A decision-analytic economic evaluation of valaciclovir prophylaxis for the prevention of cytomegalovirus infection and disease in renal 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 use of valaciclovir prophylaxis for the prevention of cytomegalovirus (CMV) infection and disease, and acute graft rejection (AGR), in patients undergoing renal transplantation.

Type of intervention
Primary and secondary prevention.

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

Study population
The study population comprised renal recipients with a moderate to high risk for CMV infection or disease. The patients were stratified into two risk groups according to donor/recipient CMV serostatus at transplantation. More specifically, donor-positive/recipient-negative (D+R-) and recipient-positive regardless of the donor’s status (R+).

Setting
The setting was secondary care. The economic study was conducted in Australia.

Dates to which data relate
The effectiveness data were derived from literature published from 1996 to 1999. The resource use data were derived mainly from literature published between 1993 and 1999, although for some costs there was no reference to the year to which they related. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies.

Modelling
A decision analytic Markov model was developed to compare the costs and health outcomes associated with valaciclovir prophylaxis, compared with placebo, for 30 years following renal transplantation. The model ran in 6-month cycles. After transplantation, the patients were assumed to have a healthy graft and entered one of four alternative health states according to their CMV disease and AGR status. These health states were CMV-/AGR-, CMV+/AGR-, CMV-/AGR+ and CMV+/AR+. Each of these states ultimately resulted in a state of either graft failure or death. Graft failure led to death either directly, or via a subsequent successful transplantation.

Outcomes assessed in the review
The outcomes assessed were:

- the probabilities of the four alternative cases of CMV/AGR status after transplantation in D+R- and R+ patients, with and without valaciclovir prophylaxis;
- the probability of death within 6 months of transplantation, with and without valaciclovir prophylaxis;
- the probability of graft failure;
- the probability of re-transplantation following graft failure; and
- the age-specific probabilities of death with functioning graft or with graft failure.

**Study designs and other criteria for inclusion in the review**
The outcomes used in the economic analysis were derived mainly from a published, randomised controlled trial (RCT) (see Other Publications of Related Interest). Data from two other published studies and a national renal transplant registry were also used.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
The main source of the effectiveness data was a multi-centre, double-blind RCT.

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

**Number of primary studies included**
Three primary studies were included in the review.

**Methods of combining primary studies**
The results of the individual primary studies were not combined as they referred to different effectiveness parameters.

**Investigation of differences between primary studies**
Not applicable.

**Results of the review**
For D+R- patients, the probability of CMV-/AGR- after transplantation was 0.667 with valaciclovir and 0.349 with placebo. The corresponding probabilities for R+ patients were 0.721 (valaciclovir) and 0.637 (placebo), respectively.

For D+R- patients, the probability of CMV+/AGR- after transplantation was 0.088 with valaciclovir and 0.160 with placebo. The corresponding probabilities for R+ patients were 0.000 (valaciclovir) and 0.025 (placebo), respectively.

For D+R- patients, the probability of CMV-/AGR+ after transplantation was 0.196 with valaciclovir and 0.264 with placebo. The corresponding probabilities for R+ patients were 0.270 (valaciclovir) and 0.309 (placebo), respectively.

For D+R- patients, the probability of CMV+/AGR+ after transplantation was 0.049 with valaciclovir and 0.226 with placebo. The corresponding probabilities for R+ patients were 0.010 (valaciclovir) and 0.029 (placebo), respectively.
The probability of death within 6 months of transplantation was 0.03 with or without valaciclovir prophylaxis.

The probability of graft failure for the first 10 years depended on CMV/AGR status and the age of the graft. The data were only presented as a graph.

The probability of re-transplantation following graft failure was 0.061.

The probability of death with a functioning graft (6-month period) ranged from 0.005 (age 35 to 44) to 0.038 (age 65+).

The probability of death with a graft failure ranged from 0.037 (age 35 to 44) to 0.126 (age 65+).

**Methods used to derive estimates of effectiveness**
The authors made an assumption about the probability of graft failure 10 years of transplantation.

**Estimates of effectiveness and key assumptions**
A key assumption used in the economic evaluation was that the serological status of donors and recipients with respect to CMV immunoglobulin G at transplantation (donor/recipient serostatus) was considered to be the primary risk factor for the development of CMV disease after transplantation. The authors also assumed that the probability of graft failure 10 years after transplantation was 0.000.

**Measure of benefits used in the economic analysis**
The measures of benefit used in the economic analysis were the number of life-years (LYs) gained and the quality-adjusted life-years (QALYs). The utility values used were derived from a quality of life study of 168 renal transplant patients using the time trade-off technique. The benefits were discounted at an annual rate of 5%.

**Direct costs**
The direct costs to the health service were included in the analysis. The costs considered were for transplantation, ongoing medical resources used by transplant patients with a functioning graft, dialysis after graft failure, and re-transplantation. The transplantation costs covered CMV prophylaxis medication, concomitant medications, hospitalisation, physician visits, outpatient services, special procedures (e.g. bronchoscopy and ultrasound) and laboratory procedures. The costs and the quantities were not reported separately. The quantities related to transplantation were derived from the clinical trial that was the main source of the effectiveness data (published in 1999). Respective unit prices were derived from the Schedule of Pharmaceutical Benefits 2000, the Medicare Benefits Schedule 2000, and the Australian Refined Diagnosis-Related Groups (version 4) 1997/98. The ongoing cost of transplant patients with a functioning graft was taken from literature published in 1993. The cost of dialysis was derived from the Victorian Maintenance Dialysis Program. The cost of re-transplantation was based on the Australian Refined Diagnosis-Related Groups. The total costs were derived through modelling.

All the costs were adjusted to 2000 prices using the Government Final Consumption Expenditure (Hospital and Nursing Home Care) Price Index (July 1999). Discounting was appropriately carried out, as the costs were incurred over 30 years. The discount rate was 5% per annum, which was consistent with the requirements of the Australian Government.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was conducted.

**Indirect Costs**
The indirect costs were not included in the analysis.
Currency
Australian dollars (Aus$).

Sensitivity analysis
A one-way sensitivity analysis, to assess the importance of specific input parameters to the results, was conducted. The parameters examined included clinical trial efficacy data, the risk of graft failure, and the hospital and concomitant medication costs during the trial period. Also examined were the duration of the model and the discount rate. The base-case values were increased or decreased by a percentage defined by the authors.

Estimated benefits used in the economic analysis
In the D+R- group, valaciclovir resulted in 11.49 LYs and 7.98 QALYs per patient, while no prophylaxis resulted in 11.16 LYs and 7.71 QALYs per patient.

The incremental benefits of valaciclovir versus no prophylaxis were 0.33 LYs and 0.27 QALYs per D+R- patient.

In the R+ group, valaciclovir resulted in 11.48 LYs and 7.97 QALYs per patient, while no prophylaxis resulted in 11.41 LYs and 7.91 QALYs per patient.

The incremental benefits of valaciclovir versus no prophylaxis were 0.07 LYs and 0.05 QALYs per R+ patient.

All benefits referred to a 30-year period after transplantation and were discounted at a rate of 5%.

Cost results
In the D+R- group, the total cost per patient following valaciclovir prophylaxis was Aus$91,454. Without prophylaxis this cost was Aus$95,073. Valaciclovir prophylaxis resulted in a saving of Aus$3,619 per D+R- patient.

In the R+ group, the total cost per patient following valaciclovir prophylaxis was Aus$89,773. Without prophylaxis this cost was Aus$88,858. Valaciclovir prophylaxis resulted in an additional cost of Aus$914 per R+ patient.

The total costs referred to a 30-year period following transplantation and were discounted at a rate of 5%.

Synthesis of costs and benefits
The costs and benefits were combined in the form of incremental cost-effectiveness ratios (ICERs). In the D+R- group valaciclovir was the dominant option (i.e. more effective and less costly than no prophylaxis). Therefore, the ICER did not need to be calculated.

In the R+ group valaciclovir resulted in an ICER of Aus$13,931 per LY gained or Aus$17,127 per QALY gained. These results were robust to changes in variables examined in the sensitivity analysis.

Authors' conclusions
Valaciclovir was a cost-effective intervention for the prophylaxis of cytomegalovirus (CMV) disease in renal transplant recipients, significantly reducing the burden of CMV infection and disease to patients and health care providers.

CRD COMMENTARY - Selection of comparators
The selection of the comparator was explicitly justified. Valaciclovir was the first antiviral agent available through Australia's Schedule of Pharmaceutical Benefits for CMV prophylaxis in renal transplant recipients. Therefore, no prophylaxis (placebo) was selected as the most appropriate comparator. You should consider whether the comparator reflects widely used practice in your own setting.
Validity of estimate of measure of effectiveness
The authors did not explicitly state that a systematic review of the literature was undertaken. However, it was reported that the review of the literature did not identify any other clinical trials comparing valaciclovir prophylaxis and placebo in patients undergoing renal transplantation. The estimates of effectiveness from the primary studies were not combined as they referred to different outcomes. The main effectiveness outcomes were derived from an RCT, which is the 'gold' standard method for the evaluation of effectiveness.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. LYs and QALYs were used as measures of benefit. The authors adequately described the methods for measuring the utility weights.

Validity of estimate of costs
The study perspective was stated to have been that of the health service provider. As such, all the categories of cost relevant to this perspective appear to have been included in the analysis. The costs and the quantities were not reported separately, which hinders the reproducibility of the results. However, resource use pertaining to transplantation and CMV prophylaxis was derived from a published study (see Other Publications of Related Interest). A sensitivity analysis examined the impact of some cost components on the results. The costs reflected actual resource use and not charges. Discounting was undertaken, which was appropriate as the costs were incurred over 30 years. The price year was reported and this improves the generalisability of the results.

Other issues
The authors made appropriate comparisons of their findings with those of other published studies and found them to be consistent. However, the issue of generalisability to other settings was not addressed. The results of the analysis were reported in full. However, the study involved patients with a moderate or high risk for CMV infection and disease (determined by the donor/recipient CMV serostatus) and this was not reflected in the authors' conclusions.

Implications of the study
Based on the results of the analysis, it can be inferred that valaciclovir is a cost-effective intervention which should be considered as a prophylactic strategy for the prevention of CMV disease after renal transplantation, in patients with a moderate or high risk for CMV infection and disease.

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