Cost-effectiveness of sirolimus therapy with early cyclosporin withdrawal vs. long-term cyclosporin therapy in Australia

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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 considered the immunosuppressant sirolimus for prophylaxis of organ rejection in patients at mild and moderate immunological risk, who were receiving renal transplants. Sirolimus was initially given in combination with cyclosporine (CsA) and corticosteroids, with CsA withdrawal to be considered 2 to 4 months after transplantation. Calcineurin inhibitors inhibit T-cell stimulation by reducing interleukin 2 production and interleukin 2-receptor expression, while sirolimus inhibits both T- and B-cell activity by affecting cytokine-driven signal transduction. The comparator was continued CsA combined with a low dose of sirolimus.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The authors studied a hypothetical cohort of patients undergoing kidney transplantation whose age distribution (mean 45.2 years, standard deviation 12.4, minimum 16.0) and treatment corresponded to those of the population of the "310 Study" (Oberbauer et al. 2005, see ‘Other Studies of Related Interest’ below for bibliographic details).

Setting
The setting was secondary care. The economic analysis was carried out in Australia.

Dates to which data relate
The effectiveness data were derived from four studies published between 2004 and 2005. The resource use data were obtained from a study published in 2005 and a panel of 7 renal physicians practising in Australia. The price year was 2005.

Source of effectiveness data
The effectiveness data were derived from published studies.

Modelling
A state-transition model was used to calculate the total costs to the Australian health care system and health gains over a patient lifetime from the time of transplantation. The authors described this as a Markov model but, technically, it was not since the probability of moving from one state to another was time-dependent. A patient could be in one of three health states: no chronic graft rejection, chronic graft rejection, or dead. The model included half-cycle corrections.
Outcomes assessed in the review
The outcomes obtained from the literature and included as inputs in the model were the rates of chronic graft rejection and acute rejection in years 1 to 4, age-dependent probabilities of re-graft, and death. Graft survival beyond year 4 was modelled by applying the decay rate in the exponential rate of graft survival rates in years 1 to 4 in the study arm and comparator arm. Quality of life was also considered. This was measured on a scale from 0 to 1 for patients with no chronic graft rejection and patients with failed graft (who receive dialysis).

Study designs and other criteria for inclusion in the review
The only criteria the authors reported were articles comparing CsA plus low-dose sirolimus with sirolimus after 2 to 4 months.

Sources searched to identify primary studies
MEDLINE (1966 to July, week 3, 2003) and EMBASE (1974 to week 29, 2003) were searched. The search strategy was "rapamune" or "sirolimus" or "rapamycin" and "nephrotoxicity" and "kidney transplant" and "ae.fs" or "to.fs" or "po.fs". The Cochrane Library and DARE were also searched using the search terms "rapamycin", "rapamycin derivative", "sirolimus", "rapamune", "ay22989", "ay-22989" and "53123-88-9".

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
The reader is referred to the validity criteria reported above.

Number of primary studies included
A total of four trials were initially identified, where the comparator was CsA plus low-dose sirolimus. In three of these trials, patients were randomised at a mean time of 3 months after transplant. From these three studies, data from the "310 Study" (Oberbauer et al. 2005) were selected to populate the cost-effectiveness model.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
The authors did not investigate differences between the primary studies.

Results of the review
At 48 months, the probability of graft survival was significantly higher in the study group than in the comparator (86.5% versus 75.3%, p=0.004).

The probabilities of graft survival were:

97.2% (study) versus 95.3% (comparator) at year 1;
94.0% (study) versus 91.6% (comparator) at year 2; and
92.1% (study) versus 87.0% (comparator) at year 3.

In the study group, the chronic graft rejection rate was 30% at 10 years, 50% at 20 years, and 65% at 30 years. In the
comparator group, these rates were 49% (10 years), 74% (20 years) and 86% (30 years), respectively.

The rate of acute rejection between the study and the comparator was not significantly different at month 48 (10.2% versus 6.5%, p=0.223). It was assumed that the rate of acute rejection was 0 beyond the fourth year.

The probabilities of acute rejection were:

9.8% (study) versus 4.2% (comparator) at year 1;

9.8% (study) versus 5.1% (comparator) at year 2; and

10.2% (study) versus 5.6% (comparator) at year 3.

Age dependant probabilities of re-graft were within the interval 0.223 (age group 16 to 24) to 0.001 (age group 85+).

The probabilities of death for dialysis patients were within the interval 0.046 (age group 16 to 24) to 0.432 (age group 85+).

The probabilities of death for transplant patients were within the interval 0.008 (age group 16 to 24) to 0.153 (age group 85+).

Measure of benefits used in the economic analysis
The measures of benefit used were the quality-adjusted life-years (QALYs) and life-years (LYs) gained. The utilities were derived from a time trade-off study of 171 Canadian patients in an end-stage renal disease programme. The time horizon considered for the estimation of the health benefits was 20 years, and a discount rate of 5% was applied.

Direct costs
The cost/resource boundary adopted was that of the health care system. Broad expenditure areas included immunosuppressants, dialysis, and inpatient and outpatient treatment. The resource use data came from a published study and a panel of renal physicians. The price data came from the Australian Government Department of Health and Ageing, the Australian Institute of Health and Welfare, the Victorian Government Department of Human Services, and Wyeth Pharmaceuticals. The costs were inflated using the Total Health Price Index. The costs were discounted at an annual rate of 5%, which was appropriate given that a time horizon of 20 years was considered for the cost estimation. The quantities and the costs were reported separately. The price year was 2005.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
No indirect costs were included in the study.

Currency
Australian dollars (AUD).

Sensitivity analysis
Sensitivity analyses were carried out to address the issue of uncertainty around some clinical and economic data. One-way sensitivity analyses were performed on the model time horizon, graft survival decay rate, censoring graft survival rates for death, censoring graft survival rates for loss to follow-up, utilities, cost of dialysis, and discount rate.
Estimated benefits used in the economic analysis
The authors reported a survival of 19.589 LYs in the study group (11.487 discounted LYs) and 17.503 LYs in the control group (10.756 discounted LYs).

Over a lifetime, this represents a gain of 2.086 LYs (0.731 discounted LYs) and 0.938 additional discounted QALYs (9.539 versus 8.600).

Cost results
The authors reported that the discounted mean lifetime cost of immunosuppressants was AUD 74,458 greater in the study group than in the control group (AUD 202,464 versus AUD 128,006).

The discounted cost of events was reported to be AUD 54,646 in the control group versus AUD 90,053 in the study group (a mean cost-saving of AUD 35,407).

The total discounted mean life time cost per patient was reported to be AUD 257,110 in the study group and AUD 218,059 in the control group (an incremental cost of AUD 39,052).

Synthesis of costs and benefits
Incremental cost-effectiveness and cost analyses were performed.

The incremental cost per QALY gained was reported to be AUD 41,613 and the cost per LY gained AUD 53,416 in the base-case analysis.

The cost-effectiveness of sirolimus was reported to be particularly sensitive to the model time horizon.

With a time horizon of 20 years, the cost per QALY gained increased only to AUD 54,022. However, when the model was restricted to 10 years, the cost per QALY more than doubled to AUD 123,701.

Censoring the graft survival data for deaths increased the cost per QALY to AUD 49,700.

Censoring for loss to follow-up led to a 58% increase in the cost per QALY (AUD 65,718).

The change in the cost of dialysis was found to be approximately equal to the associated change in the cost per QALY.

Halving the decay rate in the study arm gave a cost per QALY of AUD 20,562.

Authors' conclusions
Given the low budget impact and less effective alternative therapies, sirolimus is the logical and cost-effective long-term treatment for patients undergoing renal transplantation.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear as CsA is the most widely used immunosuppressant in Australia. You should decide whether this represents current practice in your own setting.

Validity of estimate of measure of effectiveness
Although the authors searched MEDLINE and EMBASE for relevant literature, it was unclear from the paper whether a full systematic review was undertaken. Although this is common practice in modelling studies, it does not always ensure that the best data available are used in the model. The authors appear to have used data from the available studies selectively and did not consider the impact of differences between the studies identified when estimating effectiveness. However, to compensate for this limitation, the authors undertook sensitivity analysis to explore the impact of variability in the estimates.
Validity of estimate of measure of benefit
QALYs and LYs gained were used for the economic analysis. These are valid measures of benefits because they capture the impact of the intervention on the quality of care and survival. Although utility weights were obtained from a Canadian source, extensive sensitivity analysis investigated the possible significance of this in terms of generalisability. The use of QALYs permits comparisons to be drawn with the benefits of other health care interventions.

Validity of estimate of costs
The cost analysis was performed from the perspective of the health care system. It appears that all the relevant categories of costs have been included in the analysis. A detailed breakdown of the costs was given and, in general, comprehensive information on the unit costs, quantities of resources used, price year and the source of data was provided. These factors enhance the possibility of replicating the results in other settings and will facilitate reflation exercises in other time periods. Resource consumption reflected actual patterns of care in Australia. The costs reflected Australian national tariffs. The uncertainty surrounding some cost estimates was addressed in the sensitivity analysis, in which alternative scenarios for costs were taken into account. However, the costs were treated deterministically.

Other issues
The authors did not compare their findings with those of other studies. The authors acknowledged that the exponential decay function in graft survival beyond year 4 was based on long-term graft survival with calcineurin inhibitors, and that sirolimus is associated with a negligible rate of nephrotoxicity. Therefore, the long-term rates of chronic graft rejection might be lower than predicted. Also, adverse events were excluded from the model, and the cost of nephrectomy and preparatory outpatient visits favours the comparator. Sensitivity analyses identified key areas of uncertainty, thus partially addressing the issue of the generalisability of the study results to other settings. The results of the base-case and sensitivity analyses were extensively reported.

Implications of the study
The study suggests that the availability of sirolimus on the Pharmaceutical Benefit Scheme would increase the annual cost to government by more than 0.5%. However, this increase might be partly offset by the reduced cost of dialysis.

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None stated.

Bibliographic details

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Other publications of related interest
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information

Baboolal K. A phase III prospective, randomized study to evaluate concentration-controlled sirolimus (Rapamune) with cyclosporine dose minimization or elimination at six months in de novo renal allograft recipients. Transplantation 2003;75:998.


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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