Submission to the National Institute for Clinical Excellence on

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

by

The Society for Endocrinology

Introduction

Clinical Background

Scale of the Problem

Osteoporosis is a common skeletal disease. It is generally defined as a combination of low bone mass and abnormal bone architecture with a consequent increase in fragility and risk of fracture[1]. By itself osteoporosis causes little clinical consequence but the resulting fractures are a cause of considerable personal and financial cost. Although the usual fractures associated with osteoporosis are those of the distal forearm, vertebral body, and proximal femur there is increasing evidence that almost any fracture can be exacerbated by the presence of osteoporosis. Recent evidence from the General Practice Research Database suggests that fractures may be more common than previously recognised; according to that database, virtually one half of women over the age of 50 and 25% of men of the same age might be expected to suffer a fracture[2].

Vertebral fractures are associated with pain, deformity and limitation of activities of daily living. There is also evidence to suggest that the presence of vertebral fractures, whether or not they have caused acute symptoms, is associated with increased utilisation of health care resources[3-5]. In public health terms the largest burden is provided by hip fractures. Not only are these almost invariably associated with a period of hospital admission and operative treatment but they are also associated with a significant loss of independence resulting in considerable social care costs. In addition, this injury is also associated with significant mortality; it has been estimated that 20% of those suffering this fracture will succumb in the subsequent six months[6]. A recent estimate of the financial burden of osteoporotic fractures has suggested that these may cost our health and social services £1.75 billion per year[7] rising to over £2 billion by 2010.

It is a therefore a matter of both clinical and financial urgency that any measures which are able to minimise this personal and economic burden are taken. The Society for Endocrinology therefore welcomes this latest involvement of the Institute in the assessment of treatments for osteoporosis and hopes that the attached comments will assist its deliberations.

Involvement of Endocrinology

For many years the only effective interventions for the management of osteoporosis were hormonally based. Much of the early investigation of the causes and treatment of osteoporosis has been undertaken by endocrinologists. Although other disciplines, notably rheumatology and elderly care medicine, have been involved in a management of osteoporosis latterly, many physicians treating this condition are endocrinologists and osteoporosis and other metabolic bone diseases remain a core part of endocrine training.

In this submission the Society for Endocrinology therefore represents the opinions of a large body of clinicians involved in the day-to-day management of patients with osteoporosis.

Currently available therapies

Several therapies are currently available for both the prevention and treatment of osteoporosis. These include hormone replacement therapy, calcium supplementation, vitamin D and its active metabolites, bisphosphonates, raloxifene, and teriparatide. The last three of these have recently been subject to a technology appraisal by the Institute. The assessment undertaken as part of this appraisal indicated that each of these treatments are potentially both clinically and cost effective in the treatment of osteoporosis in post menopausal women. This was reflected in guidance regarding the appropriate use of these agents. However, none of these therapies is ideal for every patient with osteoporosis. Recent understanding about the risk-benefit profile of hormone replacement has meant that its use is restricted to the short term management of patients with climacteric symptoms; in such women it will protect against osteoporosis but widespread use to prevent or treat osteoporosis is no longer acceptable. Calcium, vitamin D and its more potent metabolites are generally accepted as being rather weak agents and recent results suggest that calcium and vitamin D may only have role in the primary prevention of fracture rather than being of use in its secondary prevention. Although bisphosphonates are the mainstay of therapy they are unsuitable in a significant minority on account of pre-existing gastrointestinal disease or upper gastrointestinal intolerance. Raloxifene is contraindicated in a significant minority of women and has no proven efficacy against peripheral fractures. Teriparatide is limited by cost to use in the most severely affected women.

The lack of acceptability of the existing therapies for osteoporosis can be inferred from the relatively low continuance with therapy reported for them.

Furthermore, with the exception of teriparatide all the above therapies have a similar mode of action in that they inhibit the breakdown of old bone. Therefore if one of these treatments fails to be effective in any individual it is likely that the other treatments may not be successful either.

There remains a need for further treatments for osteoporosis which have both different modes of action and different side effect profiles.

Strontium Ranelate

Strontium ranelate has recently been licensed for the management of osteoporosis. Its mode of action is not fully understood but it appears to act as a weak inhibitor of bone resorption and simultaneously as a weak stimulator of bone formation. The overall effect of this is to lead to an increase in bone mass. However, this cannot be assessed by the usual techniques such as dual x-ray absorptiometry (DXA). This is because the strontium atoms get incorporated into bone and, as their atomic number is higher than that of calcium, this will lead to an apparent increase in bone density without any real

change in skeletal structure[8]. This means that the commonly used surrogate end point of bone density is of no use in assessing the clinical effectiveness of strontium ranelate and the only legitimate end point for such studies is fracture rate.

Clinical Evidence

Two large phase 3 studies using strontium ranelate to reduce fracture rate in postmenopausal women with osteoporosis have been undertaken. The first of these was aimed at examining the effect upon vertebral fractures in younger women. The results of this study have been published[9] and indicate a similar reduction in vertebral fractures as has been seen with the aforementioned treatments[10-15]. A larger study in slightly older women has looked at the ability of strontium ranelate to reduce peripheral fractures[16]. The results of this study have not yet been published in the peer reviewed literature but were presented at the World Congress on Osteoporosis last year. This study demonstrated that, in women who achieved adequate plasma strontium levels, there was a significant reduction of 16% in all non-vertebral fractures[17] and of 36% in femoral neck fractures[18]. The magnitude of these reductions is similar to that reported for other treatments for osteoporosis.

Drawbacks

In general, strontium ranelate was well tolerated in clinical trials. There was an increased risk of diarrhoea although this did appear to settle with prolonged use. Combination of the results of the two phase 3 studies suggested an increased risk of venous thromboembolic disease. There is no plausible biological explanation for this but it does mean that strontium ranelate must be used with caution in women at increased risk of thromboembolism, as is the case with raloxifene and hormone replacement therapy. This apart, the side effect profile is distinct from other osteoporosis treatments and therefore strontium ranelate is an attractive option for use in patients in who the other osteoporosis therapies are contraindicated or not tolerated.

Another drawback to the use of strontium ranelate comes from the effect of strontium on bone density measurements. This means that not only can bone density measurements not be used to monitor the effect of treatment but that the deposition of strontium within the skeleton may influence future skeletal measurement for an indefinite period of time.

Unanswered questions

There is currently no evidence which allows any recommendation to be made regarding the duration of therapy.

Teriparatide, the only other therapy which stimulates bone formation, has its action abrogated by prior treatment with alendronate. There is no evidence to demonstrate whether or not this is the case with strontium ranelate. Equally

there is no evidence of the use of strontium ranelate in combination with other therapies.

Conclusion

Strontium ranelate appears to be effective in the reduction of fractures in postmenopausal women with osteoporosis. It has a different side effect profile from other agents approved for the condition and the Society would encourage the Institute to bear these clinical factors in mind when reaching its conclusion about the technology.

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