Cost-effectiveness of different strategies of cytomegalovirus prophylaxis in orthotopic liver transplant recipients

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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 cytomegalovirus (CMV) prophylaxis in orthotopic liver transplant recipients. Chemoprophylaxis comprised ganciclovir (GCV), CMV immunoglobulin (Ig) or acyclovir (ACV). The regimens considered were:

oral GCV, 1,000 mg, given 3 times daily for 100 days;
intravenous GCV, 6 mg/kg per day for 30 days, then 5 mg/kg per day for 100 days);
intravenous CMV Ig, 150 mg/kg within 72 hours of transplant, then at 2, 4, 6 and 8 weeks, and 100 mg/kg at 12 and 16 weeks;
oral ACV, 800 mg, given 4 times daily for 3 or 6 months).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of a hypothetical cohort of 1,000 orthotopic liver transplant recipients who had a mean weight of 70 kg.

Setting
The setting was secondary care. The economic analysis was carried out in Cleveland, USA.

Dates to which data relate
The effectiveness data were obtained from the literature. The resource data were derived from a University hospital and from the literature. The dates to which the data related were unclear. The price year was 1995.

Source of effectiveness data
The effectiveness data were derived from a review of the literature and expert opinion.

Modelling
A Markov model was developed to evaluate the cost effectiveness of the different health care interventions. Seven post-transplantation states were defined. These were healthy transplant recipients, acute rejection, chronic rejection, CMV
infection, CMV disease, CMV disease complicated by severe opportunistic infection(s), and death. The model was run for a total of 12 cycles, each cycle being of one month in duration. Half cycle corrections were made for both the cost and utility values.

Outcomes assessed in the review
The major effectiveness model parameters assessed in the review were the probabilities of CMV infection and CMV disease with each health care intervention.

Study designs and other criteria for inclusion in the review
The data on the effectiveness of different chemoprophylactic regimens were obtained from available randomised, controlled clinical trials.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
Five studies were included in the review.

Methods of combining primary studies
It appears that the parameter estimates have been taken selectively from the literature.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability of CMV infection was 5% (range: 1 - 10) with oral GCV, 25% (range: 10 - 40) with intravenous GCV, 57% (range: 25 - 75) with intravenous CMV Ig, 42% (range: 20 - 70) with oral ACV for 6 months, and 61% (range: 25 - 75) with oral ACV for 3 months.

The probability of CMV disease was 1% (range: 0 - 5) with oral GCV, 5% (range: 1 - 10) with intravenous GCV, 19% (range: 5 - 30) with intravenous CMV Ig, 29% (range: 10 - 50) with oral ACV for 6 months, and 28% (range: 10 - 50) with oral ACV for 3 months.

Methods used to derive estimates of effectiveness
The author made assumptions about the effectiveness.

Estimates of effectiveness and key assumptions
The author assumed that a CMV-seronegative patient could not develop CMV disease without transition through the
state of CMV infection.

It was also assumed that all non CMV-related deaths were uniformly distributed over the first post-transplantation year.

**Measure of benefits used in the economic analysis**
The main measure of benefit used in the economic analysis was the quality-adjusted month (QAM). The average time spent in the CMV-disease state and the annual CMV-related mortality were also reported. The costs and benefits were combined by calculated the mean and incremental cost per quality-adjusted life-years (QALY) saved. The quality weights in the measure of benefit were derived from expert opinion.

**Direct costs**
The quantity/cost boundary adopted was that of the hospital. The direct costs were for standard follow-up care for the first year after liver transplantation, the diagnostic work-up of CMV disease, treating CMV disease for one month, treating acute rejection, and antilymphocyte antibody treatment (OKT3). The costs of standard follow-up care included medications, readmission, office visits, and outpatient and inpatient procedures with estimated professional fees. The cost of the diagnostic work-up covered, for example, serological and virology tests, organ specific tests, liver biopsy, endoscopy and bronchoscopy. The cost of treating CMV disease included medication and follow-up. The cost estimates were obtained from a University hospital-based medium-sized liver transplantation programme. The actual cost was derived from hospital charges using a cost-to-charge ratio. The unit costs were reported. A one-year time horizon was used. The price year was 1995.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were performed by varying:

- the probability estimates of the proportion of donor-positive, recipient-negative serological status;
- the probability of developing steroid-resistant rejection;
- the probability of overall mortality in the first post-transplantation year;
- the probability of recurrent CMV disease; and
- cost variables.

A two-way sensitivity analysis was performed by simultaneously varying the probability of steroid-resistant rejection and the proportion of the cohort with donor-positive, recipient-negative CMV serological status. A second-order Monte Carlo simulation was performed to provide confidence intervals (CIs) for the outcome variables.

**Estimated benefits used in the economic analysis**
Intravenous GCV was the most effective strategy with 11.1076 QAM (95% CI: 10.9586 - 11.2573), followed by oral
GCV with 11.0987 QAM (95% CI: 10.9529 - 11.2436). CMV Ig was the next most effective strategy with 11.0722 QAM, followed by oral ACV for 6 months (11.0694 QAM) and oral ACV for 3 months (10.9581 QAM).

Cost results
The mean cost was $58,933 (95% CI: 58,191 - 59,676) with intravenous GCV, $53,165 (95% CI: 52,509 - 53,822) with oral GCV, $59,160 (95% CI: 58,225 - 60,095) with CMV Ig, $55,243 (95% CI: 54,742 - 55,744) with oral ACV for 6 months, and $53,482 (95% CI: 52,351 - 54,613) with oral ACV for 3 months.

Synthesis of costs and benefits
The mean cost per QALY was $5,334 (95% CI: 5,225 - 5,375) for intravenous GCV and $4,867 (95% CI: 4,828 - 4,906) for oral GCV. The incremental cost-effectiveness ratio (ICER) of intravenous GCV over oral GCV was $7,523,478 per QALY gained. CMV Ig was clearly dominated by the first strategies. Both oral ACV strategies (6 and 3 months) were dominated by oral GCV.

In the second stage of the decision analysis, strategies with either intravenous or oral GCV administered to all transplant recipients were both more effective and more costly than those restricted to the high-risk groups. The ICER was $26,044 per QALY gained for oral GCV administered to all transplant recipients, and $43,367 per QALY gained for intravenous GCV.

The model was insensitive to changes in different parameters in the one-way and two-way sensitivity analyses. Intravenous GCV restricted to high-risk groups was more cost-effective only when the proportion of patients with CMV status associated with the highest risk of CMV disease comprised more than 90% of the cohort population.

Authors' conclusions
The decision analysis established the superiority of ganciclovir (GCV)-based regimens in general, and the strategy of oral GCV universally administered to all liver transplant recipients, in particular, for cytomegalovirus (CMV) prophylaxis from a point of cost-effectiveness.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparators was clear. The comparators represented the potential chemoprophylaxis regimens against CMV in the author's setting. You should consider whether they are a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The author stated that all available published controlled studies were included in the review. The author acknowledged that the studies were few in numbers and reflected the experience of only a few large transplantation centres. The Monte Carlo simulation performed to assess the effect of variability of assumptions, was adequate.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The decision analytical model used was appropriate and well described. Quality of life estimates were derived from utilities perceived by a group of physicians. More appropriate estimates would have been based on the patients' preferences. It is likely that the duration of follow-up was too small (one year) to enable a synthesis of the costs and benefits in terms of the incremental cost per QALY gained.

Validity of estimate of costs
The cost/resource boundary adopted was unclear, but it is likely to have been that of the hospital. In which case, all the categories of cost relevant to the perspective adopted appear to have been included in the analysis. The costs and the quantities were not reported separately. The price year was reported. A sensitivity analysis on the cost variables was...
conducted.

**Other issues**
The author did not compare the findings with those from other studies. Also, the issue of generalisability to other settings was not addressed. The author did not present the results selectively. The author reported some further limitations to the study. First, the study did not consider the role of CMV in worsening the severity of recurrent hepatitis C disease in liver transplant. Second, the study did not consider the protective effect of CMV against opportunistic infections. This study was a well-conducted cost-effectiveness analysis.

**Implications of the study**
The author concluded that a strategy of targeted pre-emptive therapy is promising, and well-designed controlled trials comparing this strategy with that of oral GCV-based prophylaxis are definitely warranted.

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**Bibliographic details**

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

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