Comparison of the efficacy and cost effectiveness of pre-emptive therapy as directed by CMV antigenemia and prophylaxis with ganciclovir in lung 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 health technology examined was pre-emptive therapy with ganciclovir, guided by cytomegalovirus (CMV) antigenemia. CMV antigenemia assay was conducted routinely and pre-emptive therapy was initiated if greater than 25 CMV positive cells per 100,000 polymorphonuclear cells were found. This consisted of 5 mg/kg IV every 12 hours for 5 days, followed by 5 mg/kg daily for a total of 4 weeks of therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients receiving a single or double lung transplant who were at risk of developing CMV infection or disease (R+ and R-D+ patients).

Setting
The setting was hospital. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness, resource use, and cost data were collected between September 1995 and December 1997. The price year was not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Twenty-five consecutive patients were enrolled. Four were excluded because they were CMV recipient and donor negative, and two died the day of transplant. There were 21 patients in the control group and 19 in the study group. Seventeen patients in the control group and 7 in the study group had a single lung transplant. There were 15 R+ patients in the control group and 17 in the study group. Twenty-one patients in the control group and 13 in the study group had standard immunosuppression. Six patients in the study group had second line immunosuppression. No power
calculations were reported.

**Study design**
This was a non-randomised study with historical controls carried out at a single centre. The mean duration of follow-up was 455 days in the study group and 430 days for controls. No patient was lost to follow-up.

**Analysis of effectiveness**
The analysis of the clinical study was based on intention to treat. The primary health outcomes used in the analysis were incidence and onset of CMV disease, recurrence of CMV disease, mortality, and adverse effects. The two groups were comparable in terms of patient characteristics, except for second line immunosuppression and the smaller number of R-D+ patients in the study group.

**Effectiveness results**
Six patients received 12 courses of pre-emptive therapy, with one patient receiving 5 courses. The incidence of CMV disease was 26% in the study group compared with 38% in the control group. The onset of CMV disease was earlier in the study group (63 days after transplant) compared to the control group (145 days). Of the 6 patients who received pre-emptive therapy, none developed CMV disease following therapy. There were 11 episodes of recurrent disease in 5 patients in the study group and 13 episodes in 8 patients in the control group. There was no mortality directly related to CMV disease and no significant adverse effects.

**Clinical conclusions**
The authors argued that pre-emptive therapy with ganciclovir is as safe and effective as universal prophylaxis in preventing CMV disease in lung transplant recipients.

**Measure of benefits used in the economic analysis**
As the effectiveness results showed no difference in clinical benefit between the intervention and the comparator, the economic analysis was based on cost differences only (cost-minimisation).

**Direct costs**
Direct costs were not discounted due to the short time horizon of the study (less than one year). Quantities and costs were reported separately. Direct costs were related to the costs of prophylaxis or pre-emptive therapy and included costs of episodes of CMV disease, antigenemia assay, and CMV antibody titers. The quantity/cost boundary adopted was that of the hospital. The price year was not reported. Cost estimates were taken from the authors’ hospital. There were 21 courses of therapy in the control group and 12 in the study group. There were 13 episodes of CMV disease in the control group and 11 in the study group.

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

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

**Currency**
US dollars ($).
Sensitivity analysis
No sensitivity analyses were reported.

Estimated benefits used in the economic analysis
See effectiveness results above.

Cost results
Total costs amounted to $181,979 in the control group and $115,847 in the study group.

Synthesis of costs and benefits
As the effectiveness results showed no difference in clinical benefit between the intervention and the comparator, the economic analysis was based on cost differences only (cost-minimisation).

Authors' conclusions
The authors argued that pre-emptive therapy with ganciclovir is as safe and effective as universal prophylaxis in preventing CMV disease in lung transplant recipients, and is less expensive.

CRD COMMENTARY - Selection of comparators
The justification for the choice of comparator was that it represented previous practice. You, as a user of the database, should decide if these health technologies are relevant to your setting.

Validity of estimate of measure of effectiveness
The analysis was based on a study with historical controls, which was appropriate for the study question but may be associated with various biases or confounding variables. The authors did not show whether or not the study sample was representative of the study population. The authors reported demographic characteristics and showed that the groups were comparable, except for the number of R-D+ patients and the number of second line immunosuppressions. The authors did not consider late complications such as chronic rejection and bronchiolitis obliterans, which would be relevant for a wider appraisal of effectiveness.

Validity of estimate of measure of benefit
The analysis of benefits was based upon the therapeutic equivalence of treatment alternatives. The economic analysis therefore included only costs.

Validity of estimate of costs
Good features of the cost analysis were that all relevant direct cost categories were included, and quantities and costs were reported separately. However, the price year was not reported and the authors did not conduct sensitivity or statistical analyses on quantities or costs. Moreover, cost estimates were based on local rates, thus limiting the generalisability of the results.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, but did not address the issue of generalisability to other settings. The authors did not seem to present their results selectively. The study considered patients receiving a single or double lung transplant who were at risk for developing CMV infection or disease (R+ and R-D+ patients) and this was reflected in the authors’ conclusions. The study suffered from a small sample size, potentially limiting the extent to which statistically significant results could be found. The authors noted the potential bias created by the smaller number of R-D+ patients in the study group, recognising that such patients have a greater
risk of developing CMV disease.

**Implications of the study**
Pre-emptive therapy is effective in preventing CMV disease in lung transplant recipients, does not increase mortality or morbidity compared to universal prophylaxis, is less expensive than universal prophylaxis, and has the potential to improve patients' quality of life and reduce the incidence of CMV resistance to ganciclovir. More research is needed into the appropriate level and timing of CMV antigenemia, and the effect of pre-emptive therapy on late complications of CMV disease.

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