Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis

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Executive summary

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Executive summary

Background and aims

Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a subsequent increase in bone fragility and susceptibility to fracture. Aside from postmenopausal osteoporosis, the most common secondary cause of osteoporosis is that due to the long-term use of oral glucocorticoids.

The most serious clinical consequence of osteoporosis is hip fracture, which increases in incidence exponentially with age and incurs high morbidity, mortality and healthcare expenditure. Other common fractures occur at the spine, forearm and shoulder, but the osteoporotic skeleton is liable to fracture at many sites.

Glucocorticoids are widely used in medicine and long-term use is characterised by a significant increase in fracture risk. Approximately 250,000 men and women take long-term glucocorticoids in the UK, but few are treated for skeletal disease.

The mechanism for increased fracture risk is multifactorial and includes loss of bone tissue mass, disturbances in skeletal architecture, myopathy and the underlying disorders for which glucocorticoids are prescribed.

There are various agents available for the treatment of osteoporosis, and several are licensed for use in the prevention and treatment of glucocorticoid-induced osteoporosis (GIO). The evidence for their efficacy is examined and their cost-effectiveness is modelled in a case-finding strategy.

Methods

Therapeutic intervention

A systematic review was undertaken of all randomised controlled trials in which fracture was measured as an outcome. The interventions reviewed were bisphosphonates, vitamin D, 1α-hydroxylated derivatives of vitamin D, calcitonin, calcium, oestrogens, oestrogen-like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, testosterone and parathyroid hormone. Effectiveness was compared with effectiveness in postmenopausal osteoporosis.

Epidemiology, costs and utilities

The annual risk of osteoporotic fracture was characterised for men and women from the UK. For the purpose of this report, fractures of the femur, pelvis, spine, distal forearm, tibia and fibula, clavicle, scapula and sternum and humerus were designated as being osteoporotic. The most common fractures (hip, spine, forearm and proximal humerus) account for approximately 70% of osteoporotic fractures and more than 70% of the morbidity.

The risk of osteoporotic fractures at any given *T*-score for bone mineral density (BMD) was determined from published meta-analyses of the relationship between BMD and fracture risk. The risk of an osteoporotic fracture in the presence of a prior osteoporotic fracture was computed from a published meta-analysis of the relationship between the prior occurrence of fracture of each type and the risk of a future fracture of each type. The additional risk due to exposure to glucocorticoids was determined by meta-analysis of prospectively studied population-based cohorts.

The consequences of fracture on mortality were assessed for each fracture type.

Costs and utilities were determined for osteoporosis in the UK by updating systematic reviews of the literature.

Health economics model

The model used comprised an individual patient-based approach that simulated whether or not events occurred in each subsequent year for each patient.

Transition states included fracture states (e.g. hip, wrist, vertebral and proximal humerus), death from hip fracture, nursing home admission due to hip fracture and death from other causes.

The model simulated cohorts at fixed ages (50–80 years at 5-year intervals) and fixed *T*-scores for BMD. The proportion of the population ▶

with different fracture types was simulated from the known distribution of these fractures at different ages.

Effectiveness was populated from a systematic review of interventions in GIO and postmenopausal osteoporosis. Treatments were given for 5 years using a 5-year offset time (in this context, offset time is the duration for which an effect on fracture persists after the treatment stops). The analytic framework was set at 10 years. Because of the many uncertainties, extensive sensitivity analysis was undertaken.

Results

The results of the systematic review of RCTs indicated that the bisphosphonate risedronate and calcidiol reduced the incidence of vertebral fracture. The risk of non-vertebral fractures, including hip fracture, was not significantly decreased.

For several agents, failure to demonstrate efficacy, particularly for hip fracture, was largely due to the lack of appropriate RCTs. When data were pooled, the combined effects of all bisphosphonates on vertebral and non-vertebral fracture incidence were comparable to that observed in postmenopausal osteoporosis.

Previous glucocorticoid use was associated with a significantly increased risk of any osteoporotic fracture and hip fracture when adjusted for BMD. For osteoporotic fracture, the range of relative risk with age was 2.63–1.71 and for hip fracture 4.42–2.48 (i.e. decreasing with age). No significant difference in risk was seen between men and women. The risk was independent of prior fracture. In the three cohorts that documented current glucocorticoid use, BMD was significantly reduced at the femoral neck, but fracture risk was still only partly explained by BMD.

Analysis of cost-effectiveness was undertaken for risedronate using the empirical data in glucocorticoid-induced osteoporosis. Further analysis of bisphosphonate used data on efficacy that assumed that their effects were comparable to those shown for bisphosphonates in postmenopausal osteoporosis. The results at each age were presented as a central estimate of cost per quality-adjusted life-year (QALY) gained compared with no treatment. Costs were discounted at 6% and QALYs at 1.5% in base-case scenarios. The estimate was bounded by a 95% confidence interval representing the range of cost–utility that was incurred by 95% of the combinations of relative risks for efficacy.

When risedronate was assumed to have efficacy on vertebral fracture alone, without effects on appendicular fractures, cost-effectiveness ratios fell with age, but at no age did treatment become cost-effective at the average *T*-score for women at each age. When account was taken of BMD, cost-effectiveness was confined to less than 10% of individuals with very low *T*-scores.

Further analysis with bisphosphonate showed cost-effective scenarios in patients with a prior fracture. In patients without a prior fracture, cost-effectiveness was observed in the elderly (aged 75 years or more) and in others with low *T*-scores for BMD.

In sensitivity analysis, important determinants of cost-effectiveness included age and cost of intervention. Cost-effectiveness ratios were sensitive to changes in discount rates for benefits and changes in the assumption concerning offset of effect (offset time). Cost-effectiveness improved markedly by selecting patients according to BMD.

The results were not markedly affected by the threshold used for cost-effectiveness, poor compliance, varying the assumptions about mortality after hip fracture or differences in discount rates. The inclusion of costs of added years of life (direct costs only) had little effect. By contrast, the inclusion of all vertebral fractures (in addition to clinically overt fractures) had a marked effect on improving cost-effectiveness, as did the avoidance of BMD and associated medical supervision. Cost-effectiveness was also sensitive to offset time, duration of treatment and the time horizon used.

Several patient assessment algorithms were tested. The current guidance of the Bone and Tooth Society was unsatisfactory, since the age threshold at which treatment was recommended (age 65 years or more) did not provide cost-effective intervention. Moreover, the use of a *T*-score threshold of –1.5 standard deviation (SD) in patients without a prior fracture was cost-ineffective.

The following strategy was considered appropriate in patients receiving long-term glucocorticoids. Patients with a prior fragility fracture would be eligible for treatment, as would individuals aged 75 years or more, irrespective of BMD. ▶

At other ages, patients without prior fractures would be eligible for treatment contingent upon a BMD threshold, with a *T*-score of –2.0 SD or less.

The strategy would demand BMD testing in 73.4% of patients and render 47% eligible for treatment.

In patients taking higher than average doses of glucocorticoids, less stringent *T*-score cut-offs may be appropriate because of the higher fracture risks using the higher doses of glucocorticoids.

Conclusions

Cost-effective scenarios for risedronate in the management of GIO were identified, but only at the extremes of age and *T*-score, such that less than 10% of the population of patients aged 50 years or more would be eligible for treatment.

Greater cost-effectiveness was observed assuming that the effects of bisphosphonate in GIO were similar to those observed in postmenopausal osteoporosis, an assumption tested by meta-analysis.

An assessment algorithm is proposed based on age, the presence of a prior fragility fracture and BMD tests in individuals aged 50 years or more with no fracture.

The conclusions we derive are conservative, mainly because of the assumptions that were made in the absence of sufficient data. The conservative assumptions include:

1. Not all vertebral fractures are included.
2. The risk of re-fracture in the few years after a fracture is likely to be underestimated. It should be noted, however, that, if short-term risks are underestimated, then long-term fracture risks will be overestimated.
3. Long-term effects of osteoporotic fractures on utilities are ignored.
4. The costs of BMD tests and medical supervision are included for all patients.
5. Only average doses of glucocorticoids are modelled, but the risk of fractures is increased in a dose-dependent manner.
6. A relatively short time horizon (10 years).

Thus, conclusions that treatment scenarios are cost-effective are reasonably secure. By contrast, for the reasons outlined above, scenarios shown not to be cost-effective are less secure. As information in these areas becomes available, the implications for cost-effectiveness of interventions should be reappraised. In the meantime, account needs to be taken of these factors in applying these analyses to practice guidance.

Recommendations for research

Intervention thresholds differ substantially from diagnostic thresholds, and should be based on the absolute fracture probability that depends not only on the *T*-score but also on other independent risk factors. Health economic assessment based on probability of fracture is an important area for further research.

Other areas for further research arise from gaps in our empirical knowledge on utilities and side-effects which are amenable to primary research. We also recommend that further secondary research be undertaken to evaluate more closely the impact of all vertebral fractures (rather than clinically overt vertebral fractures) on cost-effectiveness and methods of monitoring treatment.

Publication

Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M. Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis. *Health Technol Assess* 2007;**11**(7).

NIHR Health Technology Assessment Programme

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/06/02. The contractual start date was in April 2002. The draft report began editorial review in November 2004 and was accepted for publication in May 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. 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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