Costs and outcomes of prolonged cytomegalovirus prophylaxis to cover the enhanced immunosuppression phase following lung 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 comparison of long- and short-term ganciclovir prophylaxis for the treatment of cytomegalovirus (CMV)-positive patients undergoing lung transplantation or receiving a lung from a seropositive donor. The long-term protocol consisted of intravenous ganciclovir (5 mg/kg/day) administered for 20 weeks following transplantation, until prednisone steroid therapy was tapered. The shorter prophylaxis protocols were 3, 5 and 12 weeks in duration; the dose was unclear.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population included consecutive patients who had undergone single or double lung transplantation, and who were at risk of CMV infections based on either donor or recipient seropositive status.

Setting
The setting was tertiary care. The economic study was carried out in Switzerland.

Dates to which data relate
The effectiveness evidence for the 20-week ganciclovir prophylaxis regimen was collected between 1 July 1993 and 30 June 1997. The effectiveness evidence for shorter-term ganciclovir prophylaxis regimens was collected from studies published between 1994 and 1996. The resource use data were not collected alongside the effectiveness data. The price year was stated as “at this time of writing” and the manuscript was submitted for publication in March 1999.

Source of effectiveness data
The effectiveness data were derived from a single study, and were combined with a review and/or synthesis of previous studies.

Link between effectiveness and cost data
The costing was carried out on a different patient sample from that used in the effectiveness study.

Study sample
There were no power calculations reported. The study sample comprised consecutive patients at risk of CMV infections. Of the 30 consecutive patients screened, 23 were found to be at risk; one of these died on the first post-
operative day and was excluded from the analysis, although was included in the cumulative survival rate. The intervention group subsequently included 22 patients. No control group was used and the comparative effectiveness data were taken from published studies. No details were provided on the suitability of the initial study sample to the clinical study question.

**Study design**

This was a single-centre cohort study of a 20-week ganciclovir prophylaxis regimen, compared with published studies of shorter duration. The duration of follow-up for the latter, i.e. control groups, was: 25 months for the 3-week course; 8 months for the 5-week course and 23 months for the 12-week course. Clinicians assessed outcome and were not blinded.

**Analysis of effectiveness**

All patients (n=22), with the exception of one who died on post-operative day 1, were included in the analysis. In addition, the total sample (n=23) was used to calculate the cumulative overall survival rate.

The primary outcome was the number of patients who developed CMV infections, although the presence of CMV disease and CMV-attributed mortality were also recorded. Infection was defined as detection of CMV through the shell vial assay on the blood, sputum or BAL fluid samples. CMV disease was established when a symptomatic infection was accompanied by lung function decline, radiological infiltrates, or the presence of viral inclusions of histologic specimens obtained through biopsies, without the presence of any other identified pathogen to suggest a concomitant causal disease. Patients measured their own lung function status on a daily basis at home. Bronchoscopy procedures were performed at 0, 2, 7, 14 and 28 days, and at 3, 6, 9 and 12 months. CMV infection was evaluated twice a month in the first year following transplantation, and once a month thereafter. Adverse effects of ganciclovir were monitored using a 20% increase in serum creatinine and/or a polymorphonuclear count of less than 2 mL. The indications for lung transplantation varied in the patient sample. Patients (n=22) undergoing the 20-week prophylaxis with ganciclovir received standardised immunosuppressive therapies. In 15 patients, the CMV serotype (positive or negative) did not match the donors.

**Effectiveness results**

For the 20-week course the results were as follows:

- reported number of CMV infections, 11;
- cumulative CMV infections at 1 year, 29%;
- reported number of patients with CMV disease, 1;
- reported number of patients with CMV-attributed mortality, 0.

No confidence intervals were reported. Ten patients in the intervention group presented at least one complication that could be attributed to either ganciclovir use or to long-term catheter use.

**Clinical conclusions**

See 'Results of the Review' for a comparison of the results from this study with those from a review of the literature. The authors stated that their results showed lower long-term rates of CMV infections in patients treated with the 20-week ganciclovir regimen, than in those treated with shorter-term regimens. They concluded that there were additional benefits with extended ganciclovir prophylaxis during the period of maximal immunosuppression, which both decreased short-term rates of CMV infection and delayed their onset.

**Modelling**

The Kaplan and Meier product-limit method was used to calculate the cumulative overall survival rate and the incidence
Outcomes assessed in the review
The outcomes assessed were the number of patients who developed CMV infections, the presence of CMV disease, and CMV-attributed mortality.

Study designs and other criteria for inclusion in the review
Not stated.

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
Two primary studies were included.

Methods of combining primary studies
Not applicable; only one study provided the estimate for each duration of treatment.

Investigation of differences between primary studies
The primary studies were compared in terms of diagnostic criteria, immunosuppression protocol, and duration of follow-up.

Results of the review
The reported number of CMV infections were: 19 for the 3-week course (see Other Publications of Related Interest no.1), 13 for the 5-week course (see Other Publications of Related Interest no. 2), and 16 for the 12-week course (see Other Publications of Related Interest no. 3).

The cumulative CMV infections at 1 year were: 75% for the 3-week course, 31% for the 5-week course, and 58% for the 12-week course.

The reported number of patients with CMV disease were: 4 for the 3-week course, 29 for the 5-week course, and 0 for the 12-week course.

The reported number of patients with CMV-attributed mortality were: 0 for the 3-week course, not reported for the 5-week course, and 0 for the 12-week course.

No confidence intervals were reported.

Measure of benefits used in the economic analysis
NHS Economic Evaluation Database (NHS EED)
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The authors estimated the number of infections prevented by comparing the 20-week course with the 12-week course.

**Direct costs**
The direct costs were not discounted because the time period of the analysis was less than one year. Resource use was not reported. The cost of CMV prophylaxis per patient was estimated, assuming a daily dose of 300 mg per patient. The unit cost of ganciclovir was estimated from the market prices for drugs in Switzerland. The date for this unit cost data was unclear, but it is implicit that the costs relate to 1999. It was unclear if the total cost also included the cost of the placement and ablation of an intravenous catheter for ganciclovir administration. The cost of out-patient treatment of a CMV infection was also estimated. The estimated average cost per patient per course of prophylaxis was reported.

**Statistical analysis of costs**
No analysis was reported. Costs were treated stochastically.

**Indirect Costs**
The indirect costs were not included in the study.

**Currency**
Swiss francs (SFr) were used. These were converted to US dollars ($) assuming 55.68 SFr were equivalent to $39.98, although the year for this currency conversion was not reported.

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
See effectiveness results reported previously.

**Cost results**
The total reported cost of CMV prophylaxis per patient was: $1,202 for the 3-week course, $2,226 for the 5-week course, $7,347 for the 12-week course, and $13,357 for the 20-week course. The costs associated with adverse events were not reported.

**Synthesis of costs and benefits**
The authors estimated that the additional length of 20 weeks’ treatment, compared with 12 weeks’ treatment, would prevent one CMV infection in 4.4 patients at an extra cost of $17,585 per infection prevented.

**Authors’ conclusions**
The study suggests there are additional benefits associated with extended ganciclovir prophylaxis during the period of maximum immunosuppression, which both decrease short-term rates of CMV infection and delay their onset. However, the prolonged duration of prophylaxis markedly increases the costs of the intervention without clear changes in the long-term outcome. There is a need to assess other strategies in order to provide better, safer and longer lasting protection against CMV.

**CRD COMMENTARY - Selection of comparators**
The reason for the selection of the intervention and control groups was not supported by detailed evidence from the literature. This study reported a detailed clinical assessment of a 20-week ganciclovir treatment for the prevention of
CMV infection in at risk patients who have had a lung transplant. The optimum duration of prophylaxis with ganciclovir is unknown and it was unclear whether either the intervention or control groups reflected current clinical practice. You, as the user of the database must, therefore, consider whether these are relevant to your own setting.

Validity of estimate of effectiveness:

The study did not use a randomised controlled trial design, but rather chose to collect prospective data on the intervention only and compare these data with published studies. No details were given of whether the published studies were comparable in terms of the study design, inclusion and exclusion criteria, or study patients. Thus, it was difficult to make direct comparisons in terms of the effectiveness of the intervention and alternative management strategies. This study also made no attempt to value the risk and discomfort of either avoidable CMV infections, their treatment, or the side-effects associated with long-term ganciclovir prophylaxis.

Validity of estimate of costs

The cost estimate was of limited value because the costs were not calculated from resource use data, but were estimated assuming a standard daily dose of ganciclovir. The omission of a clear time horizon, study perspective, clear incremental analysis and sensitivity analysis limited the generalisability of this study to other health care settings.

Other issues

The issue of generalisability was not discussed, although some comparison was made to the results of other studies. There was also no statistical analysis of differences between groups, although the validity of this would be questionable given the use of different study samples and the lack of details concerning the participant characteristics. The authors' conclusions were based on their role in a prospective study population, despite there being no information on the population of the other studies.

Implications of the study

The authors do not suggest that clinicians should adopt the 20-week course of ganciclovir prophylaxis for post-lung transplant patients. They do, however, suggest that further studies are required to assess other therapeutic strategies based on new viral replication inhibitors, or on techniques aimed at the restoration of CMV-specific immunity using T-cell clones.

Source of funding

None stated.

Bibliographic details


PubMedID

10559085

Other publications of related interest


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Adult; Antibiotic Prophylaxis /economics /methods; Antibodies, Viral /analysis; Antiviral Agents /administration & dosage /economics /therapeutic use; Bronchoalveolar Lavage Fluid /virology; Child; Cost-Benefit Analysis; Costs and Cost Analysis; Cytomegalovirus /immunology /isolation & purification; Cytomegalovirus Infections /economics /epidemiology /prevention & control /virology; Female; Follow-Up Studies; Ganciclovir /administration & dosage /economics /therapeutic use; Graft Rejection /immunology /prevention & control; Humans; Immunosuppressive Agents /therapeutic use; Incidence; Infusions, Intravenous; Lung Transplantation; Male; Middle Aged; Pneumonia, Viral /economics /epidemiology /prevention & control /virology; Prospective Studies; Survival Rate; Switzerland /epidemiology; Treatment Outcome

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