Health Technology Appraisal

The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women

Assessment Report
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Executive Summary

The report is correct to identify possible side effect issues but the relative risk of all adverse events should be quoted rather than just statements on some being "more common" in patients on strontium ranelate (where the calculation has not been possible this should also be stated).
The choice of algorithm for use in making absolute fracture risk is an advance on just using BMD, but the evidence for using some of the criteria such as smoking status is still debatable. Body mass index (BMI) is recognised as important by the majority of authors on this subject but this factor has been omitted (or standardised to 26 for the purposes of analysis).
Although the report identifies the failings in comparison with bisphosphonates there is no comment in the summary on the role in patients who are unsuitable for or unable to tolerate bisphosphonates. This should be addressed in the next draft of the report.
There is no mention of the efficacy dependence on the prevailing concentration of strontium that is measured after the patient is stabilised on treatment. This is rather surprising as this is important data that has either not been supplied to or considered by the committee. For this drug to be used effectively the committee should consider the value/role of measurement of strontium ranelate in plasma.

Background

Table 2 is illegible in my copy. Also page 20, Table A and Table B were only partially legible.
This is a significant improvement on previous methodology but still requires further work. In future it is assumed the final report of the WHO group will used for all such assessments.
The report should include the date that was used when the current service provision data was established. Did this include changes that may have happened when generic alendronate prescription was possible?

Product Characteristics

It is surprising that a rather "generic" renal function cut-off of 30 ml/min for creatinine clearance has been quoted as the recommended level below which strontium ranelate should not be prescribed. What data has been produce to support this statement and the recommendations relating to other levels of renal impairment?
Surprisingly there is no mention in this section either of the effect of the prevailing concentration of strontium ranelate nor the effect of strontium ranelate and the interpretation of BMD. How can the appropriateness of therapy be established by BMD when the molecule itself makes a significant contribution to BMD measurement?

Clinical Effectiveness

Continuance and compliance may be reflected in the prevailing strontium concentration in the blood not just by measurements of the therapeutic response. Since fracture outcome can be related to these measurements these should be taken into account by the committee.
The report quotes the data on BMD increase but no mention of the confounding factor of the molecular mass of the strontium molecule in BMD measurement is mentioned. This is rather surprising considering the importance of the document.
It should be made clear that the magnitude of effect on "bone stimulation" by strontium ranelate and teriparatide are significantly different. The simple expedient of comparing the changes in bone formation markers demonstrates this long before the changes in BMD.
The authors should update the comments on teriparatide and bisphosphonate use using the recent articles published in the New England Journal of Medicine in particular.

Alendronate

The report needs updating to comment on the availability of generic alendronic acid.

Economic Analysis

The modelling looks very interesting but not all outcomes have been included as there is surely a difference between residence in the community where the individual is dependent on other carers or independent. The cost will be completely different and so the analysis will be unfavourable to the intervention. GP and hospital costs are also going to be greater in this population. Chronic or repeated pain as a result of fracture(s) will also vary in these patients and is not equivalent between the groups. If the comparison uses the generic priced alendronate then this will presumably show an even greater advantage in this analysis.

Alternative Identification Approaches

It is correct to state that it is appropriate for clinicians to treat women at a high risk of fracture without performing a DXA scan if it is unlikely that the DXA scan would change the decision to treat. It is easy for us to define a severely affected group falling into this category but precise recommendations regarding this approach are not available. Further detailed guidance is required on the patients meeting the criteria for DXA measurement. The RCP approach was defined many years ago when the current level of knowledge was not available.
I do not agree with the statements regarding BMI and the lack of references in this section may suggest that the authors felt that the work involved to use BMI in the calculations would be excessive for an assumed modest return. BMI measurement is much cheaper than a BMD and could quite appropriately be included in the GP algorithm. This may also have a significant effect in younger women where the identification cost using BMI would be cheaper.
It is interesting that the cost implications are expected to be low for strontium ranelate. However if 30% of patients on alendronate are “unwilling or unable” to take this therapy after 6 months and an even greater number come into this category with the passage of time a substantial number of women would become eligible for strontium ranelate. The costs would then be significant.
Alternative methods of DXA scanning are available and a significant literature, especially on peripheral scanning, is now available. This should be considered and costed.

Discussion

The comments above should be reviewed in the context of the discussion.
Although subjects do not enter nursing homes significant costs will accrue for care in other environments as discussed above. These need to be taken into account. The assumption that there are not high costs from patients residing outside nursing homes is incorrect. Research in this area should be recommended.

It is highly unlikely that a comparator study of bisphosphonates and strontium ranelate with fracture outcome as the primary end-point will be performed. The “false” increase in BMD seen with strontium and the differences in action on bone metabolism also make it impossible to perform comparator studies using these end-points as comparators with bisphosphonates. It is surprising that these problems with strontium are not mentioned in detail within the document.
The interference with calcium depends on the concentration of strontium circulating in the blood and the methodology used to measure calcium. The mean concentration of strontium circulating in the blood in the vast majority of patients on strontium ranelate does not cause interference in the methods used in most clinical biochemistry laboratories in the UK. The urine Ca concentration may be subject to interference in some methods after collecting an overnight sample containing a large proportion of the excreted dose and sampling immediately following ingestion of the 2g sachet can cause interference. The problem however in comparison to other issues raised is minimal.

Review of the comparative data suggests that strontium has significant advantages over raloxifene in the models used and is significantly closer to the bisphosphonates in terms of cost effectiveness. This presumably has significant implications for the current recommendations and raloxifene will be replaced by strontium in the algorithms for secondary prevention or included alongside as an

alternative when there are issues with bisphosphonates. Further classification depending on hip fracture prevention will need to be addressed in the recommendations.