Economic evaluation of zoledronic acid for the prevention of osteoporotic fractures in postmenopausal women with early-stage breast cancer receiving aromatase inhibitors in the UK

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study assessed the cost-effectiveness of zoledronic acid for the prevention of fractures in postmenopausal women, with hormone receptor positive, early breast cancer (stages I to IIIa), who were being treated with aromatase inhibitors. The authors concluded that both delayed and immediate zoledronic acid appeared to be cost-effective. On the whole, the methods and results were reported clearly. The authors’ conclusions appear to be appropriate, but there were some limitations to the study.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of zoledronic acid for the prevention of fractures in postmenopausal women, with hormone receptor positive, early breast cancer (stages I to IIIa), who were being treated with aromatase inhibitors.

Interventions
Two interventions were compared against no zoledronic acid. All patients were given adjuvant letrozole at 2.5mg daily for five years.

The first intervention was six-monthly intravenous zoledronic acid (4mg), beginning at the same time as the adjuvant letrozole. The second intervention was zoledronic acid delayed until the patient’s bone mineral density T-score decreased to more than two standard deviations below normal; until they had a non-traumatic fracture; or until they were found to have an asymptomatic fracture upon assessment three years after starting letrozole.

Location/setting
UK/primary care.

Methods
Analytical approach:
A Markov model was developed to combine the cost and effectiveness data from published sources. The model’s cycle length was one year and the time horizon was the patient’s lifetime. The authors stated that the perspective was that of the UK NHS.

Effectiveness data:
The effectiveness data for zoledronic acid in retaining bone mineral density (BMD) was from a three-year interim analysis of several published trials. After treatment ceased, zoledronic acid was assumed to have no further effect. BMD without treatment was from a bone subanalysis of a published trial. Mortality in the first five years was from standard sources, and incorporated additional mortality due to hip fracture. After five years, mortality was from published cancer survival data. The main clinical effectiveness estimate was the fracture risk and these data were from published studies.
Monetary benefit and utility valuations:
The utility weights for fractures, including hip fractures that led to nursing home residency, were from published literature. It was assumed that the utility weight was reduced for one year, before recovering to a level between that of the first year after fracture and that before the fracture.

Measure of benefit:
The primary measure of benefit was quality-adjusted life-years (QALYs) and these were discounted at 3.5% per annum.

Cost data:
The cost categories were drug acquisition; medical supplies to administer zoledronic acid; physician and nurse time; physician visits; BMD scans; and fracture treatment. The drug acquisition costs were from the British National Formulary. Other costs were from published literature. The costs were reported in 2007 UK pounds sterling (£) and discounted at 3.5% per annum.

Analysis of uncertainty:
The uncertainty was explored, using probabilistic sensitivity analysis, with 1,000 simulations. Normal distributions were assumed for the changes in BMD and the relative risk of subsequent fracture. Beta distributions were assumed for the utilities, gamma for the costs, and triangular for the percentage of hip fractures leading to nursing home residency. The results of this sensitivity analysis were presented in a cost-effectiveness acceptability curve.

Results
The total QALYs were 12.45 with immediate zoledronic acid; 12.40 with delayed zoledronic acid; and 12.37 with no zoledronic acid. The total costs were £8,960 with immediate zoledronic acid; £7,637 with delayed zoledronic acid; and £7,218 with no zoledronic acid.

The incremental cost-effectiveness ratio was £21,973 per QALY for immediate, compared with no zoledronic acid; £16,069 per QALY for delayed, compared with no zoledronic acid; and £24,868 per QALY for immediate, compared with delayed zoledronic acid.

The probabilistic sensitivity analysis found that at a willingness-to-pay threshold of around £20,000 per QALY, delayed zoledronic acid was likely to be the most cost-effective strategy, while at a willingness-to-pay threshold of around £30,000 per QALY, immediate zoledronic acid was most cost-effective.

Authors' conclusions
The authors concluded that both delayed and immediate zoledronic acid, for the prevention of osteoporotic fractures in postmenopausal women with early stage breast cancer, appeared to be cost-effective. More research was required on its cost-effectiveness in subgroups with different fracture risks.

CRD commentary
Interventions:
The interventions were described and appear to have been relevant for the study setting. Other bisphosphonates were not considered as comparators and it was not clear if the usual practice was included.

Effectiveness/benefits:
The details of the trials that provided the effectiveness data were not reported, but the references were given. These articles should be consulted to assess the quality of the data. It was unclear if a systematic review was conducted, making it unclear if all the relevant available evidence was analysed. Adverse events were not included and these might have reduced the effectiveness of the interventions. The health state utilities were clearly presented, but the methods used to measure them were not described. The referenced paper should be consulted to assess their suitability and quality. The benefit measure appears to have been appropriate, as it incorporated both morbidity and mortality; it was appropriately discounted.

Costs:
The perspective was clearly presented and the cost categories appear to have been relevant to this perspective. The sources for the unit costs were presented and appear to have been appropriate. The costs were discounted and adjusted for inflation.

Analysis and results:
The analytic approach appears to have been appropriate and was sufficiently described. The Markov model was presented in a diagram. The results were combined into incremental cost-utility ratios and were reported clearly. The uncertainty was assessed in probabilistic sensitivity analysis, which was transparently reported. One-way sensitivity analysis might have been a useful addition to the study, to assess which inputs were most uncertain. The authors discussed the limitations of their analysis.

Concluding remarks:
On the whole, the methods and results were reported clearly. The authors' conclusions appear to be appropriate, given the limitations of the study.

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