Strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women with osteoporosis

INTRODUCTION

The Primary Care Rheumatology (PCR) Society seeks to improve GPs' knowledge and understanding of rheumatology, and hence the care GPs provide to patients with musculoskeletal problems. The PCR's membership consists of GPs with an interest in all aspects of musculoskeletal medicine. The PCR has a high and growing reputation, both nationally and abroad. The PCR's work on rheumatoid arthritis and its guidelines for managing both RA and osteoporosis have all been critically acclaimed. The Society was heavily involved in developing the Diploma in Primary Care Rheumatology at the University of Bath. This course is well established and attracts primary care physicians from around the globe.[1]
This submission seeks to give GPs' views on the use of strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women with osteoporosis.

BACKGROUND

Osteoporosis is a global problem whose prevalence is rapidly rising due to increased life expectancy and an ageing population. Osteoporosis is a progressive disease which leads to disabling fractures causing substantial morbidity and mortality, impaired quality of life and a massive increase in the socio-economic burden. The economic burden is equal to if not greater than that from most of the other major diseases.[2]
Osteoporosis is most prevalent in postmenopausal women but despite a 1 in 3 risk of developing osteoporosis during their lifetime, 80% of women do not feel it will affect them personally.[3] This major European survey by the International Osteoporosis Foundation also found poor doctor-patient communication and a considerable variation in the availability and access to diagnostic investigations as well as the medical treatment of osteoporosis. This presents major problems in health care education in convincing these women of the benefits of identifying and treating asymptomatic osteoporosis.
The vertebral column is the commonest site for osteoporotic fractures and these are associated with considerable morbidity, and increased mortality over 5 years.[4,5,6]
However, only a small proportion of vertebral fractures present clinically and of the ones that present, only a proportion are detected by spinal imaging.[7] Studies show that 50% of women have at least one vertebral fracture by the age of 80-84 years but only 15% have a clinically diagnosed vertebral fracture.[8, 9, 10, 11]
A recent study has shown that 20% of women will have another fracture within a year of an incident vertebral fracture.[12] Another study has shown that vertebral fractures are predictive of future fracture risk at the spine, hip and to a lesser extent, at all other sites.[13]
New vertebral fractures are associated with substantial increases in back pain and the resulting functional disability in elderly women.[14] Prevention of new vertebral fractures should reduce the burden of back pain disability.

The hip is the next commonest fracture site and there is a lifetime risk of 1 in 6 for postmenopausal women with the majority occurring in women over the age of 80

years.[15,16,17] The morbidity and mortality of hip fractures is considerable with 1 in 5 dying within 1 year of sustaining an osteoporotic fracture and over 50% remain permanently disabled and have an impaired quality of life.[18,19] NNT analysis for women over 70 years with 3 risk factors was between 32 and 71 to prevent one hip fracture, assuming intervention reduced fracture rates by 30 or 50%.[20]
The annual cost of treating osteoporotic fractures in the UK is £ 1.8 billion and the average PCT of 100,000 patients will have costs of nearly £1.5 million. There are an estimated 3,000,000 people with osteoporosis in the UK at present which means that the each general practitioner has approximately 100 patients with the disease.[21, 22, 23]
The high prevalence of osteoporosis in our society means that the majority of osteoporotic patients have to be managed in primary care.

1) What are the problems with osteoporosis treatment in primary care at present?
2) Why do we need another drug for osteoporosis treatment?
3) What are the advantages of strontium ranelate?
4) Will it be suitable for use in primary care?

There are a limited number of options available at present for the treatment of osteoporosis.
Hormone replacement therapy is no longer considered a first-line option for the management of postmenopausal osteoporosis.[24] The increased risks of cardiovascular and cerebrovascular disease, deep vein thrombosis and breast cancer means that its use is limited to perimenopausal symptoms but it may have a limited use in postmenopausal osteoporosis if the risk/benefit profile is favourable and patients have been unable to tolerate alternative treatments, such as bisphosphonates.[25,26,27,28]
Tolerability and compliance.
Compliance in osteoporosis treatment is known to be poor with one study showing one year compliance rates below 25%.[29]
Side-effects of drugs can reduce compliance considerably. In particular, the gastro-intestinal symptoms associated with bisphosphonates can result in loss of compliance. Although, once weekly preparations result in better compliance, there are still a considerable proportion of patients who stop taking bisphosphonates because of gastro-intestinal symptoms, such as dyspepsia, nausea and diarrhoea.[30,31,32,33]
Additionally, the detailed instructions for the dosage regime of the once weekly bisphosphonates can confuse the elderly patient who is often on multiple drugs for co-existent chronic diseases.
Again, compliance can be a problem with the use of calcium and vitamin D preparations where the palatability of some formulations counterbalances any cost disadvantage.[34] Calcium and vitamin D alone is insufficient to correct established osteoporosis.[35]
In women with increase risk of breast cancer in whom HRT is contra-indicated, the use of selective oestrogen receptor modulators (SERMS) has considerable benefit because of the dramatic reduction in risk of invasive breast cancer (76% reduction during three years treatment).[36] However, SERMS may increase the risk of deep venous thombosis and therefore, must not be used in patients with a history of thrombo-embolism. They can also aggravate menopausal symptoms of flushes and sweats. Although, SERMS reduce the risk of vertebral fractures, they have minimal effect on the prevention of non-vertebral fractures and therefore, have a limited role in the treatment of postmenopausal osteoporosis.[37]

Calcitonin, in the form of synthetic salmon calcitonin, is not available as an oral preparation and has to be given by injection or nasal spray. The evidence for its use in the treatment of osteoporosis is limited but one study of nasal spray calcitonin has shown a significant reduction in vertebral fractures but not non-vertebral fractures.[38]However, compliance of the nasal spray is limited due to local nasal irritation.
Teriparatide is a new anti-osteoporotic agent whose use is restricted to the severe progressive osteoporotic patient who has failed to respond to bisphosphonates. NICE guidance recommends its use as a treatment option for secondary prevention of osteoporotic fragility fractures in women over 65 years who have had an unsatisfactory response to bisphosphonates and who have an extremely low BMD (T score -4SD or more) or a very low BMD (T score -3SD or below) and multiple fractures plus one or more additional age-independent risk factors.[39] It is not usually given in a primary care setting but is given by subcutaneous daily injections over a maximum 18 month period, usually initiated in secondary care.

Therefore, general practitioners have a limited range of drugs available for the management of postmenopausal osteoporosis in primary care. A lack of options may lead to referral into secondary care and resorting to the use of other options, such as teriparatide. The availability of a new drug, like strontium ranelate, will enable treatment to be maintained in primary care and reduce the number of referrals to secondary care with the corresponding reduction in costs.

Strontium ranelate has a number of benefits which are advantageous to its use in primary care.
It is the first drug for osteoporosis treatment which has been shown to have a dual action on bone metabolism. It combines the anti-resorptive effects by inhibiting osteoclastic differentiation and activity with an anabolic effect on bone formation by stimulating osteoblastic differentiation, activity and collagen synthesis.[40] Strontium ranelate increases bone mass whilst maintaining bone mineralization, resulting in improved bone quality and strength.
Two phase 111 studies over 3 years (SOTI and TROPOS trials) have confirmed strontium ranelate reduces the risk of vertebral fractures by 41% and of clinical vertebral fractures by 38%.[41,42] The effect was significant at the end of the first year. The number needed to treat for 3 years to prevent one vertebral fracture was nine and to prevent one clinical vertebral fracture was seventeen. There was also an improvement in the quality of life score in the SOTI study which was statistically significant.
In the TROPOS study, there was a 16% reduction in non-vertebral fractures and there was a 36% reduction in hip fracture risk in a subset of women, age over 74 years, with a baseline femoral neck BMD of T-score less than -3SD.[42]
In very elderly women (i.e. over 80 years) in both trials, strontium ranelate reduced the risk of vertebral fractures by 32% and of non-vertebral fractures by 31% over 3 years.[43] This is the first demonstration of a significant reduction in both vertebral and non-vertebral fractures in very elderly osteoporotic women by anti-osteoporotic treatment.
In a retrospective study of the SOTI and TROPOS trials, there was a 72% reduction in the risk of a first vertebral fracture over 3 years in a subgroup of osteopenic patients (lumbar and/or femoral neck T-score between -1 and -2.5) with no prevalent fractures.[44]

Although there are no direct comparison studies with other treatments for osteoporosis, the figures for reduction in fracture risk in these trials are comparable to those obtained with bisphosphonates.[45,46]

Apart from the proven reduction in vertebral and non-vertebral fracture risk, what are the other advantages of strontium ranelate?

It is a well tolerated oral preparation taken once daily at night. The granules are tasteless and form a suspension with water which is easily swallowed. There are no complicated dosage regimes and there is no requirement to remain upright after intake which makes it easier for the frail elderly patient to comply. No dosage adjustment is required for moderate renal impairment (30-70 ml/min creatinine clearance) and, as strontium ranelate is not metabolised, no dosage adjustment is required for hepatic impairment.[47]
There are no significant clinical interactions with most of the major drug groups (see disadvantages below).
Most adverse side-effects are mild and transient e.g. nausea and diarrhoea, resulting in excellent compliance rates of 83% in trial data (similar to placebo).[41]
Compliance rates in trials were monitored by measuring strontium blood levels and this may be a useful way of checking compliance in a primary care setting.

What are the disadvantages of strontium ranelate?
Absorption is impaired by food which means that no food should be taken 2 hours prior to, or after dosage.
Patients must take adequate calcium and vitamin D which, in the elderly, usually means calcium and vitamin supplementation. Calcium must be taken at a different time during the day to avoid impaired absorption of the strontium.
Strontium causes impairment of absorption of tetracyclines and quinolones and, therefore, should be stopped during treatment with these antibiotics.
There is a small but statistically significant increased risk of deep vein thrombosis and pulmonary embolus with strontium ranelate treatment. Therefore, caution is required in patients at risk of thromboembolism.[48]
Bone mineral density measurement by dual-energy x-ray absorptiometry is amplified by the strontium content of bones and will result in overestimation of BMD unless corrective adjustment is made.[49] This may cause problems in the monitoring of osteoporotic patients by DXA scanning.
Other minor abnormalities, e.g.a transient rise in creatine kinase levels should have minimal effect on the use of strontium ranelate in primary care.[41]

SUMMARY

Strontium ranelate is a promising new anti-osteoporotic agent which has a unique dual action on bone formation and resorption. It has a similar fracture reduction profile to bisphophonates and has a significant effect in rapidly reducing the risk of both vertebral and non-vertebral fractures. It has an excellent safety profile with good tolerability and compliance, making it a useful alternative choice to bisphosphonates for initial treatment of osteoporosis in all postmenopausal women from the age of 55 years to the very elderly.
The Primary Care Rheumatology Society welcomes the addition of strontium ranelate to our anti-osteoporotic agent formulary and hopes that it will help us manage the vast

iceberg of yet to be diagnosed osteoporosis in primary care. We hope that NICE will strongly support and recommend the use of this drug in primary care.

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