Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer

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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.

Health technology
The health technology examined in the study was 4 mg zoledronic acid, every 3 weeks, in men with advanced-stage prostate cancer and a history of metastatic bone disease.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis; cost-utility analysis.

Study population
The study population comprised advanced-stage prostate cancer patients enrolled in a multinational, randomised, controlled trial (RCT). An overview of the population, plus exclusion/inclusion criteria, was not presented here, but the RCT was published separately (Saad et al 2002, see "Other Publications of Related Interest" below for bibliographic details).

Setting
The setting was secondary care. Effectiveness data collection was carried out primarily in the USA but also in Canada, Australia, New Zealand, 5 South American and 8 European countries.

Dates to which data relate
The dates for effectiveness and resource use data collection were not explicitly reported; please refer to the published RCT (Saad et al 2002 - see "Other Publications of Related Interest" below for bibliographic details). The cost of zoledronic acid was based on 2002 prices, while other costs were based on 2000 prices.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on a subset of the patients who participated in the effectiveness study. Only those patients for whom resource use data were prospectively collected during the clinical trial were included in the economic evaluation.

Study sample
No details of the sample selection were reported in the economic evaluation. Refer to the RCT paper (Saad et al 2002 -
see "Other Publications of Related Interest" below for bibliographic details). 643 patients were enrolled in the RCT of whom 214 patients were randomised to zoledronic acid and 208 to placebo. Excluding patients without resource use data, 181 and 179 were randomised to the zoledronic acid and placebo groups, respectively. Thus, 360 patients were included in the economic evaluation. Demographic and baseline characteristics were not provided by treatment group. The authors stated that there were no significant differences between treatment groups in baseline characteristics and that mean follow-up did not differ across treatment groups. Demographic and baseline characteristics were compared for all patients with resource use data versus all patients without resource use data, with no significant differences. The median age of all patients included in the economic evaluation was 73. Ethnicity was split 85.3% white, 9.7% black, 1.1% Asian and 3.9% 'other'. 35.6% of the patients had previously suffered an SRE. Baseline Eastern Cooperative Oncology Group (ECOG) rating showed 42.8% of patients rated ‘fully active’, 48.9% ‘strenuous activity limited’ and 8.3% ‘self-care but no work’. The majority of patients (59.9%) were receiving baseline analgesic treatment. The largest group of patients came from the USA (53.3%), followed by Canada (21.1%) and Australia (10.6%).

**Study design**
The clinical study was a multinational, double-blind, placebo-controlled randomised trial. Patients received zoledronic acid or placebo every 3 weeks for 15 months. Randomisation method and loss to follow-up was not described here (please refer to Saad et al 2002 - see "Other Publications of Related Interest" below for bibliographic details).

**Analysis of effectiveness**
It was stated that all analyses of the clinical study were based on the intention to treat principle. The primary endpoint was the proportion of patients experiencing one or more SREs. No adjustments for confounding factors were made.

**Effectiveness results**
During the trial, 33.2% of patients receiving zoledronic acid and 44.2% of patients receiving placebo experienced at least 1 SRE.

The mean number of SREs per patient was 0.78 in the zoledronic acid group and 1.24 in the placebo group.

Confidence intervals and detailed results were not reported.

**Clinical conclusions**
The authors found that zoledronic acid decreased the incidence of SREs relative to placebo. This result coincided with the conclusions of several other cited studies investigating the efficacy of zoledronic acid in the prevention of SREs.

**Measure of benefits used in the economic analysis**
Outcome measures included SREs avoided and patients free of SREs. A further outcome measure, quality-adjusted life-years (QALYs), was estimated from enrolment times and the numbers and types of SRE experienced by each patient. During the study, the EQ-5D questionnaire was administered to patients at baseline and every 3 months. Quality of life adjustments used mean EQ-5D thermometer values. Because of missing EQ-5D responses, preference weights were assigned randomly to each type of SRE per patient. The preference weights were derived from patients who completed the EQ-5D within 30 days before or after an SRE. The authors assumed that patients experienced a decrement in quality of life for 60 days due to each SRE.

**Direct costs**
Discounting was not carried out as the costs were incurred over a period of 15 months. Unit costs were reported separately from quantities. The following direct medical costs were included: study medications, administration, hospitalisations, outpatient visits, treatments, procedures, concomitant medications and institutionalised care. Resource use, based on data from a subset of patients, was mostly collected alongside the clinical trial; mean and SD of quantities were reported. Administration costs were drawn from a microcosting study of zoledronic acid (please refer to Saad et al
2002 - see "Other Publications of Related Interest" below for bibliographic details). Estimation of USA prices was based on Medicare reimbursement rates (hospitalisations and other medical care), Red Book average wholesale prices (concomitant medications) and the Federal Supply Schedule from the Department of Veterans’ Affairs National Formulary (zoledronic acid). Estimation of non-USA prices was based on country-specific unit cost estimates obtained from local health economists (no sources supplied) and on the USA ex-factory price excluding VAT (zoledronic acid). It was reported that costing methods have been described in greater detail elsewhere (please refer to Saad et al 2002 - see "Other Publications of Related Interest" below for bibliographic details). All costs were based on 2000 prices. Only zoledronic acid was costed at 2002 prices.

Statistical analysis of costs
Wilcoxon rank sum tests were used to compare costs of resource use. Nonparametric bootstrapping was used to test for differences in costs between treatment groups.

Indirect Costs
Indirect costs were not incorporated into the analysis.

Currency
US dollars ($). Unit costs in countries other than the USA were converted to year 2000 dollars using purchasing power parities.

Sensitivity analysis
In sensitivity analyses, the investigators varied the price of zoledronic acid, used the community-based utility weights derived from the EQ-5D and varied the number of days that patients experienced lower quality of life due to SREs. Univariate (parameters listed) and bivariate (cost of zoledronic acid with number of days experiencing lowered quality of life) analyses were performed.

The ranges for within-trial cost of zoledronic acid, $1,000-$8,000 (base case: $5,119), and number of lower-quality days associated with SREs, 30-120 days (base case: 60 days), appeared to be based on authors' assumptions although the SD of the cost of zoledronic acid had been reported. Variability in estimated effectiveness was not investigated.

Estimated benefits used in the economic analysis
Patients receiving zoledronic acid experienced approximately 0.46 fewer SREs per patient than those receiving placebo over the 15-month trial duration. In addition, approximately 11.0% fewer patients experienced one or more SRE during the trial.

The average incremental gain in quality-adjusted time during the study period was approximately 2 weeks for patients receiving zoledronic acid.

Cost results
The authors reported total medical costs excluding study medication.

The cost per patient receiving zoledronic acid was $5,365, while the cost per patient receiving placebo was $5,689.

This difference of -$324 was insignificant (95% CI: -$1,781 - $1,146; p = 0.6687), and the authors concluded that the incremental cost of the intervention could be calculated as the cost of zoledronic acid and its administration at $5,677 +/- $3,809.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios (ICERs) and cost-utility ratios were calculated as the cost of zoledronic acid plus its administration divided by the incremental difference in outcomes between treatment groups using the full randomised cohort of patients in the trials.

The ICERs were $12,300 per SRE avoided (95% CI: $6,900 - $48,700) and $51,400 per additional patient free of SREs during the trial (95% CI: $26,900 - $243,700). The incremental cost per QALY was $159,200 (95% CI: $88,500 - $786,600).

The sensitivity analyses showed that, upon varying the cost of zoledronic acid, the incremental cost per SRE avoided ranged from approximately $2,000 to $18,000 and the incremental cost per SRE-free patient ranged from approximately $9,000 to $72,000.

The incremental cost per QALY using community-based utility weights was $145,900.

The incremental cost per QALY in the bivariate analysis ranged from less than $20,000 to almost $400,000.

The cost per QALY was most sensitive to changing the number of days a patient was affected by an SRE.

Authors’ conclusions
The authors concluded that there were no significant differences in the cost of medical care in patients receiving zoledronic acid versus placebo. However, patients receiving zoledronic acid experienced fewer SREs, and it is possible patient benefits could accrue beyond the time horizon of the trial. The estimated cost-effectiveness ratios, while higher than the thresholds used by many decision-makers to determine cost-effectiveness, were consistent with those reported in other evaluations of biphosphonates (in breast cancer).

CRD COMMENTARY - Selection of comparators
The reason for the choice of comparator (placebo) was not clear, nor did the authors provide a justification for the choice. Implicitly, current practice does not seek to prevent SREs in prostate cancer patients. You should decide if this reflects practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled clinical trial, which was appropriate for the study question. The study sample was multinational and this adds to its generalisability. However, most countries enrolled a very small number of patients, with the majority of patients coming from the USA, therefore transferability of results is not necessarily valid. It is otherwise unclear whether the study sample was representative of the study population due to lack of reporting. It is difficult to comment on internal validity as the exclusion/inclusion criteria and loss to follow-up were reported elsewhere. It was stated that treatment groups were comparable at baseline but no evidence for this was reported. It appears that statistical analyses taking account of potential biases or confounding factors were not conducted, thus lessening the credibility of the analysis of effectiveness.

Validity of estimate of measure of benefit
Randomisation increases the validity of the estimates of benefit, which came directly from the effectiveness study. If, as was stated, there were no significant differences across treatment groups at baseline, estimates are likely to be valid. The methodology of deriving preferences and applying them to the clinical data was clearly reported and justified. Utility weights were drawn from the same population to which they were later applied. This tends to enhance the validity of the QALY estimates. QALYs, unlike the other two benefit measures, are not disease-specific, thus enhancing ease of comparison with the benefits of other technologies.

Validity of estimate of costs
Resource use was prospectively collected alongside the clinical study, adding to the internal validity. However, it was
only collected for a subset of patients, excluding those in South America, and was assumed to apply to all patients. Unit costs, apart from the cost of zoledronic acid, were not quoted. Sources of non-USA medical costs were not adequately described. The costs of treating an SRE were not included, although they were relevant to the analysis. Quantities were treated deterministically and medical costs (excluding zoledronic acid costs) were tested for differences using nonparametric bootstrapping. Only drug costs were considered in the incremental analysis and these were varied in the sensitivity analysis.

**Other issues**
The authors found no significant saving in resource use or direct medical costs for patients receiving zoledronic acid, despite reductions in SREs experienced, suggesting that there is little clinical benefit to patients. The authors suggested that this is due to large variability in costs of treating cancer patients as well as costs of treating SREs. This claim should be further investigated. The cost per QALY was high in the base-case and in all sensitivity scenarios. Therefore, it is open to question whether decreasing the occurrence of SREs is a valid and cost-effective aim of therapy. In the absence of similar studies in prostate cancer, the authors favourably compared the methodology of their evaluation with two studies into the cost-effectiveness of biphosphonates in breast cancer. The results of these studies were dissimilar, but the authors stated that their own results were consistent with the results reported. On the basis of the contents of the paper alone, it would be impossible to reproduce the economic evaluation.

**Implications of the study**
The authors acknowledge that their evaluation shows that zoledronic acid in this indication has a higher cost per QALY than the thresholds applied by decision-makers. They recommend that future studies should minimise missing (resource use) data and administer quality of life instruments more frequently when patients experience SREs. The authors also suggest that patient benefits may accrue beyond the 15-month time frame of their analysis.

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**Other publications of related interest**


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