Use of Markov modeling for evaluating the cost-effectiveness of immunosuppressive therapies in renal transplant recipients


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 compared the de novo use of conventional cyclosporin A (Sandimmune, Sim) with the microemulsion (Neoral) formulation of cyclosporin A, as immunosuppressive therapy for primary cadaveric kidney transplant recipients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who had undergone primary cadaveric kidney transplant. The study sample comprised two Neoral- and three Sim-treated cohorts of patients, who were enrolled in prospective randomised double-blind clinical trials in the USA and Europe. In addition, there was a cohort of 4,727 Sim-treated first cadaveric transplant recipients selected from the US Health Care Financing Administration (HCFA) databases. The selection criteria were as follows:

- the patients were aged 18 to 65 years;
- the transplantation took place during 1992 or 1993;
- cyclosporin A was used proceeding the transplantation;
- Medicare was documented as the primary provider at the time of the transplantation; and
- the patients were not enrolled in the US de novo trial OLM 103.

The authors reported that because no black patients were enrolled in the European trials, an additional non-concurrent, Sim-treated control group was established by modifying the HCFA database to include only non-African-American patients (n=3,339). This cohort was used for a comparative analysis with the Neoral group of patients enrolled in the European trials.

Setting
The setting was secondary care. The study was conducted in the USA and Europe.

Dates to which data relate
The effectiveness and resource data were collected during 1992 and 1993. The price year was not reported.
Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies.

Modelling
A Markov decision-analytic model was used to compare the cost-effectiveness of the de novo use of Sim and Neoral formulations of cyclosporin A in cadaveric kidney transplant recipients.

Outcomes assessed in the review
The outcomes used as input parameters to the model were the probabilities of rejection, graft loss due to rejection, graft loss due to other courses, and death. These data were calculated for each of 6 cycles, where each cycle was of 15 days’ duration to encompass a 3-month observation period.

Study designs and other criteria for inclusion in the review
The data were derived from 3 prospective, parallel group, randomised, double-blind, comparative trials of de novo Sim versus Neoral conducted during 1992 and 1993. Additional data were derived from a cohort study of patients selected from a US administrative database. The authors did not report the inclusion or exclusion criteria used to select the studies for inclusion in the review. In addition, they did not provide details of the sources of the data.

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
Four primary data sources were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
The authors reported there were differences between the primary studies in terms of the participants and the organ rejection rates. The cohorts were adjusted to control for differences in the ethnic group. Other differences between the studies were not investigated or explained in terms of the study design or the outcomes.

Results of the review
The only results reported were the 3-month acute rejection rates. These were:

for the Neoral (US) cohort, 32%;
for the Neoral (European) cohort, 45%;
for the Sim (US) cohort, 26%;
for the Sim (HCFA patients) cohort, 57%; and
for the modified Sim (HCFA patients excluding African-Americans) cohort, 57%.

The probabilities of graft loss due to rejection, graft loss due to other causes, or the probability of death, were not reported.

**Measure of benefits used in the economic analysis**
The measures of health benefit used in the economic analysis were the clinical outcomes of the number of functioning grafts and the rejection-free clinical course at 12-weeks' post-transplant.

**Direct costs**
The following direct costs were included in the analysis:

- the cost of transplantation was $65,644;
- the cost of rejection was $24,783 (cycle 1), $24,381 (cycle 2), $23,473 (cycle 3), $22,411 (cycle 4), $20,660 (cycle 5), or $17,883 (cycle 6);
- the acquisition cost of cyclosporin A (Neoral or Sim) per cycle was $456;
- the health state cost per cycle was $934 for no rejection, $1,040 for a functioning graft, $1,805 for dialysis, and $0 for death.

The cost data were obtained from HCFA sources. These included the end-stage renal disease Program Management and Medical Information System, the National Claims History 100% Nearline File, the Inpatient 100% Standard Analytical File, and the Outpatient 100% Standard Analytic File. Discounting was not undertaken because of the short timeframe of the study (3 months). The resource use and the costs were not reported separately. The authors made the following assumptions:

- the lengths of inpatient stay for the transplant admission were the same for the Neoral and Sim groups;
- the patients only received 1 kidney transplant during the study period;
- the costs of the health state in the model were constant over the 3-month timeframe; and
- the acquisition costs of Neoral and Sim were the same.

The authors did not report whether the data used represented the costs or charges. The price year was not reported. No currency conversions were undertaken.

**Statistical analysis of costs**
No statistical analysis of costs was conducted.

**Indirect Costs**
No indirect costs were included in the analysis.

**Currency**
US dollars ($). No currency conversions were reported.
Sensitivity analysis
Sensitivity analyses were used to determine the robustness of the cost-effectiveness ratios to changes in the aetiology of end-stage renal disease and the variation in rejection rates. Also, to changes in the acquisition costs of both Neoral and Sim. The type of sensitivity analysis used was not reported.

Estimated benefits used in the economic analysis
The authors did not report the numbers of functioning grafts or rejection-free clinical courses at 3 months.

Cost results
The mean cost of care per patient for the first 12 weeks following transplant was:

- for the Neoral (US) cohort, $80,900;
- for the Neoral (European) cohort, $84,367;
- for the Sim (US) cohort, $79,493;
- for the Sim (HCFA patients) cohort, $87,157; and
- for the modified Sim (HCFA patients excluding African-Americans) cohort, $87,100.

The incremental costs of Neoral were $1,407 higher than Sim in the US comparison and $2,733 lower in the European comparison.

Synthesis of costs and benefits
The average cost per rejection-free clinical course and the average cost per functioning graft were calculated. However, the authors only reported the average cost-effectiveness ratios. They did not calculate the incremental cost-effectiveness ratios necessary to synthesise the costs and the outcomes in an economic evaluation.

The average cost per rejection-free clinical course and the average cost per functioning graft would remain lower in the Neoral cohort even if there were no cost for Sim. In the comparison of the Neoral (European) and modified Sim (HCFA patients excluding African-Americans) cohorts, the cost of Sim would need to be reduced by 78% for the mean cost of care in each group to become equivalent. The authors stated that the cost of Neoral would have to be reduced by 34%, to equalise the average cost of care in the Neoral (US) and the Sim (US) groups. Varying the frequencies of each of the aetiologies of end-stage renal disease had no impact on the per patient cost of care.

Authors' conclusions
The results did not conclusively show a consistent difference in the costs and effectiveness of Neoral and Sandimmune (Sim), because of the wide variation observed within these cohorts in terms of the rejection rates. The rejection rates ranged from 32 to 45% in the Neoral cohorts, and from 26 to 61% in the Sim cohorts.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was justified on the grounds that it represented conventional practice in the authors' setting. You should decide whether this is a widely used health technology in your own setting. The authors reported alternative products for use in immunosuppression therapies, but did not include them in the analysis.

Validity of estimate of measure of effectiveness
The authors did not report whether a systematic search or review of the literature had been undertaken. The authors used data from the available studies selectively, and did not consider the impact of the differences between primary
studies when estimating effectiveness. The criteria used to select the studies for the review, and to assess the quality of
the included studies and the data, were not reported. In addition, there were no details provided of the methods used to
extract the data. The authors did not report all the data used as inputs to or outputs of the model. It was therefore not
possible to assess the validity of the estimates used in the baseline analysis of the model.

Validity of estimate of measure of benefit
The measures of health benefits used for the analysis were the clinical outcomes, i.e. the number of functioning grafts
and the rejection-free clinical course over a 3-month time period. These measures of benefit do not reflect the longer-
term impact on the mortality and morbidity of renal transplant or organ rejection. The authors did not report the
number of functioning grafts or rejection-free clinical courses estimated by the Markov model. A comprehensive
description of the Markov model was not provided. In addition, the authors did not report whether or how the structure
of the model was validated in terms of the range of events included, the timeframe, and the structure or sequence of
events. It was therefore not possible to assess the validity of the model or the results.

Validity of estimate of costs
The authors did not explicitly report the perspective from which the study was conducted. Thus, it was not possible to
determine whether all the relevant categories of cost were included in the analysis. The costs and the quantities were not
reported separately. A statistical analysis of the outcomes, but not the costs, was performed. The authors did not report
whether the costs or the charge data were used in the analysis. The authors used the costs from a database of patients
treated in the USA, but they did not report whether these data were applicable to patients enrolled in the European trials
of Neoral.

A limited sensitivity analysis of both the costs and the outcomes was performed. However, the authors did not provide
details of the type of sensitivity analysis used, or the criteria used to select the variables for the analysis. In addition, the
ranges of values used were not reported. Discounting was not performed because of the short timeframe of the study (3
months). The price year was not reported. No currency conversions were undertaken.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, but did not fully address the
issue of generalisability to other settings. The authors reported two main limitations in relation to their study. First, the
small sample sizes in each of the de novo clinical trials. Second, the differences in European and US practice, which
were not characterised in the de novo clinical trials. The authors compared data from patients treated in the European trials
to the data extracted from a US database of patients, without adjusting for differences in practice patterns.

Implications of the study
The results did not conclusively show a consistent difference in the cost-effectiveness of the two formulations of
cyclosporin A (Neoral and Sim), because of the wide variation observed within the Neoral and Sim cohorts in terms of
the rejection rates.

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