The economic impact of cytomegalovirus infection after liver transplantation

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
Two strategies for the antiviral prophylaxis of cytomegalovirus (CMV) disease in liver transplant recipients were examined. One strategy was oral acyclovir 800 mg administered four times daily for 120 days (ACV). The other was intravenous ganciclovir administered at 5 mg/kg every 12 hours for 14 days, followed by acyclovir (800 mg four times daily) for 106 days (GCV). The dosages were adjusted, if required, according to serum creatinine levels.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult, orthotopic liver transplant recipients. Patients were excluded if they had undergone prior organ transplantation, or had a known allergy to GCV or ACV. They were also excluded if their serum creatinine was greater than 3 mg/dL or their creatinine clearance was less than 10 mL/minute, or if they had been in a Stage III or IV coma after transplantation. Patients with pre-existing CMV infection were also excluded.

Setting
The setting was a transplant centre. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from January 1991 to June 1994. The price year was 1990.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were conducted in the preliminary phase of the study. These suggested that a sample of 150 patients was required to show a 23% decrease in the rate of CMV infection, with 90% power at a 5% significance level. A sample of 170 consecutive patients who were eligible for enrolment into the trial was identified over the study period. However, 3 patients dropped out of the study within 48 hours of enrolment. Of these, 2 had pre-existing CMV infection and one was treated for a pre-transplant positive CMV culture that later turned out to be false-positive. Therefore, the
final sample comprised 167 patients. The ACV group comprised 84 patients, of which 54.8% were women. The GCV group comprised 83 patients, of which 60.2% were women.

**Study design**

This was a prospective randomised trial that was conducted in two centres, the Mayo Clinic in Rochester (Minnesota) and the University of Nebraska Medical Center in Omaha (Nebraska). A block randomisation scheme was used. The patients were followed until death or for at least one year. Fifty-two patients in the ACV group and 39 in the GCV group had their treatment discontinued, mainly due to treatment failure. A comparable number of patients in both groups terminated treatment before the scheduled 4 months because of haematologic, renal, neurologic, or hepatic complications. The outcome assessment was not conducted blind.

**Analysis of effectiveness**

The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome was the incidence of CMV infection and disease after one year of follow-up. The secondary outcome measures were:

- the rates of infection-specific manifestations (asymptomatic CMV viremia, symptomatic CMV viremia, and organ involvement);
- the severity of initial CMV infection, measured using a 6-point scale based on whether the infection was symptomatic or asymptomatic and whether the patient was hospitalised;
- the survival rate of patients who died or were re-transplanted within the first year;
- the rates of cellular rejection, chronic rejection, OKT3 use, and treated opportunistic infections.

The study groups were comparable at baseline in terms of age, gender distribution, final diagnosis, co-morbidities, disease severity and laboratory data. However, there were significantly more Caucasian patients in the GCV group. There was also a trend towards more patients with encephalopathy in the ACV group.

**Effectiveness results**

After one year of follow-up, the incidence of CMV infection was 57% in the ACV group and 37% in the GCV group (p=0.001). The incidences of disease were 23% (ACV) and 11% (GCV), respectively, (p=0.03).

The incidence values were estimated for sub-groups of patients classified by CMV serological status. The sub-groups considered were donor negative and recipient negative (D-/R-), donor negative and recipient positive (D-/R+), donor positive and recipient positive (D+/R+), and donor positive and recipient negative (D+/R-).

The incidences of CMV infection and disease were all 0 in the D-/R- group.

In the D-/R+ group, the infection incidence rate was 47% with ACV versus 18% with GCV, (p=0.06). The disease incidence rates were 10% (ACV) and 0% (GCV), respectively, (p=0.15).

In the D+/R+ group, the infection incidence rate was 64% with ACV versus 40% with GCV, (p=0.005). The disease incidence rates were 24% (ACV) and 15% (GCV), respectively, (p=0.22).

Finally, in the D+/R- group, the infection incidence rate was 83% with ACV versus 75% with GCV, (p=0.27). The disease incidence rates were 58% (ACV) and 25% (GCV), respectively, (p=0.04).

In terms of infection-specific manifestations, the rate of asymptomatic CMV viremia was 16% with ACV versus 9% with GCV, (p=0.12). The rates of symptomatic CMV viremia were 23% (ACV) and 8% (GCV), respectively, (p=0.003), and the rates of organ involvement were 18% versus 8%, (p=0.03).

No statistically significant differences were observed between the two groups in terms of the following:
severity of initial CMV infection;
survival (91.6% versus 92.8%);
the rate of patients who died or were re-transplanted within the first year (12% versus 10%); and
the rates of cellular rejection (57% versus 54%), chronic rejection (2.5% versus 3.9%), OKT3 use (12% versus 12%),
and treated opportunistic infections (2.6% versus 5.2%).

Similar results were observed in the sub-group analyses.

Clinical conclusions
The effectiveness study showed that the two prophylactic treatments had a comparable impact on survival. However, GCV was more effective than ACV in reducing the incidence of CMV disease and infection.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was performed.

Direct costs
Discounting was not relevant since the costs per patient were incurred during a short time (120 days). The unit costs and the quantities were not reported separately. The economic evaluation considered all in- and out-patient health services associated with the post-transplantation period, including professional fees. The cost items were not broken down. The cost/resource boundary of the study was unclear, but it appears to have been that of the hospital. Resource use was estimated using individualised data that referred to those patients involved in the effectiveness study who were identified at the Mayo Clinic (sample of 147 patients: 74 in the ACV group and 73 in the GCV group). Resource consumption referred to the first 4 months starting from the day of transplantation. The charges were obtained from the Mayo Institutional Planning Database. All of the costs were adjusted for inflation to 1990 values, using an institutional fee schedule that was comparable to the medical component of the consumer price index.

Statistical analysis of costs
The impact of potential confounding factors, which had been shown to affect health care usage in liver transplantation, was assessed in a regression analysis. Logarithm transformations were required for the linear regression analysis because of the skewed distribution of the cost data. The total charges for the first 120 days were considered to be the dependent variable, while pre- and post-transplant variables (including CMV infection and disease) were considered as covariates. Standard statistical tests were conducted to test the statistical significance of differences in costs between the groups.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not reported.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The estimated median charges were $114,100 in patients who did not have CMV infection, $119,600 in patients with asymptomatic CMV infection, and $148,300 in patients who developed CMV disease. The difference between charges in CMV disease patients and asymptomatic CMV infection patients was statistically significant. These differences were mainly due to longer hospitalisation and more bacteraemia and fungal infections in CMV disease patients.

From the regression analysis, four factors were found to be positively correlated with higher charges. These were CMV disease, intraoperative blood transfusion, a Karnofsky score of less than 70, and re-transplantation. These factors explained 49% (CMV disease), 2% (blood transfusion), 13% (Karnofsky score) and 26% (re-transplantation) of the increase in charges, respectively.

The median charges were $119,400 in the GCV group and $125,000 in the ACV group. The difference was not statistically significant. However, in high-risk patients (D+/R- group), significantly lower median charges were observed in the GCV group ($113,869) than in the ACV group ($153,284), (p=0.02). There were no significant differences in charges between GCV and ACV for the other sub-groups.

Synthesis of costs and benefits
The costs and benefits were not combined because a cost-consequences analysis was conducted.

Authors’ conclusions
Cytomegalovirus (CMV) disease had a substantial impact on hospital charges. Reductions in disease incidence due to prophylactic therapy with ganciclovir (GCV) may result in cost-savings in the first 4 months post-transplantation, particularly in high-risk patients.

CRD COMMENTARY - Selection of comparators
The authors did not provide any explicit justification for the choice of the prophylactic therapies under evaluation. The therapies represented the comparators selected in the study used to provide the effectiveness data. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a prospective randomised trial, which was appropriate for the study question. The study was multicentre but almost 90% of the patients came from a single institution. The methods of randomisation and sample selection were reported. Since consecutive patients were enrolled, the study sample was representative of the study population. However, a substantial group of patients had to terminate the study treatment due to therapeutic failure or complications. The internal validity of the analysis was enhanced by power calculations and the use of intention to treat as the basis for the analysis of the clinical study. The study groups were not perfectly comparable at baseline. A sub-group analysis was also performed.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted.

Validity of estimate of costs
The authors did not state explicitly which perspective was adopted in the study, but it appears that costs relevant to the hospital have been considered. A detailed breakdown of the cost categories was not provided, neither was information on the unit costs and resource use. These factors limit the possibility of replicating the study in other settings. The
source of the cost data was reported. The costs were appropriately adjusted for inflation due to the wide timeframe of the study. The price year was given, which aids reflation exercises in other settings. Statistical tests were conducted, not only when comparing the cost estimates but also when identifying those factors that had the greatest impact on the estimated costs. Charges rather than costs were used. However, as the authors noted, charges might not have reflected the true costs of the services considered in the study. The cost estimates were specific to the study setting and sensitivity analyses were not conducted. It was also noted that the cost analysis could have been underpowered and Type-II errors may not be excluded.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the transferability of the study results to other settings. Most of the estimates were derived from a single centre and the analysis did not consider potential variation in the data. Sensitivity analyses were not conducted, which reduced the external validity of the analysis. The study referred to patients who received liver transplant and this was reflected in the conclusions of the study. The authors noted some limitations of the financial analysis, mainly due to the use of charges instead of true costs.

Implications of the study
The authors noted that controversy exists as to whether or not asymptomatic CMV should be treated. They suggested that in their series of patients, an effective antiviral prophylaxis regimen should be recommended only in high-risk patients (D+/R-).

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Other publications of related interest


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