture risk, some of them being demonstrated as effective on the secondary prevention of hip fractures [6–9]. Questions have been raised about adherence rates and long-term safety of all these agents [10].

Currently available anti-resorptive agents, such as bisphosphonates, first increase BMD by allowing the filling up of the remodelling space, then increase secondary mineralization of existing bone [11]; but they do not increase new bone formation. Anabolic agents, such as teriparatide, do increase new bone formation, but also stimulate bone resorption.

Strontium ranelate (SR) is a new oral treatment with a unique dual mode of action. *In vitro*, SR both reduces the bone resorption by osteoclasts and stimulates bone formation by osteoblasts [12, 13]; and in animal studies, it prevents bone loss and increases bone strength [14, 15]. In patients treated with SR, bone-specific alkaline phosphatase (a marker of bone formation) is increased, whereas C-telopeptide cross-link of type 1 collagen (a marker of bone resorption) is decreased compared with placebo [16]. This increase in bone-specific alkaline phosphatase and decrease in serum C-telopeptide cross-link of type 1 collagen were confirmed

over 4 years in the extension of the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial [17]. Thus, the net effect of SR is to balance bone remodelling in favour of bone formation [18]. The long-term clinical safety and efficacy of SR have been evaluated in two large multinational Phase III randomized clinical trials involving over 6000 postmenopausal women with osteoporosis.

Long-term efficacy of SR: reductions in fracture risk

The SOTI trial randomized 1649 postmenopausal women with osteoporosis and at least one confirmed prior osteoporosis-related vertebral fracture to receive either SR 2 g/day or placebo for 4 years. In this study, SR treatment reduced the risk of vertebral fracture by 33% ($P < 0.001$) and risk of symptomatic vertebral fracture by 36% ($P < 0.001$) after 4 years compared with placebo [17], continuing the pattern of the results seen at 3 years [16]. Non-vertebral fracture incidence was similar in the two groups [17].

The Treatment of Peripheral Osteoporosis Study (TROPOS) study, focusing on non-vertebral fractures, randomized 5091 postmenopausal women to receive either placebo or SR 2 g/day for 5 years. The findings of the TROPOS study at 5 years, which continues the pattern seen at 3 years [19], have recently been published [20]. Relative to placebo, at 5 years, SR significantly reduced total fracture risk by 20% (29.1 *vs* 33.9%; $P < 0.001$), the risk of total non-vertebral fracture by 15% (18.6 *vs* 20.9%; $P = 0.032$), the risk of major non-vertebral fracture by 18% (14.8 *vs* 16.9%; $P = 0.025$) and the risk of vertebral fracture by 24% (20.8 *vs* 24.9%; $P < 0.001$) [20]. The percentage of overall patients experiencing a hip fracture was 5.5% in the SR group and 5.9% in the placebo group. The risk of hip fracture was decreased by 43% (7.2 *vs* 10.2%; $P = 0.036$) in the 1128 patients at high risk for hip fracture.

Taken together, these long-term results from the SOTI and TROPOS trials clearly demonstrate the long-term efficacy of SR in reducing both vertebral and non-vertebral fracture risks. Notably, SR is the first osteoporosis treatment with efficacy over 5 years demonstrated in a pre-planned placebo-controlled clinical trial. A summary of 5-year data on fracture risk is shown in Fig. 1 [20, 21].

In comparison, bisphosphonates do not demonstrate the same benefits. In the Fracture Invention Trial 2, alendronate

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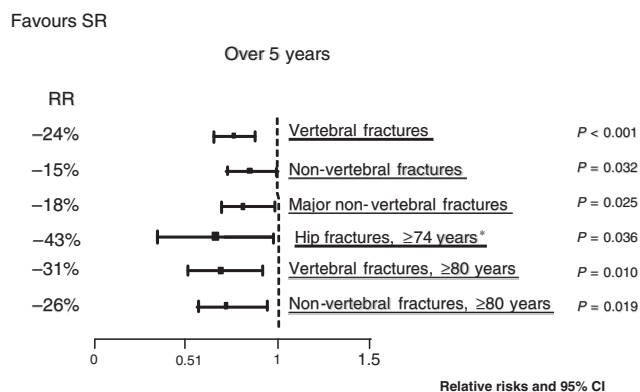E-mail: serge.ferrari@hcuge.ch

Favours SR

Over 5 years

RR

−24%	Vertebral fractures	$P < 0.001$
−15%	Non-vertebral fractures	$P = 0.032$
−18%	Major non-vertebral fractures	$P = 0.025$
−43%	Hip fractures, ≥74 years*	$P = 0.036$
−31%	Vertebral fractures, ≥80 years	$P = 0.010$
−26%	Non-vertebral fractures, ≥80 years	$P = 0.019$

0   0.51   1   1.5

Relative risks and 95% CI

FIG. 1. Efficacy of SR in reducing vertebral and non-vertebral fracture risk over 5 years. *Lumbar and femoral neck BMD T-score $\leqslant -2.4$. Adapted from Refs [20, 21].

significantly reduced the risk of vertebral fracture over 4 years by 44% and of clinical fracture (all kinds) by 36%. However, this result on clinical fractures was observed only in a subgroup of patients with established osteoporosis (T-score >2.5 S.D.). No reduction was observed among women with higher BMD [22]. Furthermore, there were no fracture data available with alendronate over 5 years.
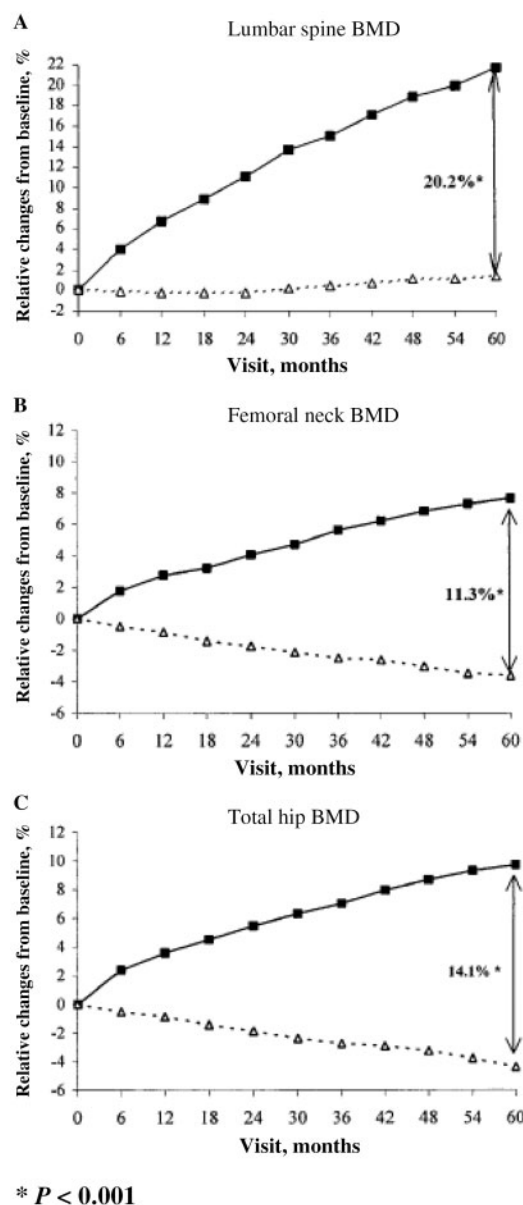
In a small extension study (265 patients) over 5 years of the Vertebral Efficacy With Risedronate Trial (VERT), risedronate significantly reduced the risk of new vertebral fracture by 59% in 4 and 5 years [23]. However, no effect on non-vertebral fractures with risedronate has been reported over 4 and 5 years [23]. Two other bisphosphonates available in most countries, ibandronate and zoledronate, have no long-term data.

A 12-month extension of the Multiple Outcomes of Raloxifene Evaluation (MORE) showed that the 4-year cumulative risk reduction for vertebral fractures was 36% with raloxifene 60 mg/day and 43% with raloxifene 120 mg/day. However, the non-vertebral fracture risk was not significantly reduced with raloxifene over 4 years [24]. No data are available for teriparatide over the long term (in fact, no data over >21 months of use).

Long-term efficacy of SR: improvement in BMD

After 4 years, patients in the SOTI trial who had received SR had increased BMD, whereas those in the placebo group lost BMD; the differences between SR and placebo groups had grown to 14.6% for lumbar spine BMD, 8.7% for femoral neck and 9.8% for total hip (all $P < 0.001$). At the 4-year point, subjects in the SOTI trial who had been receiving SR ($n = 572$) were re-randomized in a 1:1 ratio to either continue SR treatment ($n = 288$) or switch to placebo ($n = 284$) for the fifth year, and those who had been receiving placebo ($n = 577$) were started on SR. During this fifth year, lumbar spine BMD (the primary outcome variable for this phase of the study) increased by a mean of 1.2% ($P < 0.001$) in the continuous SR group and by 5.3% ($P < 0.001$) in the group that had switched from placebo to SR, but declined significantly by 3.2% ($P = 0.002$) in the group that had switched from SR to placebo. The former two groups did not differ significantly with respect to vertebral fracture incidence during the fifth year (6.9 *vs* 8.9%, respectively; $P = 0.463$). Furthermore, changes in BMD at the femoral neck and total hip followed a pattern similar to those for lumbar spine BMD [17].

It is known that strontium has an increased X-ray absorption compared with calcium, amplifying BMD measurement by ~50% [16, 25]. In the TROPOS study, BMD at the lumbar spine, femoral neck and total hip continued to increase throughout the 5-year study period in the SR group, but not the placebo group (Fig. 2).

A Lumbar spine BMD

20.2%*

Visit, months

B Femoral neck BMD

11.3%*

Visit, months

C Total hip BMD

14.1%*

Visit, months

* P < 0.001

FIG. 2. Evolution of BMD at lumbar spine, femoral neck and total hip in the TROPOS study (5-year data). Reproduced from Ref. [20] with permission of John Wiley & Sons. *$P < 0.001$.

During the last 2 years of the study, SR-treated patients increased their mean BMD by 4.9% at the lumbar spine, 1.8% at the femoral neck and 2% at the total hip relative to placebo (all $P < 0.001$), for total between-group differences over the 5-year study period of 20.2, 11.3 and 14.1%, respectively (all $P < 0.001$; Fig. 2) [20]. These data have a strong clinical implication, as increases in hip BMD produced by SR are directly correlated with clinical protection against vertebral and hip fractures [26].

Efficacy of SR treatment up to 8 years

After the 5-year double-blind study period had ended, the subjects in the TROPOS and SOTI study were offered inclusion in a 3-year open-label extension for a total follow-up of 8 years; 893 patients received SR for the entire 8-year period. During the 3-year open-label phase, lumbar BMD increased by a mean of 4.5% ($P < 0.001$); the increase over the whole 8-year interval was also significant ($P < 0.001$). The incidence of both vertebral and
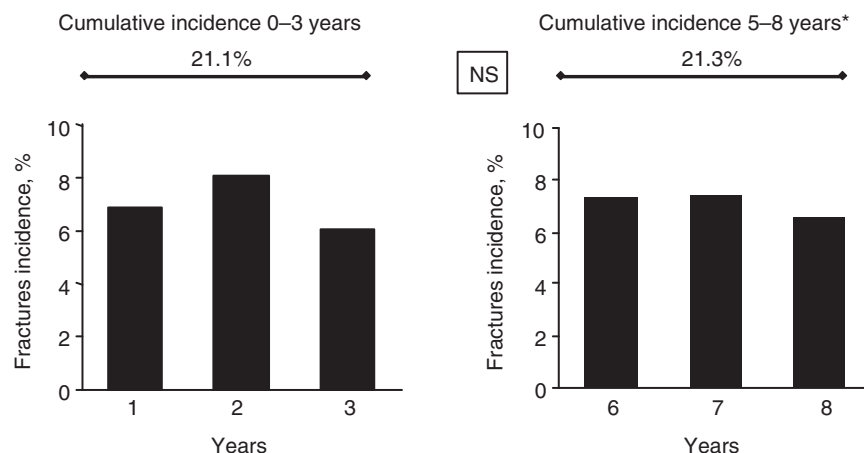
FIG. 3. Incidence of osteoporotic fractures among women in the SOTI and TROPOS trials who received SR for 8 years. *First new fractures on the period. Adapted from Reginster J-Y, Sawicki A, Roces-Varela A *et al*. Strontium ranelate: long-term efficacy over 8 years in post menopausal osteoporotic women. Arthritis Rheum 2008;58:S941.

non-vertebral fractures was relatively constant in the SR-treated women over the entire 8-year period, despite increased fracture risk due to increasing age. The cumulative incidences of any osteoporotic fractures during the first 3 and last 3 years of the studies are shown in Fig. 3. The tolerability of SR over 8 years of treatment was similar to that observed in both the SOTI and TROPOS trials [27].

In comparison, after 7 years of treatment in 164 women, risedronate demonstrated a similar incidence of fractures during the 6–7 years as compared with the 4–5 years [28]. Ten years of continuous treatment with alendronate compared with 5 years treatment with alendronate followed by placebo in the Fracture Intervention Trial Long-term Extension showed a significant further reduction of clinical vertebral fractures, but not of the other fractures [29]. Treatment with 10 mg of alendronate daily for 10 years produced a gradual increase in BMD at the spine, the trochanter and the femoral neck, as compared with baseline values [30].

Efficacy of SR in specific populations

Elderly patients

Women aged ⩾80 years account for 25–30% of all fragility fractures seen in the community, because both osteoporosis and falls are frequent in this population. Yet, there are few data on the efficacy of osteoporosis treatment in these patients. Therefore, the efficacy of SR in this population was explored using pooled data from 1488 women aged 80–100 years, who were included in the SOTI and TROPOS trials. This was a frail population with osteoporosis, with a mean age of 83.5 years and a mean femoral neck BMD T-score of −3.3. Half had already suffered at least one prior vertebral fracture and a third had had at least one non-vertebral fragility fracture (Table 1) [31].

After 1 year, compared with placebo, SR significantly reduced the risk of vertebral fracture by 59% (3.5 *vs* 8.3%; $P=0.002$), non-vertebral fracture by 41% (4 *vs* 6.8%; $P=0.027$) and symptomatic fracture by 37% (6.4 *vs* 9.9%; $P=0.012$). The corresponding risk reductions after 3 years were 32 (19.1 *vs* 26.5%; $P=0.013$), 31 (14.2 *vs* 19.7%; $P=0.011$) and 22% (19.1 *vs* 22%; $P=0.040$), respectively. In addition, SR decreased major non-vertebral fracture incidence and risk by 37% after 3 years (11.5 *vs* 17.7%; $P=0.003$). The incidence of hip fractures was lower in the SR group after 3 years, although not significantly reduced (5.2 *vs* 7.4%; $P=0.112$). SR was well tolerated, and its safety profile did not differ significantly from that seen in younger

TABLE 1. Baseline characteristics of women aged 80–100 years in the SOTI and TROPOS trials

	SR, $n=739$	Placebo, $n=749$
Age, years	83.5 ± 3	83.5 ± 2.9
Time since menopause, years	35.3 ± 6.1	35.4 ± 6.4
Patients with one or more prevalent, %	46.4	51.4
Vertebral fractures, %	37.1	35.1
Non-vertebral fractures, %		
Lumbar spine BMD T-score	−2.7 ± 1.7	−2.8 ± 1.7
Femoral neck BMD T-score	−3.3 ± 0.7	−3.3 ± 0.7
Duration of exposure to treatment, days	−952 ± 669	970 ± 659

Adapted from Ref. [31] with permission of the American Society for Bone and Mineral Research.

patients. After 5 years, SR had reduced the risk of a vertebral fracture by 31% ($P=0.010$) and non-vertebral fracture by 26% ($P=0.019$; Fig. 4) [21].

Patients after long-term bisphosphonate treatment

Is SR an option for patients who remain at high fracture risk despite long-term treatment with bisphosphonates? One recent study involved 15 such patients whose bisphosphonate treatment (mean duration 32 months) had been discontinued due to lack of efficacy or poor tolerability. Paired transiliac crest biopsies taken at baseline and after 12 months of treatment with SR ($n=10$) were analysed. After 12 months, bone volume (as measured by bone volume to tissue volume), bone formation (as measured by the ratio of osteoid surface to bone surface), trabecular thickness and trabecular interconnections had all significantly increased, whereas osteoclast number remained low and unchanged. These findings suggest that in patients who previously took bisphosphonate treatment, SR can re-stimulate bone remodelling even after long-term suppression of bone turnover [32].

Effect of SR on quality of life

With its related pain, deformity and dependence, osteoporosis has a highly negative impact on quality of life. The Quality-of-Life Questionnaire in Osteoporosis (QUALIOST), a supplement to the generic Medical Outcomes Study Short-Form Health Survey (SF-36) [33], is a validated 23-item instrument specifically directed to the physical and emotional aspects of osteoporosis-related quality of life; a lower score indicates a better quality of life [34]. In the SOTI study, 1250 patients were assessed every
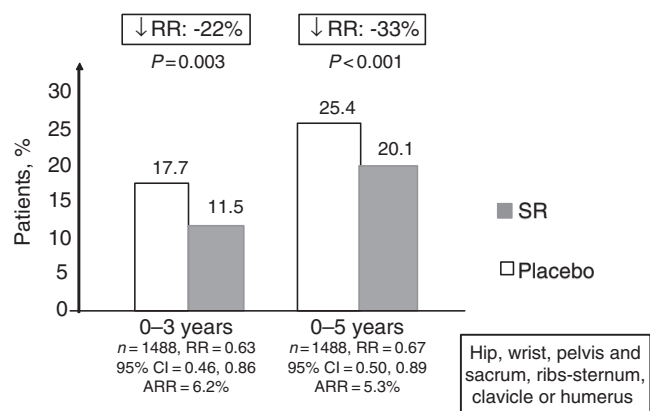
FIG. 4. Effects of SR on major non-vertebral fracture incidence over 5 years in patients aged 80–100 years. Intention-to-treat (ITT) pooled population (SOTI + TROPOS). Adapted from Reginster JY, Brixen K, Cormier C, Cannata J. Strontium ranelate demonstrates vertebral and non-vertebral anti fracture efficacy including hip fractures over 5 years in post menopausal osteoporotic women. Calcif Tissue Int 2007;80(Suppl. 1):S47; Seeman E, Vellas B, Benhamou CL *et al.* Sustained 5-year vertebral and non-vertebral fracture risk reduction with strontium ranelate in elderly women with osteoporosis. Osteoporos Int 2006;18:1–13 (OC39) and Ref. [31].
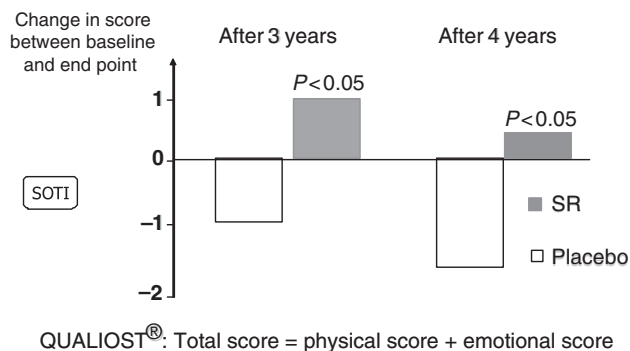

FIG. 5. Effects of SR on QUALIOST total score after 3 and 4 years in the SOTI trial ($n = 1240$), ITT under treatment. Adapted from Ref. [17] and Marquis P, Roux C, Diaz-Curiel M *et al.* Long-term beneficial effects of strontium ranelate on the quality of life in patients with vertebral osteoporosis (SOTI study). Osteoporos Int 2007;18(Suppl. 1):S123.

6 months for 4 years using both the SF-36 and the QUALIOST. SR treatment had no significant effects on SF-36 summary scores. However, after 3 years, treatment with SR significantly improved emotional, physical and global QUALIOST scores (global $P = 0.016$; emotional $P = 0.019$; and physical $P = 0.032$) compared with placebo. Patients reported having fewer negative feelings and disease-related worries (falling, becoming a burden, concerns about ageing or physical appearance), as well as reduced pain and improved mobility [35].

After 4 years, mean QUALIOST global scores had improved from baseline by 0.06 in the SR group and deteriorated by 1.92 in the placebo group ($P = 0.020$; Fig. 5). This divergence in QUALIOST total scores is clinically significant, surpassing as it does the difference between scores of patients with and without one new osteoporotic fracture. Both physical and emotional dimensions were also improved significantly by SR compared with placebo. A total of 14.6% of the SR patients and 11.2% of the placebo patients reported being free of back pain ($P = 0.005$) [17].

Adherence to treatment with SR

Adherence to osteoporosis treatment is often relatively poor; among the most often cited reasons are experiencing or fearing side effects and lacking the motivation to persevere with a preventive treatment [35]. In the two Phase III clinical trials of SR, rates of adherence to treatment exceeded 80%, attesting to the tolerability and ease of administration of this agent. In SOTI, adherence rates were 83% in the SR and 85% in the placebo group after 3 years [16]. The mean adherence rate in TROPOS was 82% in both treatment groups after 3 years [19] and 82% after 5 years [20]. This level of compliance compares favourably with those obtained with other osteoporosis drugs over 3 years: in the FIT trial: alendronate 81.3%, placebo 82.5%; VERT trial: risedronate 60%, placebo 55%; and in MORE trial: raloxifene 78%, placebo 75% [22, 36, 37]. In a prospective observational cohort study including 13 078 patients, >80% of them were continuing therapy with SR 12 months after the inclusion [38].

Safety

The overall adverse event profile of SR in the two Phase III multinational trials—including the incidence of adverse events, serious adverse events and discontinuations due to adverse events—was similar to that of placebo. Most adverse events were mild and transient; the most frequent were nausea (6.6 *vs* 4.3%) and diarrhoea (6.5 *vs* 4.6%), and the main adverse event causing discontinuation was nausea (2.2% in the SR group *vs* 1.3% in the placebo group). Transient changes included decrease in serum calcium and parathyroid hormone levels and increase in serum creatinine kinase and serum phosphorus levels; none was clinically relevant [16, 19, 34, 39]. No new safety issues regarding SR have emerged in the latter years of the SOTI and TROPOS trials, or in the open-label 3-year extensions of either trial [27].

The tolerability of SR was also confirmed in a pre-specified safety analysis of pooled data from participants in SOTI and TROPOS, who were aged ≥80 years. Again, the most frequent adverse events were gastrointestinal (nausea, diarrhoea and constipation). Serious adverse events, discontinuations caused by adverse events and deaths were all seen with similar frequency in the SR and placebo groups [30].

During post-marketing surveillance, isolated cases of hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms have been reported. The clinical manifestations (skin reaction, fever and systemic findings, hypereosinophilia, hepatic and renal abnormalities) typically occur within 2–6 weeks after initiating the therapy. The mechanism has not been elucidated. Even though this syndrome has been very rarely reported (16/570 000 patient-years), the treatment should be discontinued permanently in case of skin rash.

The incidence of venous thromboembolism (VTE) was similar in both treatment groups in the individual trials SOTI and TROPOS, but the difference between SR and placebo groups reached statistical significance [0.9 *vs* 0.6%; odds ratio (OR) = 1.4] in the pooled analysis. The two treatment groups were not balanced with regard to proportion of subjects with a history of VTE events. When these subjects were excluded from the analysis, there was no statistical difference in treatment-emergent VTE events between the two treatment arms [34].

It is also of interest that according to data from the large British General Practice Research Database [40], individuals with osteoporosis have an elevated risk of VTE compared with those without the condition (5.6 *vs* 3.2 cases per 1000 patient-years; age-adjusted relative risk (RR) = 1.42; $P = 0.007$). In this database, the risks of VTE among patients taking either SR or alendronate are equivalent, and not significantly different from the risk in the population with untreated osteoporosis (RR = 1.09; $P = 0.773$ for SR and RR = 0.92; $P = 0.646$ for alendronate) [41, 42].

Conclusion

There is an increasing demand for osteoporosis treatments with demonstrated long-term safety and efficacy. SR has a dual mode

of action that is more physiological than those of anti-resorptive (such as bisphosphonates) or anabolic agents (such as PTH), since it both increases bone formation and decreases bone resorption. Longer term clinical trial data demonstrate that SR continues to increase BMD and reduce the incidence of both vertebral and non-vertebral (particularly hip) fractures in osteoporotic women for at least 5 years of pre-planned follow-up. To date, SR is the only osteoporosis drug that has demonstrated this level of clinical efficacy over 5 years in pre-planned placebo-controlled trials. In addition, SR attenuates bone loss and reduces back pain, thereby improving quality of life. SR appears to be consistently effective across a wide variety of patient types, including those with and without predictors of fracture risk, patients with osteopaenia, younger postmenopausal patients (aged 50–65 years) and elderly patients (aged $\geqslant 80$ years). Finally, since osteoporosis requires long-term management into old age, a good safety and tolerability profile is a prerequisite for any useful osteoporosis treatment. The consistent broad-spectrum efficacy, rapid action and favourable safety profile provide support for SR as a valuable first-line choice in the pharmacological management of postmenopausal osteoporosis.

Rheumatology key messages

- SR is the first osteoporosis treatment to reduce long-term fracture risk (SOTI and TROPOS).
- Eight-year follow-up confirms sustained anti-fracture efficacy and tolerability.
- SR's efficacy and tolerability are sustained long term in patients aged >80 years.

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