Economic evaluation of everolimus vs azathioprine at one year after de novo heart transplantation

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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 study examined the use of everolimus (1.5 or 3.0 mg/day) in combination with cyclosporine in heart transplant patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised de novo heart transplant patients. No specific inclusion or exclusion criteria were reported in the present study, but this information may be available in the original paper (Eisen et al. 2003, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The setting was unclear, but it was likely to have been secondary care. The economic study was carried out in Durham (NC), USA.

Dates to which data relate
The dates when the effectiveness and resource use data were collected were not reported, but may be available in the original paper (Eisen et al. 2003). The costs were estimated at 2001 prices.

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

Link between effectiveness and cost data
The costing was undertaken prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
It was unclear whether power calculations had been used to determine sample size, but this information may be available in the original paper (Eisen et al. 2003). The choice of patient sample was not justified in relation to the generalisability of the findings. A total of 634 patients from 52 centres in 14 countries were included in the trial. These patients were randomised into three groups. Two hundred and nine patients (32.0% male) received everolimus 1.5 mg/day, 211 patients (33.0% male) received everolimus 3.0 mg/day, and the remaining 214 patients (35.1% male)
received azathioprine. The mean ages in these three groups were 51.2 (+/- 11.2) years, 52.1 (+/- 10.8) years and 50.5 (+/- 11.5) years, respectively

Study design
The study was a phase III, multinational, randomised clinical trial. Further details of the trial (such as methods of randomisation and allocation, blinding and loss to follow-up) were not given, but may be available in the original paper (Eisen et al. 2003). The duration of follow-up in the clinical trial was also not reported. For the study question the health outcomes were compared at 12 months.

Analysis of effectiveness
The analysis of effectiveness was conducted on an “intention to treat” basis. The primary health outcome used was the incidence of efficacy failure. This was defined as a composite end point of acute rejection of at least Grade 3A, rejection with haemodynamic compromise, graft loss, death, or loss to follow-up. The secondary health outcomes were the incidence of cytomegalovirus and non-cytomegalovirus infections. The three groups were shown to be comparable at analysis in terms of their demographics and disease factors.

Effectiveness results
The proportion of patients who had experienced the composite primary end point at 12 months was 41.6% among patients receiving everolimus 1.5 mg/day, 32.2% among patients receiving everolimus 3.0 mg/day, and 52.8% among patients receiving azathioprine. No statistical analysis was reported.

Patients on everolimus experienced significantly fewer rejection episodes (30.6% with 1.5 mg/day; 21.3% with 3.0 mg/day) than patients on azathioprine (45.8%).

There were no statistically significant between-group differences for graft loss and death.

The incidence of cytomegalovirus infections was significantly lower among patients receiving everolimus 1.5 or 3.0 mg/day than among patients receiving azathioprine (9.6% and 11.9% versus 23.9%; p</=0.01).

The incidence of bacterial infections was significantly higher among patients receiving everolimus 1.5 or 3.0 mg/day (62.2% and 67.8%) than among patients receiving azathioprine (46.8%), (p</=0.01).

Clinical conclusions
The findings revealed a reduction in the composite end point of efficacy failure among patients treated with everolimus compared with azathioprine. There was also a significant reduction in the incidence of cytomegalovirus infections.

Measure of benefits used in the economic analysis
The proportion of patients free of efficacy failure was considered to be the measure of benefits. It was derived from the effectiveness analysis.

Direct costs
The direct medical costs included in the analysis were inpatient costs (e.g. transplant and post-transplant hospitalisations), outpatient costs (e.g. medical visits, treatments and procedures) and concomitant medications. In the base-case, the costs did not include those of everolimus and azathioprine since a price was not available for everolimus. The resource quantities and the costs were reported separately. The resource use data were collected prospectively alongside the clinical trial.

Local unit costs were used. When cost estimates were not available from countries for individual resources, a market basket-based approach was used to impute country-level costs. Diagnosis-related group (DRG) weights from the
Centres for Medicare and Medicaid Services were used for hospitalisation costs. Estimates for costs in the USA were based on average 2001 Medicare reimbursement rates for hospitalisations and physician services. The costs of concomitant medications in the USA were derived from average wholesale prices from the 2001 Red Book trial. All the costs were converted to 2001 values using purchasing power parity currency conversion rates from the Organization for Economic Cooperation and Development.

Discounting was not undertaken and, indeed, was not relevant since the costs were incurred over a one-year period (average follow-up was 341.8 days for everolimus 1.5 mg/day, 341.0 days for everolimus 3.0 mg/day and 346.6 days for azathioprine).

**Statistical analysis of costs**
The costs were expressed as the mean +/- standard deviation using chi-squared and Wilcoxon rank-sum tests. The nonparametric bootstrap method was used to test for differences in the mean costs and to estimate the confidence intervals (CIs) for cost-effectiveness ratios.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($). The conversion rates used were not stated.

**Sensitivity analysis**
The authors considered the effects of varying the cost of everolimus. Three scenarios were created. In one, the cost of everolimus was equal to the cost of mycophenolate mofetil 3.0 mg/day, in another the costs were halved, and in a third the costs were increased by 50%.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
Only the main results from the cost analysis are reported here.

The mean total costs, excluding the study medications, were not significantly different among treatment groups ($72,065 for everolimus 1.5 mg/day, $72,631 for everolimus 3.0 mg/day, and $70,815 for azathioprine).

Differences in total costs between everolimus and azathioprine were not statistically significant.

**Synthesis of costs and benefits**
The additional costs per additional patient free of efficacy failure were $11,181 (95% CI: -98,836 - 149,528) in the comparison between everolimus 1.5 mg/day and azathioprine, and $8,823 (95% CI: -27,894 - 52,215) in the comparison between everolimus 3.0 mg/day and azathioprine.

**Authors' conclusions**
"Over 1 year of follow-up after heart transplantation, everolimus did not significantly increase treatment costs, excluding the costs of the study medications, while reducing efficacy failure." The authors did not draw a conclusion about the estimated cost-effectiveness ratios.
CRD COMMENTARY - Selection of comparators
The authors clearly justified their choice of the comparator (azathioprine). Everolimus versus azathioprine was the only comparison allowed by the Food and Drug Administration. You should judge whether this comparator is relevant in your own setting, or whether other comparators could also be relevant.

Validity of estimate of measure of effectiveness
The analysis was based on a multinational randomised trial, which was appropriate given the study question. It was not possible to comment on the internal validity of the trial as details on power calculations to determine the sample size, methods of randomisation, blinding, and loss to follow-up were not reported. However, this information may be available in the original paper (Eisen et al. 2003). Given that the study sample comprised patients from different countries, together with the fact that the comparability of the patient groups at analysis was determined, the generalisability of the findings was clearly addressed.

Validity of estimate of measure of benefit
The measure of benefit was the proportion of patients free of efficacy failure. This was derived from the effectiveness analysis. The reader is referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The authors reported that the direct medical costs were estimated from a societal perspective, which means that profit margins were excluded. However, not all the costs from a societal perspective were included for the study as a whole. Indirect costs were omitted from the analysis and, in particular, the costs of everolimus and azathioprine were not included in the base-case. Although the authors justified this exclusion, these costs were relevant to the study question, meaning that the cost-effectiveness of the intervention might have been overestimated. The costs and the quantities were reported separately, thus helping the generalisability of the study in other settings. The resource quantities were taken from the trial, but no dates were given for the collection of resource use data. A statistical analysis of resource use was carried out. There was no formal sensitivity analysis of the costs, which potentially limits the interpretation of the findings. However, the authors did explore various costs for everolimus. Discounting was, appropriately, not carried out. Currency conversions were undertaken to reflect results in US dollar, although no conversion rate was reported.

Other issues
The authors did not compare their findings with those from other studies. The generalisability of the findings to other populations and countries was fully addressed. Although the authors do not appear to have presented their results selectively, the paper was limited by incomplete information on the effectiveness analysis. However, the authors’ conclusions reflected the scope of the analysis, as their objective was to estimate and compare within-trial resource use and costs among heart transplant patients receiving either everolimus or azathioprine.

The authors reported further limitations to their study. First, the study was underpowered to detect significant cost-differences. Second, since the cost of everolimus was not available, the authors used a proxy in the sensitivity analysis. Third, the authors assigned to hospitalisations the cost of pneumonia as a proxy; therefore, they underestimated the cost. Finally, the study used an abbreviated time horizon.

The reader should be aware of a potential conflict of interest arising from the financial support provided by Novartis Pharma, the manufacturer of everolimus.

Implications of the study
The authors suggested that long-term clinical follow-up is needed to evaluate the long-term cost-effectiveness of everolimus relative to azathioprine.

Source of funding

Supported by a research agreement between Duke University and Novartis Pharma.

**Bibliographic details**

**PubMedID**
15659145

**DOI**
10.1111/j.1399-0012.2004.00312.x

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Azathioprine /economics /immunology /therapeutic use; Clinical Trials as Topic /economics; Cytomegalovirus Infections /epidemiology /immunology; Everolimus; Female; Heart Transplantation /adverse effects /immunology; Humans; Immunosuppressive Agents /economics /immunology /therapeutic use; Incidence; Male; Middle Aged; Prospective Studies; Sirolimus /anals & derivatives /economics /immunology /therapeutic use; Treatment Outcome

**AccessionNumber**
22005000346

**Date bibliographic record published**
31/01/2006

**Date abstract record published**
31/01/2006