A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis

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Executive summary

Health Technology Assessment 2005; Vol. 9: No. 22
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Epidemiology and background

Osteoporosis is a common disease in the elderly, with an estimated 2.1 million female sufferers in England and Wales. It is defined as possessing a T-score of –2.5 standard deviations or lower. The main consequence of osteoporosis is an increased incidence of fractures, notably at the hip, spine, wrist and proximal humerus, which increases as a woman ages. These result not only in morbidity for the patient, with a risk of mortality following fractures of the hip, and possibly of the vertebra, but also in the consumption of scarce health resources. A recent estimate of the cost in the UK of osteoporotic fractures in females has put this figure at £2100 million. A woman who has suffered a fracture is defined as suffering from severe osteoporosis.

Objective

The aim of this review was to evaluate the use of alendronate, etidronate, risedronate, raloxifene or teriparatide to reduce the risk of osteoporotic fracture in postmenopausal women.

Methods

Studies that met the review’s entry criteria were eligible for inclusion in the meta-analyses provided that they reported fracture incidence in terms of the number of patients suffering fractures, as this enabled calculation of the relative risk of patients in the intervention group developing a new fracture or fractures, compared with those in the control group. Ideally, only studies that had fracture as a primary end-point would have been included in the meta-analyses. However, pragmatically this was not possible as very few studies met this criterion. Meta-analysis was carried out with Review Manager, using the random-effects model, as this both allows generalisation beyond the sample of patients represented by the studies included in the meta-analysis and provides wider, more conservative, confidence intervals than the fixed-effects model. Since the end-point of interest was fracture, it seemed appropriate to include open-label studies.

To ensure comparability, the meta-analyses of vertebral fractures only pooled data from studies that used the same definition of vertebral fracture. Where possible, data were pooled from studies using a definition that required a 20% or greater reduction in anterior, middle or posterior vertebral height: as noted above, this definition was felt to identify fractures more reliably than a definition that required a 15% or greater reduction.

A model was constructed to estimate the cost-effectiveness of osteoporosis interventions. The key inputs to this model were the efficacy data for each intervention in terms of the ability to reduce the incidence of hip, vertebral, wrist and proximal humerus fractures. The model calculated the number of fractures that occurred and provided the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs) accrued by a cohort of 100 women with osteoporosis, with each fracture being detrimental to health. When the costs of the intervention are included, the marginal cost compared with no treatment (assumed to be a sufficient intake of calcium and vitamin D) can be calculated. When this figure is divided by the gain in QALYs, a cost per QALY ratio can be calculated. In addition to osteoporotic fractures, the conditions of breast cancer and coronary heart disease (CHD) were modelled, as some interventions have been shown to affect the risk of these diseases.

Results and conclusions

Number and quality of studies, and direction of evidence

Ninety randomised controlled trials (RCTs) met the inclusion criteria. They related to the five interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) and to five comparators [calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy (HRT) and exercise], as well as placebo or no treatment.

All five interventions have been shown to reduce the risk of vertebral fracture in women with severe osteoporosis with adequate calcium intakes. Alendronate and raloxifene have also been
demonstrated to reduce the risk of vertebral fracture in women with adequate calcium or vitamin D intakes who have osteoporosis without fracture. However, only risedronate and teriparatide have also been demonstrated to reduce the risk of non-vertebral fracture in women with severe osteoporosis and adequate calcium intakes. Alendronate has been shown to do so in women with osteoporosis with or without fracture and with adequate calcium or vitamin D intakes. However, none of these drugs has been demonstrated, by direct comparison, to be significantly more effective than either each other or the other active interventions reviewed in this report.

Of the five interventions, only raloxifene appeared to reduce the risk of vertebral fracture in postmenopausal women unselected for low bone mineral density (BMD). However, as the full data have not been made public, there is some uncertainty regarding this result. None of the five interventions has been shown to reduce the risk of non-vertebral fracture in women unselected for low BMD.

Summary of benefits
All of the proposed interventions provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the age of the patient.

Costs
The intervention costs of treating all osteoporotic women, for a period of 5 years, were in the region of £900–1500 million for alendronate, etidronate, risedronate and raloxifene. Teriparatide had a much higher acquisition cost, but has been used on a small subset of the population and thus this cost has not been calculated.

The estimated costs, when the reduction in the number of fractures and breast cancer events over a 10-year period was included, varied widely for the interventions. These net costs were markedly different by age, with some interventions becoming cost-saving at higher age ranges in patients with a prior fracture.

Cost per QALY
The cost per QALY ratios fell dramatically with age. Assuming the risks of a woman with severe osteoporosis at the threshold of osteoporosis, no treatment had a cost per QALY below £35,000 at 50 years of age. At 60 years of age, the cost per QALY of raloxifene was £26,000 assuming no impact on hip fractures, and £31,000 assuming an adverse effect. However, these results are driven by the effect on breast cancer and the assumptions made regarding this disease state. No other intervention had a cost per QALY below £35,000.

At 70 years of age, the cost per QALY ratios of the three bisphosphonates significantly decreased, being £10,000, £15,000 and £28,000 for alendronate, risedronate and etidronate, respectively. Etidronate had a reasonably strong observational evidence base and where this was considered the cost per QALY ratio fell to £15,000. Raloxifene, assuming no effect on hip fracture, had a cost per QALY of £24,000. At 80 years of age, both alendronate and risedronate dominated no treatment. Raloxifene, assuming no effect on hip fracture, had a cost per QALY of £28,000. This figure was £38,000 for teriparatide (when assumed to cost £2000 per annum) and £45,000 for etidronate.

Incorporating the observational data into the etidronate analysis reduced the cost per QALY ratio to £6000.

Analyses were conducted assuming that the fracture risk is doubled at each site. In these circumstances alendronate and risedronate had cost per QALY ratios below £30,000 at all ages. If the observational data were incorporated, etidronate had a cost per QALY ratio below £30,000 at all ages; however, using RCT data alone the cost per QALY fell below £30,000 only at 70 years of age and above. Raloxifene (assuming no effect on hip fracture) had a cost per QALY ratio below £30,000 at all ages; however, this again was driven by breast cancer assumptions. Teriparatide (assumed to cost £3500 per annum) had a cost per QALY of £31,000 at 80 years of age.

For women at the threshold of osteoporosis, without a prior fracture and aged 70 years, the cost per QALY of the three bisphosphonates ranged from £34,000 to £41,000. Raloxifene had a cost per QALY of £23,000, assuming no effect on hip fracture, given assumptions regarding breast cancer. At 80 years of age, the cost per QALY of alendronate and risedronate was below £20,000. This was true for etidronate when incorporating observational data, but the value rose to £69,000 when only RCT data were used. No other intervention had a cost per QALY below £35,000. It was assumed that doubling the risk of fracture for women without a prior fracture would give results similar to patients at the threshold of osteoporosis with a prior fracture.
The results for 80 years of age in all scenarios should be treated with caution as the assumed efficacy for each intervention has not been proven in this age group. The results for raloxifene should be treated with caution as the major impact on quality of life is through an effect on breast cancer and not via effects on fractures.

**Recommendations for research**

The evidence base for the efficacy of fracture prevention in the very elderly needs to be strengthened. The results calculated for women aged 80 years assumed the applicability of results from RCTs (in which only a minority of patients were of this age). If this were not true, as possibly demonstrated by an RCT by McClung, then the results would be markedly different.

To assess accurately the true potential of raloxifene, reanalysis should be conducted using a dedicated breast cancer and CHD model. Results for women at the threshold of osteoporosis and with a prior fracture that ignore these benefits produced a high cost per QALY ratio (>£70,000), which fell significantly (<£40,000) when the effect on breast cancer was included and to under £30,000 when the effect on CHD was included. The robustness of these latter results cannot be guaranteed, owing to simplifying assumptions on the aetiology, costs and QALYs of breast cancer and CHD.

The cost-effectiveness of teriparatide is dependent on the assumed efficacy on hip fracture. At present the decrease is non-significant and a further trial is recommended to reduce the uncertainty in this parameter.

**Publication**

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/58/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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