Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases

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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 examined the cost-effectiveness of denosumab versus zoledronic acid for the prevention of skeletal events in the treatment of bone metastases in men with hormone-refractory prostate cancer. The authors concluded that denosumab was more effective than zoledronic acid, but seemed to be more costly from the perspective of the US payer. The analysis relied on the results of a clinical trial. The methods were valid and key areas of uncertainty were investigated. The authors’ conclusions seem robust.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
This study examined the cost-effectiveness of denosumab versus zoledronic acid for the prevention of skeletal events in the treatment of bone metastases in men with hormone-refractory prostate cancer.

Interventions
The two treatments were denosumab 120mg and zoledronic acid 4mg, every four weeks.

Location/setting
USA/secondary care.

Methods
Analytical approach:
The main analysis used a Markov model, with a one-year time horizon. The authors stated that the perspective of the third-party payer was adopted.

Effectiveness data:
The primary source for the clinical evidence was a published phase III, randomised, head-to-head, clinical trial comparing the two treatments in 1,904 eligible patients. Additional inputs were from published literature, which appeared to include only clinical trials. The number of skeletal events was the primary endpoint of the analysis and these included pathologic fracture, spinal cord compression, radiation to bone, or surgery to bone.

Monetary benefit and utility valuations:
Not considered.

Measure of benefit:
The number of skeletal events was the summary benefit measure.

Cost data:
The economic analysis included both drug and non-drug direct costs. The drug costs included wholesale acquisition, administration by a health care professional, and monitoring. The other costs were those of disease progression, skeletal events, and terminal care. Adverse event costs were included. Drug costs were based on their average wholesale prices. Other costs were from official payer prices, and a published US study. Some adjustment to data from this published study was needed, due to the different combination of skeletal events considered, compared with the phase III trial. All
Analysis of uncertainty:
One-way sensitivity analyses were carried out to investigate how robust the main findings were to variations in the model inputs, using published or assumed ranges of values. An alternative time horizon of three years was considered and a 3% annual discount rate was applied to both clinical and cost outcomes. The authors applied quality-of-life weights to the skeletal events to estimate the incremental cost per quality-adjusted life-year (QALY). A multivariate probabilistic sensitivity analysis was performed, using Monte Carlo simulation with 1,000 iterations. The types of probability distribution were clearly stated.

Results
Over one year, the number of skeletal events per patient were 0.60 with zoledronic acid and 0.49 with denosumab. The expected total costs were $27,528 with zoledronic acid and $35,341 with denosumab. The difference in costs was almost entirely due to the drugs; denosumab was more expensive. The incremental cost per skeletal event avoided with denosumab over zoledronic acid was $71,027 ($51,319 over three years).

In the deterministic sensitivity analysis, the incremental cost per skeletal event avoided ranged from $27,318 to $161,680. The most influential inputs were the cost of denosumab or zoledronic acid and the time to first skeletal event with zoledronic acid or denosumab. In most circumstances the incremental cost per skeletal event avoided ranged from $50,000 to $100,000. Excluding the adverse event costs from the analysis did not alter these results.

At one year, denosumab was cost-effective over zoledronic acid in 49.5% of simulations (79.0% at three years) at a willingness-to-pay threshold of $70,000 per skeletal event avoided, 17.5% of simulations (49.8% at three years) at a threshold of $50,000, and 0.3% of simulations (4.1% at three years) at a threshold of $30,000. When quality-of-life scores were applied to skeletal events, the incremental cost per QALY gained with denosumab over zoledronic acid was over $2 million.

Authors’ conclusions
The authors concluded that denosumab was more effective than zoledronic acid, but it seemed to be a costly alternative from the perspective of the US payer.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear as the proposed treatment was compared with the usual treatment to prevent skeletal events in men with prostate cancer and bone metastases.

Effectiveness/benefits:
The clinical data were mainly from a very large head-to-head randomised phase III trial, which should have had high internal validity. The results of this trial were reported in detail and the methods used to translate the primary outcomes into model probabilities appear to have been appropriate. Other clinical trials were used where data were not available from the main trial. An extensive sensitivity analysis was conducted on all model inputs. The authors justified their selection of the rate of skeletal events as the summary benefit measure; both treatments had similar rates of disease progression and overall survival in the clinical trial. This measure was also used in previous cost-effectiveness evaluations, allowing comparisons with these results, but it was disease-specific and might not be generalisable to other health care technologies.

Costs:
The cost categories were consistent with the perspective of the payer. Some unit costs and quantities of resources were reported, improving the transparency of the analysis. The cost calculations and assumptions were clearly reported. The data sources appear to have been consistent with the viewpoint of the payer, but some costs were from an earlier study, and the details were not reported. The authors stated that adjustments were made for values taken from the literature where needed. The price year was reported, allowing deflation exercises. Cost-to-charge ratios were applied where necessary. The impact of variations in the economic inputs was appropriately investigated in the sensitivity analyses.
The results were extensively presented and an incremental approach was appropriately used to combine the costs and benefits of the two treatments. Appropriate tools were used to assess uncertainty, and the methods and results were clearly reported. The authors provided clear details of the structure and assumptions of the model. They acknowledged some limitations to their analysis mainly due to the need for simplifications in the model, but these appear to have been addressed in the sensitivity analysis. The results were specific to the USA, but might be relevant to other settings with similar relative drug prices.

Concluding remarks:
The analysis relied on the results of a clinical trial. The cost-effectiveness methods were valid and key areas of uncertainty were investigated. The authors’ conclusions appear to be robust.

**Funding**
Funded by Novartis Pharmaceuticals Corporation, USA, the manufacturer of zoledronic acid.

**Bibliographic details**
Xie J, Namjoshi M, Wu EQ, Parikh K, Diener M, Yu AP, Guo A, Culver KW. Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases. Journal of Managed Care Pharmacy 2011; 17(8): 621-634

**PubMedID**
21942303

**Original Paper URL**
http://www.amcp.org/JMCP/2011/October/12815/1033.html

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antibodies, Monoclonal /administration & dosage /economics; Antibodies, Monoclonal, Humanized; Bone Density Conservation Agents /administration & dosage /economics; Bone Neoplasms /drug therapy /economics /secondary; Cohort Studies; Cost-Benefit Analysis /economics; Denosumab; Diphosphonates /economics /therapeutic use; Disease Progression; Drug Costs; Health Care Costs; Humans; Imidazoles /economics /therapeutic use; Male; Markov Chains; Models, Economic; Multivariate Analysis; Neoplasms, Hormone-Dependent /drug therapy /economics /pathology; Prostatic Neoplasms /drug therapy /economics /pathology; Sensitivity and Specificity; United States

**AccessionNumber**
22012005639

**Date bibliographic record published**
09/03/2012

**Date abstract record published**
20/10/2012