Two-hour post-dose cyclosporine levels in renal transplantation in Argentina: a cost-effective strategy for reducing acute rejection

Balshaw R, Machnicki G, Agost Carreno C, Toselli L, Otero A, Keown P A

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 monitoring of cyclosporine (CsA) at 2-hours post-dose (C2) and through trough (C0) concentrations was examined.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients treated with a CsA-based regimen that included steroids and azathioprine or mycophenolate mofetil.

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

Dates to which data relate
The clinical data were obtained from studies published between 1999 and 2003. The resource use data came from studies published between 1999 and 2001. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from published studies, authors’ assumptions and expert opinion. The published studies were obtained from an earlier application of the model in this paper (Keown et al 2001. see ‘Other Publications of Related Interest’ below for bibliographic details).

Modelling
A decision model, based on Keown et al. 2001, was used to evaluate the clinical outcomes and health resources used associated with the two monitoring strategies for CsA during the first year post-transplantation.

Outcomes assessed in the review
The outcomes assessed in the review were:

the probability of being within the CsA therapeutic range;

the probability of being beyond the CsA therapeutic range;
the probability of acute rejection when the CsA concentration was within the therapeutic range;
the probability of acute rejection when the CsA concentration was beyond the therapeutic range;
the number of acute rejection episodes given per patient with acute rejection;
the incidence of graft loss; and
the relative CsA dose.

Study designs and other criteria for inclusion in the review
A prospective clinical trial with 295 patients, conducted in 30 centres in 10 countries, was the key source of evidence for the C2 strategy. Other studies, both experimental and observational, were used.

Sources searched to identify primary studies
The published studies appear to have been identified from an earlier application of the model used in this paper (Keown et al. 2001).

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
The effectiveness data were derived from eight primary studies.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The probability of being within the CsA therapeutic range was 0.5 with the C0 strategy and 0.73 with the C2 strategy.

The probability of being beyond the CsA therapeutic range was 0.5 with the C0 strategy and 0.27 with the C2 strategy.

The probability of acute rejection when the CsA concentration was within the therapeutic range was 10% with both strategies.

The probability of acute rejection when the CsA concentration was beyond the therapeutic range was 40% with both strategies.

The number of acute rejection episodes given per patient with acute rejection was 1.42 with both strategies.

The incidence of graft loss was 10% with the C0 strategy and 8.6% with the C2 strategy.
The relative CsA dose when using C2 versus C0 was 1.051.

**Methods used to derive estimates of effectiveness**
Some assumptions were made in the decision model. In addition, general patterns of clinical practice and expert opinion were applied to estimate evidence that was not available in the published studies.

**Estimates of effectiveness and key assumptions**
The authors assumed that the number of acute rejections and patient survival were the same in both strategies. The number of acute rejections was 1.42 per patient.

Argentinean expert opinion was used to derive the percentage of acute rejections occurring during initial hospitalisation and the treatment of acute rejection episodes.

**Measure of benefits used in the economic analysis**
The summary measure of benefit was the incidence of acute rejection. The number-needed-to-treat for benefit (NNTB) was reported as the relevant model output.

**Direct costs**
The direct costs to the health service were evaluated. The treatment of ambulatory-based adverse events not requiring hospitalisation was excluded as it was assumed to be almost equivalent in both strategies. The unit costs were not presented separately from the quantities of resources used. The costs were estimated from published retrospective studies and confirmed by expert opinion. Discounting was not conducted because of the short time horizon. All the costs were inflated to 2002 values and converted to US dollars from Argentinean pesos (ARS).

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

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

**Currency**
US dollars ($). These were converted from ARS using the conversion rate $1 = 2.85 ARS.

**Sensitivity analysis**
One-way sensitivity analyses were performed to examine the robustness of the cost results to variations in the key model inputs. The ranges of variables were derived from the published literature, cumulative clinical information and clinical expertise.

**Estimated benefits used in the economic analysis**
The incidence of acute rejection was 25% with the C0 strategy and 18% with the C2 strategy. The NNTB for the C2 strategy compared with the C0 strategy was 72.

**Cost results**
The first-year average costs per patient were $16,269 with the C0 strategy and $16,343 with the C2 strategy. The two strategies would appear to be cost-equivalent.
**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio was not actually calculated, as both monitoring strategies were cost-equivalent and the C2 monitoring strategy led to better outcomes.

The sensitivity analyses revealed that average daily dose of CsA was the most influential factor affecting the incremental cost per patient. When the relative CsA dose was larger then 3.4%, the C2 monitoring strategy incurred higher expected total costs. The probability of rejection when patients were or were not maintained within the therapeutic range had little impact on the expected costs of both monitoring strategies.

**Authors' conclusions**
The 2 hours post-dose (C2) strategy resulted in a reduction in the risk of acute rejection, without increasing the estimated cost of care, in the first year post-transplantation.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. The C0 strategy represented the traditional monitoring approach. You should decide whether it is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The model parameters were mainly derived from published studies that appear to have been identified from an earlier application of this model. The authors did not conduct their own systematic review of the literature, although they did provide information on some of the primary studies. The use of data derived from clinical trials ensured the validity of the clinical estimates. The robustness of the results was addressed by sensitivity analyses on the clinical inputs.

**Validity of estimate of measure of benefit**
The summary benefit measure was appropriate for examining the influence of the health intervention specified in the study, although it was not possible to estimate the impact of the intervention on quality of life.

**Validity of estimate of costs**
The authors explicitly stated the perspective adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. The costs and the quantities were not reported separately, which limits the generalisability of the authors' results. The costs were treated deterministically in the base-case, but extensive sensitivity analyses were conducted. Discounting was not performed as it was irrelevant. The price year was reported, which aids reflation exercises in other settings.

**Other issues**
The authors did not compare their findings with those from other published studies. The issue of the generalisability of the study to other settings was addressed by performing sensitivity analyses, the results of which were satisfactorily reported. The authors' conclusions reflected the scope of the analysis. The costs and resource use were not directly measured in Argentina, the data being extrapolated to Argentina from a Canadian clinical trial instead. This was a limitation of the study. Another limitation was that the analysis only adopted a short time horizon.

**Implications of the study**
The study results support the use of the C2 monitoring strategy in the first year post-renal transplantation.

**Source of funding**
None stated.