Evaluation of the cost-effectiveness of sirolimus versus cyclosporin for immunosuppression after renal transplantation in the United Kingdom

McEwan P, Baboolal K, Conway P, Currie C J

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 use of two immunosuppressants, sirolimus and cyclosporin, after renal transplantation. The daily doses of sirolimus used were 2 mg from commencement to 3 months, 6 mg for 4 to 12 months, and 4 mg for maintenance therapy. Cyclosporin dosing was based on 6 mg/kg daily for the first 6 months and 4 mg/kg daily for maintenance therapy.

Type of intervention
Primary prevention.

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

Study population
The study population comprised a hypothetical cohort of patients who had received a renal transplant.

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1985 and 2005. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A discrete event stochastic simulation model was developed to assess the costs and benefits of sirolimus versus cyclosporin in the post-transplant management of patients over 10- and 20-year time horizons. A simplified schematic of the model was reported. Monthly cycles were considered. The model forecast the incidence of acute rejection episodes, graft failures and re-transplants, the frequency of haemodialysis (HD) and peritoneal dialysis, and death. Patient survival was defined as the time between the most recent transplant and recorded death. Graft survival was defined as the time between any transplant and end-stage renal failure (defined as return to dialysis, re-transplant, or a serum creatinine level of >500 micromol/L). Acute rejection episodes were identified by histology, a 10% increase in serum creatinine (with no other clinical explanation), or at least 3 consecutive prescriptions of methyl prednisolone.

Outcomes assessed in the review
The outcomes estimated from the literature were:

Kaplan-Meier baseline survivorship functions of transplant to graft failure, graft failure to transplant, transplant to acute rejection, and first transplant to death;

HD events;

mean transplant survival;

relationship between creatinine levels and graft survival (as shown using Cox proportional hazard models);

the difference in quality-adjusted life-years (QALYs) between a patient with a functioning graft versus a patient on dialysis;

serum creatinine values; and

the proportion of patients switching from sirolimus to tacrolimus because of intolerance.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The simulation model was based (and validated) using a database of 937 transplant cases performed at the University Hospital of Wales from 1982 to 2001 (inclusive). The probabilities of clinical events were estimated using Cox proportional hazard regression models. HD events were derived from Cardiff data. Serum creatinine values were derived from a multinational clinical trial. Age, gender, weight and the percentage of patients with pre-existing diabetes were based on observational data from the University of Wales renal database. The sources of the other data were not described.

Sources searched to identify primary studies
Not reported.

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

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Fourteen primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The results of the estimated baseline survivorship functions were reported in detail for each year of the model (from year 0 to year 20).
Mean transplant survival was 11 years.

Post-transplant serum creatinine at 3 months and 1, 2 and 3 years represented a significant predictor of graft success and patient survival. Age, diabetes mellitus and number of previous transplants were other significant predictors of graft failure and death in some circumstances. Approximately 29% of patients whose serum creatinine level was >500 micromol/L received HD.

The difference in QALYs between a person with a functioning graft and a person in dialysis was 0.27.

The baseline serum creatinine value (in micromol/L) with sirolimus was 154.8 at 3 months, 141.6 at 1 year, 128.4 at 2 years and 126.8 at 3 years. The corresponding values with cyclosporin were 146.0 (3 months), 150 (1 year), 165 (2 years) and 176 (3 years).

The age of the patients was 43.0 years and 63.2% were men. The mean weight of the patients was 77.0 kg, and 7.0% of the patients had pre-existing diabetes.

The proportion of patients switching from sirolimus to tacrolimus because of intolerance was 27% in year 1 and 5% per year thereafter.

**Methods used to derive estimates of effectiveness**
The authors made a key assumption about graft survival.

**Estimates of effectiveness and key assumptions**
It was assumed that graft survival would prevail for the entire time horizon for a proportion of patients treated with sirolimus (50% in the base-case).

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the expected QALYs and survival associated with the two treatments. The QALYs were calculated by combining utility and survival data that had been derived from the literature. An annual discount rate of 1.5% was applied. Other disease-specific model outputs were reported, such as the number of deaths, acute rejections, dialysis events, graft failures, re-transplants and functioning grafts.

**Direct costs**
The cost analysis took the perspective of the NHS. It included the costs of sirolimus, cyclosporin, immunosuppressive agents, anti-hypertensives, prophylaxis for cytomegalovirus (CMV), cardiovascular treatment, bone treatment, anaemia treatment, management of acute rejection, transplant, graft loss and dialysis. The unit costs were not presented separately from the quantities of resources used, and total monthly costs were reported for most items. Details on resource consumption were not reported. The costs were estimated on the basis of event rates derived from the literature. The costs estimates were derived from national reference costs and drug costs from the British National Formulary. Hospital charges were estimated from the University Hospital of Wales. Discounting was relevant, owing to the long timeframe of the analysis, and an annual rate of 6% was used. The price year was 2003.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.
Currency
UK pounds sterling (£). The conversion rate to US dollars ($) was 1 = $1.76.

Sensitivity analysis
Univariate sensitivity analyses were carried out to assess the impact of variations in key model inputs on the cost-utility ratios. Alternative values for the discount rate, proportion of patients maintaining graft function, patients switching to cyclosporin, doses and patient weight were investigated. The authors appear to have defined these alternative values. A cost-effectiveness acceptability curve was generated from bootstrapping, using thresholds of 30,000 and 20,000 for effectiveness.

Estimated benefits used in the economic analysis
The expected QALYs were not reported. Discounted life expectancy was 8.39 with sirolimus and 8.33 with cyclosporin (difference 0.06) over a 10-year time horizon. When a 20-year timeframe was considered, the discounted life expectancy was 13.84 with sirolimus and 13.68 with cyclosporin (difference 0.16).

Sirolimus resulted in a lower number of deaths, acute rejections, graft failures and re-transplants, both at 10 and 20 years.

Cost results
The discounted total costs per patient were 43,031 with sirolimus and 43,307 with cyclosporin (difference -276) over 10 years. Using a time horizon of 20 years, the total costs were 62,120 with sirolimus and 69,525 with cyclosporin (difference -7,405).

Synthesis of costs and benefits
An incremental analysis was carried out to combine the costs and benefits, but cost-utility ratios and cost-effectiveness ratios were not calculated since sirolimus dominated cyclosporin, which was both more expensive and less effective.

The sensitivity analysis showed that the model input with the greatest impact on the results of the analysis was the proportion of patients with continuous graft function. For example, for the 10-year time model, sirolimus was dominant in the base-case but the incremental cost per QALY reached 51,778 for sirolimus over cyclosporin when assuming that 0% of patients would have continuous graft function throughout the time horizon. For the 20-year time model, the corresponding values were dominant in the base-case and reached 11,161 for 0% maintaining graft function.

The cost-effectiveness analysis curves showed that using a threshold of 30,000, over 10 years, more than 5% of the bootstrap replicates exceeded the ceiling only when 10% and 0% of patients had continuous graft function. Sirolimus would be the preferred strategy in all other cases and in most cases would be dominant.

The 20-year model demonstrated less sensitivity to graft maintenance. A cost-saving was noted in all simulations, except for those in which 10% and 0% of patients had continuous graft function.

Authors’ conclusions
From the perspective of the UK National Health Service (NHS), sirolimus used after renal transplantation was cost-effective compared with cyclosporin for 10 or 20 years. The cost-effectiveness of sirolimus decreased only when less than 10% of patients experienced continuous graft function over 10 years.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was appropriate and was consistent with the aim of the study. The doses of the two treatments were reported. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from selectively identified studies. It would appear that a systematic review of the literature was not performed to identify the primary studies. With the exception of a multinational clinical trial, there was limited information on the design and other characteristics of the primary studies. It was generally difficult to assess the validity of the primary estimates. Moreover, the authors did not explain how the primary estimates were extracted from the primary studies and whether these studies were homogeneous and comparable. The robustness of key clinical estimates was investigated in a sensitivity analysis.

Validity of estimate of measure of benefit
QALYs are an appropriate benefit measure because they capture the impact of the intervention on both quality of life and survival, which are relevant dimensions of health. No information on the approach used to derive the utility weights was reported. Other disease-specific measures and survival were also reported. QALYs are comparable with the benefits of other health care interventions. Discounting was applied, as economic evaluation guidelines recommend, and the impact of applying different discount rates was investigated in the sensitivity analysis.

Validity of estimate of costs
The perspective taken in the study was explicitly stated and the conduct of the cost analysis was consistent with this perspective. A breakdown of the cost items was not provided, and details of the unit costs and quantities of resources used were not presented. This limits the possibility of replicating the analysis in other settings. The source of the costs, but not resource consumption, was reported. However, the cost estimates were specific to the study setting. Discounting was applied at the recommended rate. The price year was reported, which enhances the possibility of performing reflation exercises in other time periods. Statistical analyses of the costs were not carried out.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. However, some key sensitivity analyses were carried out, which enhance the external validity of the analysis, although they were restricted to clinical variables. The authors noted some limitations of their analysis. First, they made assumptions about the use of creatinine values to derive the survival equations describing transition from functioning graft to graft failure and death. Second, only pharmaceutical costs were included in the management of related chronic diseases. These issues might have introduced some uncertainty into the analysis. However, the most important assumption of the analysis (i.e. graft maintenance for the entire time horizon) was varied extensively in the sensitivity analysis.

Implications of the study
The study results suggested that sirolimus could effectively and efficiently replace cyclosporin for patient management after renal transplantation.

Source of funding
None stated.

Bibliographic details

PubMedID
16368455

DOI
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Cost-Benefit Analysis; Cyclosporine /economics /therapeutic use; Diabetes Complications; Female; Graft Rejection /economics /immunology; Graft Survival /immunology; Great Britain; Health Care Costs; Humans; Immunosuppressive Agents /economics /therapeutic use; Kidney Transplantation; Male; Proportional Hazards Models; Sirolimus /economics /therapeutic use

AccessionNumber
22006006258

Date bibliographic record published
30/11/2006

Date abstract record published
30/11/2006