Valaciclovir prophylaxis of cytomegalovirus infection and disease in renal transplantation: an economic evaluation

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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 (VP) to reduce the incidence of cytomegalovirus (CMV) infection following renal transplantation.

Type of intervention
Treatment.

Economic study type
Cost-effective analysis.

Study population
The study population comprised patients who had undergone a renal transplant.

Setting
The setting was the community. The economic study was carried out in the USA and eleven European countries.

Dates to which data relate
The dates during which the effectiveness data were obtained were not indicated. The authors stated that the clinical outcomes had been reported in a different paper (see Other Publications of Related Interest). The resource data were gathered between 1997 and 1998. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single study (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costs were derived prospectively using the same patient sample as that used in the effectiveness study.

Study sample
The study included patients aged at least 13 years who had received a cadaveric renal transplant graft at the hospitals in the study. Since the development of CMV disease is related to the serostatus of both graft recipient and donor, two study strata were considered: the stratum of donor seropositive and recipient seronegative (D+R-), and the stratum of recipient seropositive (R+). Other studies have shown that the incidence of CMV is greater in the D+R group than in the R+ group. Ten patients (2 in the D+R- group and 8 in the R+ group) were classified as outliers, and were therefore excluded. The final study population comprised 616 patients: 208 patients in the D+R- group and 408 in the R+ group. In the D+R- group, 106 patients received the placebo and 102 the VP. In the R+ group, 204 patients received the
placebo and 204 the VP. No power calculations were performed to determine sample size.

**Study design**
The study was a multicentre, multinational, randomised placebo-controlled trial conducted in the USA and eleven European countries. The duration of follow-up was 6 months for clinical efficacy and 1 year for patient and allograft survival. The outcome of evidence for CMV was assessed, where the assessor was blinded to the details of the patient.

**Analysis of effectiveness**
The clinical study was analysed on an intention to treat basis. The primary end point for clinical efficacy was the development of CMV disease at 6 months after renal transplantation, according to the Kaplan-Meier method. The diagnosis of CMV had to be confirmed by laboratory tests, or by blood and urine cultures. The clinical outcome measures of acute graft rejection, and the incidence of herpes simplex virus, varicella zoster virus and other non-herpes opportunistic infections, were also considered. Any differences between the treatment groups were assessed using Student’s t-test.

**Effectiveness results**
In the D+R- stratum, the incidence of CMV disease at 6 months was significantly lower for the VP group (16%) than for the placebo group (45%), (p<0.0001).

In the R+ stratum, the incidence of CMV disease at 6 months was also significantly lower for the VP group (1%) than for the placebo group (6%), (p<0.03).

Acute graft rejection and rates of herpes simplex virus, varicella zoster virus and other infections were also lower for the VP group, in both the D+R- and R+ strata.

**Clinical conclusions**
The analysis of effectiveness indicated that VP was a more effective strategy for patients in both the D+R- and R+ groups, compared with placebo.

**Measure of benefits used in the economic analysis**
The most appropriate measure of benefit was the percentage of CMV cases avoided at 6 months.

**Direct costs**
The direct costs were not discounted because the timeframe of the study was less than 1 year. The quantities and costs were estimated from actual data collected between 1997 and 1998. The 1997 unit costs for hospital days and home visits were inflated by a factor of 1.3% (Consumer Price Index) to reflect the increase in inflation in France.

The resources used were collected as:

- inpatient costs, i.e. the numbers of hospital admissions per patient, total hospital days, physician consultations, special procedures and laboratory tests;
- outpatient costs, i.e. the numbers of physician consultations, home health visits, special procedures and laboratory tests; and
- drug medication costs, i.e. the numbers of days of ganciclovir, aciclovir, oral cyclosporine, or other immunodepressives.

The average cost of each resource was reported. The quantities and costs were analysed separately. The economic analysis was conducted from the perspective of the French health care system.
Statistical analysis of costs
A Student’s t-test was performed to compare the mean use of medical resources between the groups. Analysis of variance (ANOVA) was used to investigate whether the country of treatment had a significant effect on differences in the duration of inpatient stay. The ANOVA was performed for two scenarios: France compared with the rest of Europe and the USA, and the USA compared with Europe.

Indirect Costs
Indirect costs were not included.

Currency
French francs (Ffr).

Sensitivity analysis
One-way sensitivity analyses were carried out to assess whether variations in the data substantially affected the cost-effectiveness estimates. Two parameters that may influence the cost estimates were tested: the number of inpatient hospital days, and the cost of the actual average daily dose of valaciclovir administered in the study (adjusted for renal function), instead of the protocol dose of 8 g/day.

Estimated benefits used in the economic analysis
In the D+R- stratum, the proportion of CMV cases avoided at 6 months was 55% in the placebo group and 84% in the VP group. The corresponding values in the R+ stratum were 94% (placebo group) and 99% (VP group).

Cost results
In the D+R- stratum, the total costs per patient were 112,832 Ffr in the placebo group and 103,095 Ffr in the VP group. The corresponding values in the R+ stratum were 89,028 Ffr (placebo group) and 92,151 Ffr (VP group).

The adoption of VP resulted in a mean saving of 9,737 Ffr for a D+R- patient. In addition, there was a mean rise in cost of 3,121 Ffr for a R+ patient.

The statistical analysis showed that in both strata, patients who were administered VP used significantly fewer resources in many cost categories. These included the number of hospital admissions, the total number of hospital days, the number of special procedures, the number of laboratory tests, and the number of days of drug medication (ganciclovir or oral aciclovir).

There was no significant difference between the two groups in terms of outpatient resource use.

The ANOVA demonstrated that the country of treatment had no significant effect on the duration of inpatient stay for the USA compared with Europe, (p=0.84). Similar results were found for France compared with the rest of Europe and the USA, (p=0.074).

Synthesis of costs and benefits
The costs and benefits were synthesised in order to calculate the incremental cost-effectiveness ratio (ICER).

In the D+R- group, the incremental cost-effectiveness analysis indicated that the VP strategy was dominant, as it was associated with lower costs and greater effectiveness than the placebo group.

In the R+ group, the ICER of VP was equal to 62,429 Ffr per case of CMV disease avoided, compared with placebo.

Sensitivity analyses were performed to investigate the effect of varying the number of inpatient hospital days. The results showed that in the D+R- stratum, the 95% confidence intervals (CIs) for the ICERs ranged from -75,709 to
+8,880 Ffr per case of CMV prevented at 6 months after transplant. For the placebo group, the CIs for the ICERs varied from -76,074 to 8,771 Ffr. The VP was still dominant when varying the second parameter, the average daily dose of valaciclovir.

The sensitivity analysis showed that in the R+ stratum, the 95% CIs for the ICERs ranged from -74,152 to +188,108 Ffr per case of CMV prevented at 6 months after transplant. For the placebo group, the CIs varied from -98,828 to +192,321 Ffr. The ICER was 9,095 Ffr when varying the average daily dose of valaciclovir.

The results of the sensitivity analyses validated the economic benefits of VP for the D+R- population.

**Authors' conclusions**
The use of valaciclovir prophylaxis (VP) significantly reduced the incidence of cytomegalovirus (CMV) infection in the 6 months following renal transplantation, for patients at both high (D+R-) and moderate (R+) risk. It also resulted in large cost-savings in high-risk patients, and provided a clinically effective therapeutic option for moderate-risk patients at a modest incremental cost.

**CRD COMMENTARY - Selection of comparators**
Since the study was a clinical trial, the choice of the comparator was a placebo strategy.

**Validity of estimate of measure of effectiveness**
The analysis was based on a randomised controlled trial that seemed appropriate for the study objective. The authors reported much of the effectiveness data and details of the statistical analyses in a different paper. The sample sizes seemed sufficient to assure the groups of patients were comparable.

**Validity of estimate of measure of benefit**
The estimation of benefits was obtained directly from the effectiveness analysis. The authors did not justify the choice of the benefit measure.

**Validity of estimate of costs**
The analysis included all the categories of cost that were relevant to the perspective adopted. The costs and quantities were reported separately, and an extensive statistical analysis of resources and unit costs was undertaken.

**Other issues**
The issue of generalisability to other settings was partially addressed by sensitivity analyses on the effectiveness and cost data. In order to compare their findings with those of other studies, the authors also reported the results of case-control studies and meta-analyses.

**Implications of the study**
From the perspective of the French health care system, the study's findings suggested that VP should be adopted for the treatment of CMV infection in high-risk patients, following renal transplantation.

**Source of funding**
None given.

**Bibliographic details**
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**Other publications of related interest**

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