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REVIEW

The position of strontium ranelate in today's management of osteoporosis

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Abstract Osteoporosis accounts for about 3 % of total European health-care spending. The low proportion of costs for the pharmacological prevention of osteoporotic fracture means that it is highly cost saving, especially in patient with severe osteoporosis or patients who cannot take certain osteoporosis medications due to issues of contraindications or tolerability. Following recent regulatory changes, strontium ranelate is now indicated in patients with severe osteoporosis for whom treatment with other osteoporosis treatments is not possible, and without contraindications including uncontrolled hypertension, established, current or past history of ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease. We review here today's evidence for the safety and efficacy of strontium ranelate. The efficacy of strontium ranelate in patients complying with the new prescribing information (i.e. severe osteoporosis without contraindications) has been explored in a multivariate analysis of clinical trial data, which concluded that the antifracture efficacy of strontium ranelate is maintained in patients with severe osteoporosis without contraindications and also demonstrated how the new target population mitigates risk. Strontium ranelate is therefore an important alternative in today's management of osteoporosis, with a positive benefit-risk balance, provided that the revised indication and contraindications are followed and cardiovascular risk is monitored. The bone community should be reassured that there remain viable alternatives in patients in whom treatment with other agents is not possible and protection against the debilitating effects of fracture is still feasible in patients with severe osteoporosis.

Keywords Efficacy · Osteoporosis · Safety · Strontium ranelate · Treatment

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Introduction

Osteoporosis is the most common bone disorder and is a major cause of fracture. It is a substantial drain on health-care spending and represents about 3 % of the total European health-care budget [1]. It has been estimated that European countries spent a total of €37.4 billion on osteoporotic fracture in 2010 [1], a number that included €10.7 billion for the costs of long-term disability, but only €2.1 billion for pharmacological intervention. The relatively low proportion of costs for the pharmacological prevention of osteoporotic fracture means that proper management of osteoporosis is highly cost saving.

It can also be expected to make a substantial contribution to the quality of life of patients by preventing debilitating fracture and associated morbidities. This is especially the case in difficult-to-treat patients, such as those with severe osteoporosis or patients who cannot take certain osteoporosis medications due to issues of contraindications or tolerability.

Today's therapeutic armamentarium for osteoporosis encompasses bisphosphonates, the selective oestrogen receptor modulators (SERMs), receptor activator of nuclear factor kappa-B ligand (RANKL) agents, parathyroid hormone (1–34) and strontium ranelate. The prescription of strontium ranelate is currently indicated in male and female patients with severe osteoporosis, at high risk of fracture, for whom treatment with other osteoporosis treatments is not possible, i.e. secondary prevention. In terms of health economics, this implies that strontium ranelate may be more cost-effective compared with previous calculations for this agent in more global osteoporotic populations at lower baseline risk [2–4]. In addition to previous prescribing information, strontium ranelate is now contraindicated in patients with uncontrolled hypertension and those with established, current or past history of ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease [5]. These recent changes in the indication and contraindications to strontium ranelate have led to some confusion among clinicians over the position of the agent in today's management of osteoporosis. With this in mind, we review here current evidence for the safety and efficacy of strontium ranelate, notably exploring when it can be prescribed in the management of osteoporosis.

Today's prescribing information for strontium ranelate

The current recommendations for the prescription of strontium ranelate result from regulatory re-evaluation procedures for the agent. These began in April 2013, when the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) recommended a re-assessment of the overall benefit-risk ratio of strontium ranelate in view of concerns over cardiac safety following the annual periodic safety update report [5–7], which is part of the mechanism by which the manufacturer makes regular submissions of safety data to the EMA.

The signal reported to the PRAC was an increase in myocardial infarction observed in pooled analyses of safety data from all randomized controlled trials with strontium ranelate [6, 8]. On the other hand, there has been no evidence for such a signal in post-marketing studies, prescription event monitoring, an observational cohort study [9] or studies in prescription databases in the UK and Denmark [10–12]. Moreover, the analysis of the trial data showed that the signal could be mitigated by removing patients with elevated diastolic blood pressure from the analyses and this formed the basis for a new contraindication for strontium ranelate in patients with uncontrolled hypertension [6]. Indeed, cardiovascular risk can also be mitigated by excluding patients with all of the new contraindications to strontium ranelate (medical history of ischaemic heart disease, including myocardial infarction, peripheral artery disease, cerebrovascular disease and uncontrolled hypertension). Similar results were found when the analyses were restricted to patients aged 75 years and older. The final conclusion of the EMA was adopted officially a year later by the European Commission, in April 2014, with a positive opinion in terms of benefit-risk ratio, but with a restriction of the indication to severe osteoporosis in patients in whom other treatments are not possible. There were also additional recommendations linked to monitoring for cardiac safety (i.e. monitoring for cardiovascular risk every 6 to 12 months). Provided these measures are implemented, the EMA considers that the benefit-risk ratio for strontium ranelate is positive. This information has been communicated to health-care professionals, and a programme of additional risk minimization is under way.

Efficacy of strontium ranelate in today's clinical practice

The evidence for the antifracture efficacy of strontium ranelate in postmenopausal osteoporosis originally came from two large pivotal randomized controlled trials, for which the results were reported in 2004 and 2005 [13, 14]. The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial included 1442 women aged >50 years with postmenopausal osteoporosis with at least one prevalent vertebral fracture and a femoral neck *T* score of −2.8 and a lumbar spine *T* score of −3.5 [13]. The women were randomly allocated to receive 2 g/day strontium ranelate or matched placebo. The rate of vertebral fracture over 3 years in the strontium ranelate group was 20.9 % versus 32.8 % in the placebo group (relative risk 0.59, 95 % confidence interval (CI) 0.48 to 0.73, $p<0.001$). The TReatment Of Peripheral OSteoporosis (TROPOS) trial [14] allocated 5091 postmenopausal women with osteoporosis to 2 g/day strontium ranelate or placebo. In the TROPOS trial, 11.2 % of the strontium ranelate patients had at least one incidence of osteoporosis-related nonvertebral fracture over 3 years versus 12.9 % of the placebo group. Treatment with strontium ranelate was therefore associated with a 16 % reduction in the adjusted relative risk for all nonvertebral fractures versus placebo ($p=0.04$) and 19 % for major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus) versus placebo (8.7 % with strontium ranelate versus 10.4 % with placebo, $p=0.031$). This study report included an analysis of 1977 postmenopausal osteoporotic women aged 74 years or older with

a femoral neck *T* score of −2.4, in whom the event rate for hip fracture in patients receiving 2 g/day strontium ranelate was 4.3 % versus 6.4 % with placebo (relative risk 0.64, 95 % CI 0.412 to 0.997, $p=0.046$) [14]. On the basis of these results, the regulatory authorities granted an indication for the prevention of hip fracture.

The efficacy of strontium ranelate in patients complying with the new prescribing information (i.e. severe osteoporosis without contraindications) has been explored in a multivariate analysis of participants in SOTI and TROPOS trials [15]. In the pooled population of patients, treatment was associated with a 20 % reduction in osteoporotic clinical fractures and a 40 % reduction in vertebral fractures, as assessed by semi-quantitative morphometry. In this retrospective analysis [15], the primary data from SOTI and TROPOS trials were used to identify patients who had been included in the trials with the current contraindication, as well as those with severe osteoporosis. The results found that there was no significant interaction between the treatment effect and the presence or absence of contraindications, or between the treatment effect and severity ($p>0.30$). When patients with the current contraindications were excluded, the antifracture efficacy was clearly maintained with a 16 % (95 % CI 0 % to 30 %) reduction in relative risk for clinical osteoporotic fracture and a 36 % (95 % CI 3 % to 44 %) reduction in relative risk for vertebral fracture. Moreover, when only patients with severe osteoporosis were included in the analysis, the risk reduction for clinical osteoporotic fractures was maintained [24 % (95 % CI 6 % to 39 %) or 26 % (95 % CI 5 % to 33 %)], according to whether severity was defined using the World Health Organization (WHO) criteria or FRAX® score, respectively. Thus, it was concluded that the antifracture efficacy of strontium ranelate is maintained in patients with severe osteoporosis without contraindications [15].

The global results of the recent benefit-risk analysis for strontium ranelate in postmenopausal osteoporotic women complying with the current prescribing information for treatment are presented in Fig. 1 in terms of relative risk with 95 % CIs. These patients had severe osteoporosis and had none of the current contraindications for treatment with strontium ranelate. As regard to benefits, the antifracture efficacy of strontium ranelate in the whole osteoporosis population was confirmed in this more restricted population with highly significant reductions in relative risk for vertebral fracture ($p<0.001$) and clinical vertebral fracture ($p=0.009$). In this pooled population, there were also reductions in relative risk for nonvertebral fracture ($p=0.34$), major nonvertebral fracture ($p=0.24$) and hip fracture ($p=0.13$). The absence of a significant impact on nonvertebral fracture in the pooled population of SOTI and TROPOS trials is likely due to the small size of the population as well as the inclusion of relatively low-risk patients in the SOTI trial, which was designed to detect impact on vertebral fracture. By contrast with the main study, the reduction in hip fracture in the high-risk subgroup of the TROPOS trial did not reach significance which was also due to the small size of the population. These results on antifracture efficacy for strontium ranelate weigh favourably against the potential risks of treatment, whether it is serious cardiac events ($p=0.44$), myocardial infarction ($p=0.99$), ischaemic heart disease ($p=0.21$) or embolic and thrombotic venous events ($p=0.45$), none of which showed a significant impact (Fig. 1). This demonstrates how the new target population for strontium ranelate mitigates the risk of treatment.

Discussion

The conclusion of the EMA is that the benefit-risk balance for strontium ranelate is positive in patients with severe osteoporosis who do not have contraindications to treatment, and the agent is therefore suitable in those who cannot be treated with other agents. Moreover, the contraindications for strontium ranelate are relatively easy to identify and monitor in routine medical practice (medical history and measurement of blood pressure), which means that they should not hamper administration in appropriate patients. Despite this and even though the risk-benefit analysis indicated that the new contraindications also mitigated cardiovascular risk in elderly patients, caution should be exercised in this group of patients. Indeed, observational data from the UK suggest that 71 % of patients aged between 70 and 79 years and 80 % of those over 80 years have hypertension, even though nearly two thirds may be controlled with antihypertensive treatment [16]. The regulator's decision to retain strontium ranelate in the therapeutic armamentarium for osteoporosis has been welcomed by the bone community [7] for a number of reasons.

First, it is important to have a broad choice of treatments for osteoporosis, with viable alternatives for patients who need them. Indeed, many patients are unable to take oral bisphosphonates due to contraindications, adverse effects or issues surrounding treatment administration, mostly related to the gastrointestinal system [17]. Even though in the majority of cases adverse events are mild, it is not surprising that persistence at 1 year is low (45 %) [18, 19] and adverse events are a frequent reason for cessation of treatment [17, 20]. Annual intravenous preparations have a different side effect profile, but have been associated with flu-like symptoms and there is also a need for caution in patients with impaired renal function. There have also been concerns surrounding the effects of long-term treatment with some antiresorptive agents, with reports of rare but severe side effects such as atypical fracture or osteonecrosis of the jaw. It is therefore essential to have an alternative for severe patients who cannot tolerate other treatments or who have been taking antiresorptive agents for many years.

Second, adherence with strontium ranelate has been reported to be good [9], which may also be important in patients who have

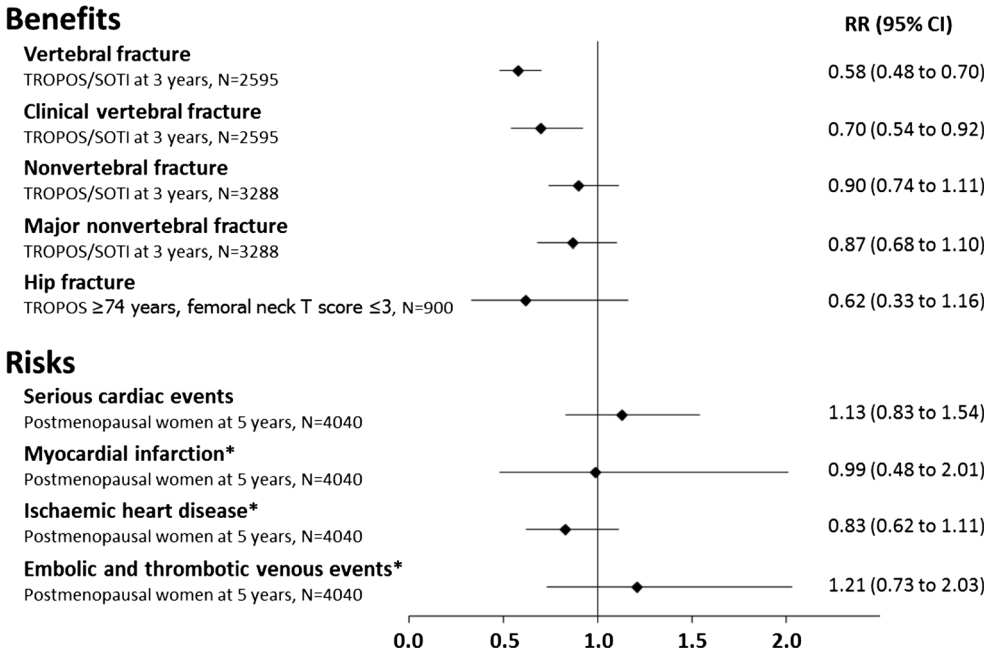

Fig. 1 Benefit and risks with strontium ranelate in patients with postmenopausal osteoporosis meeting the indications and contraindications for treatment, in terms of relative risk (*RR*) and 95 % confidence interval (*CI*) (Wald test). *SOTI* Spinal Osteoporosis Therapeutic Intervention (trial), *TROPOS* TReatment Of Peripheral OSteoporosis (trial). *Asterisk* indicates adverse events defined according to the standardized MedDRA Queries (narrow terms for myocardial infarction and embolic and thrombotic venous events, and broad term for ischaemic heart disease)

ceased taking other osteoporosis treatments due to tolerability issues. An informal audit in hospitals in Southampton, UK, indicated that 30 % of osteoporotic patients discontinued or were unable to tolerate bisphosphonates, among whom 50 % had no contraindication to strontium ranelate. This suggests that at least 15 % of a typical postmenopausal osteoporosis population could qualify for treatment with strontium ranelate (C. Cooper, unpublished results). Moreover, since good adherence is recognized as an important component of cost-effectiveness [21], then this may further contribute to the cost-effectiveness of strontium ranelate [2, 3].

Third, it is important to take into consideration the mode of action of strontium ranelate in comparison with the other osteoporosis agents. There is a wide variety of treatments for osteoporosis, which can generally be categorized into antiresorptive agents (bisphosphonates, SERMs and anti-RANKL agents) and bone-forming agents (parathyroid hormone 1–34). In this context, strontium ranelate stands apart from the other members of the osteoporosis class since it appears to have an action on both bone remodelling and the material properties of bone [7]. This unique mode of action may attenuate concerns over the long-term suppression of bone turnover with antiresorptive agents. Access to alternative agents with different mechanisms of action can prevent interruption of pharmacological therapy, allowing continued protection against osteoporotic fractures in the long term.

Conclusion

Strontium ranelate is an important alternative in today's management of osteoporosis, with a positive benefit-risk balance, provided that the new indication and contraindications are followed. It is also useful to have a solution for the management of patients who have been taking antiresorptives for many years, especially those who suffer a fracture on treatment. The bone community should be reassured that there remains a range of viable alternatives in patients with severe osteoporosis in whom treatment with other agents is not possible and protection against the debilitating effects of fracture is still possible in these difficult-to-treat patients.

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