

Strontium ranelate in the treatment of osteoporosis



Osteoporotic fractures are a common and important cause of disability and death worldwide. Antiresorptive agents like the bisphosphonates or the oestrogen analogues have been shown in large randomised controlled trials (RCTs) to significantly reduce the rate of osteoporotic fractures. These agents do not, however, abrogate fractures or the deranged skeletal microarchitecture that characterises osteoporosis; they only modestly and often transiently increase bone mineral density (BMD), and are not free of side-effects. Moreover, since bone formation and resorption are usually tightly coupled, even in most types of osteoporosis, the decrease in bone resorption induced by antiresorptive drugs is invariably followed by a decrease in osteoblastic bone formation.¹

Strontium ranelate, a new orally active drug recently released in this country, has been shown in animal and *in vitro* studies to have a dual action – it decreases bone resorption and stimulates bone formation. While its exact molecular mode of action is poorly understood, the drug is thought to decrease bone resorption by the inhibition of osteoclastogenesis as well as a reduction in the bone resorbing activity of mature osteoclasts. Strontium ranelate also stimulates the proliferation of pre-osteoblasts and their differentiation into mature osteoblasts. The net result is an increase in bone volume, mass, diameter and strength.²⁻⁴

Following earlier studies,^{5,6} the results of two large RCTs that examined the effects of strontium ranelate on vertebral and non-vertebral fractures were recently published.^{7,8} The Spinal Osteoporosis Therapeutic Intervention (SOTI), a 3-year RCT, examined 1 649 postmenopausal women (mean age 69 years) with osteoporosis or osteopenia. Strontium ranelate significantly decreased markers of bone resorption and increased biomarkers of formation. Spinal BMD increased by 14%, while vertebral fractures decreased by 49% within the first year, a reduction that was sustained over time (41% at 3 years). Quantitative bone histology in a smaller subset of patients revealed no evidence of mineralisation defects or osteomalacia.⁷

The Treatment of Peripheral Osteoporosis Study (TROPOS) employed more than 5 000 elderly (mean age 76 years) women with dual energy X-ray absorptiometry (DEXA)-confirmed osteoporosis.⁸ Following administration of strontium ranelate 2 g/d for 3 years, femoral BMD increased by 8 - 10%, while the relative risk for hip fractures decreased by 20 - 36% (depending on age and severity of bone loss).

Strontium ranelate was extremely well tolerated in both the SOTI and TROPOS studies. Nausea, diarrhoea, headache and dermatitis were reported more commonly in those taking strontium. This was, however, evident during the first 3 months of treatment only, after which there was no difference between groups. Laboratory data revealed slight, clinically insignificant changes in serum calcium, phosphate, parathyroid hormone and creatine kinase levels. Initially, the incidence of venous thrombo-embolic events (VTE) appeared to be higher in the strontium group, but this was readily accounted for by the fact that more subjects in this group had a previous history of VTEs – the presence of VTE antecedents is known to markedly increase the risk of subsequent VTEs. If subjects with a history of VTE were excluded from both groups, the incidence of VTE was similar.

The addition of strontium ranelate to our therapeutic armamentarium would appear to have a number of potential advantages. The drug has a novel, dual action on bone, possibly mediated by the activation of the calcium-sensing receptor,⁴ and has been shown in large RCTs to reduce the rate of both spine and hip fractures. Anti-fracture effects on the spine are evident as early as the first year. The drug appears to be effective, not only in severely osteoporotic subjects, but also in those with osteopenia. Moreover, the drug is effective in reducing both vertebral and peripheral fracture risk in patients aged 80 years and older – i.e. those with the highest propensity to fracture and also those in whom antiresorptive drugs have been shown to be less effective, unless severe osteoporosis is present.^{9,10} The drug has been studied in women with postmenopausal osteoporosis – theoretically, it also holds promise in the treatment of low-formation osteoporoses, like steroid-induced and male osteoporosis.

The ultimate efficacy and safety of pharmaceutical agents are, however, not determined by drug trials, but by long-term clinical use. Strontium ranelate causes an impressive increase in BMD, which remains our most reliable surrogate marker of fracture risk. Strontium is, however, incorporated in bone and because it has an atomic number greater than calcium will decrease the penetration of X-rays, resulting in an overestimation of measured BMD.¹¹ Although formulae have been developed to correct for this artificial increase in BMD,⁷ its documentation does confirm compliance and adherence to therapy, one of the major management obstacles in osteoporosis, and it may in fact prove to be an advantage. Strontium levels can also be

measured in blood, unlike most other agents used in the treatment of osteoporosis.

The reduction in fracture risk reported in the SOTI and TROPOS trials is not dissimilar to that reported with antiresorptive drugs and slightly lower than the reduction with the bone formation stimulating drug, teriparatide. The theoretical advantage of employing a combination of an antiresorptive agent plus a bone-forming drug to reduce fractures was seriously challenged in studies using teriparatide plus a potent antiresorptive like alendronate.^{12,13} No data are available on the potential benefits of combining strontium ranelate with an antiresorptive drug.

Strontium ranelate appears to be safe and well tolerated. Especially reassuring are the results of bone histomorphometric studies showing no evidence of a mineralisation defect – a problem which plagued the earlier use of strontium and fluoride salts in the treatment of osteoporosis.^{14,15} In RCTs, the incidence of adverse events (AEs), as well as serious AEs and withdrawals due to AEs, were similar in the strontium and placebo groups. Caution is, however, necessary in extrapolating the results of rigid drug trials to the real world of clinical practice – this is well illustrated by the not too uncommonly encountered gastro-intestinal side-effects of the bisphosphonates, which were seldom reported in the formal trial setting.

In summary, strontium ranelate has been shown in RCTs to be an effective and safe drug to reduce the risk of fracture associated with postmenopausal osteoporosis. Its launch has provided physicians in

this country with yet another potentially useful agent to treat this common, serious disease.

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