Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection


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
Three different interventions for prophylaxis of cytomegalovirus (CMV) disease after renal transplantation were investigated:

3 months’ therapy with oral ganciclovir (Cymevene; Hoffman-La Roche) at a dose of 1 g three times per day;

3 months’ therapy with valacyclovir (Valtrex; Glaxo Wellcome) at a dose of 2 g four times a day; and

no anti-CMV prophylaxis, with patients managed by deferred therapy.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult recipients of renal transplants. Patients with seronegative donor/seronegative recipient (D-/R-) CMV serostatus before renal transplantation were excluded from the study, as were those taking systemic antivirotics.

Setting
The study setting was tertiary care. The economic study was conducted in the Czech Republic.

Dates to which data relate
The effectiveness and resource use data were derived between April 1999 and January 2003. The price year was not reported.

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

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

Study sample
No study sample size appears to have been determined in the planning phase of the study. The authors did not report any power calculations. From April 1999 to December 2000, 38 patients were randomised to any of the three groups. However, after data from this period of the study had been analysed, the enrolment of patients in the control group was stopped for ethical reasons. Additional patients (n=45) were randomised only to therapy with either ganciclovir or valacyclovir from January 2001 to January 2003. Therefore, overall, 83 patients were included in the study. Of these patients, 36 (25 males) with a mean age of 48 (+/- 11) years were treated with ganciclovir. An additional 35 (26 males) with a mean age of 45 (+/- 12) years received valacyclovir. Finally, the remaining 12 (6 males) patients had no prophylaxis and were managed by deferred therapy. The mean age in this group was 46 (+/- 13) years.

**Study design**
The study used was a randomised controlled trial (RCT), which was conducted at a single centre in the Czech Republic. The patients were randomised to the three groups in a 1:1:1 ratio. When deferred therapy was discontinued, the patients were then randomised to either of the two prophylaxis interventions using a 1:1 ratio. The patients were followed up for a total of 24 months post renal transplantation (median 24; range: 12.5 - 24). The authors did not report the loss to follow-up. The physicians assessing methods of CMV detection were blinded to the study group and the clinical status of the patients.

**Analysis of effectiveness**
The analysis of effectiveness was conducted on an intention to treat basis. The primary end point in the study was the incidence of CMV disease within the first 12 months post renal transplantation. The secondary end points included CMV DNAemia, acute rejection, patient survival, incidence of other infections, graft function and safety profile. Active CMV infection was defined as symptomatic active infection. Clinical symptoms included CMV syndrome (fever plus one or more of constitutional symptoms, leucopenia, thrombocytopenia, or liver enzyme elevations) or tissue-invasive CMV disease. The patient groups were shown to be comparable in terms of their basic demographic characteristics, immunologic parameters and immunosuppressive therapy.

**Effectiveness results**
During the 12 months post renal transplantation, there were two episodes of CMV disease in 2 patients (5.7%) in the ganciclovir group and one episode of CMV disease in one patient (2.9%) in the valacyclovir group, (p=0.575). In the deferred therapy group, there were 13 CMV disease episodes in 8 patients (66.7%; p<0.001). There was no case of CMV disease after the first year post renal transplantation in either prophylactic group.

There was no case of CMV-related death or ganciclovir resistance.

The cumulative incidence of CMV DNAemia throughout the course of prophylaxis was 8.6% in the ganciclovir group and 8.8% in the valacyclovir group. At the end of 6 months after renal transplantation, although the incidences of DNAemia after stopping prophylaxis increased to 20% in the ganciclovir group and 32.4% in the valacyclovir group, (p=0.267), the differences remained highly significant in comparison with the 91.7% incidence in the deferred therapy group (p<0.001 for both ganciclovir versus deferred therapy and valacyclovir versus deferred therapy).

Compared with the deferred therapy group, there was a decrease in clinical herpes simplex viral infection in the ganciclovir group, (p=0.018), and valacyclovir group, (p=0.009).

The incidence of biopsy-confirmed acute rejection in the valacyclovir group was significantly lower than that in the ganciclovir group, (p=0.030), and deferred therapy group, (p<0.001). The biopsy-confirmed acute rejection rates at 12 months were 11.8%, 34.3% and 58.3% in the valacyclovir, ganciclovir and deferred therapy groups, respectively. The difference between the ganciclovir and deferred groups did not reach statistical significance, (p=0.087).

There were no statistically significant differences in delayed graft function incidence between the three groups, although the incidence was higher for the ganciclovir group.

Patient and graft survival rates were similar between the groups.
The cumulative incidence of treatment failure at 24 months was significantly lower in the ganciclovir (19.8%) and valacyclovir (11.8%) groups than in the deferred therapy group (66.7%; p<0.001).

There was no difference in the number of adverse events requiring dose reduction or prophylaxis discontinuation between the ganciclovir and the valacyclovir groups.

Clinical conclusions
The authors concluded that 3 months' treatment with valacyclovir for renal transplant recipients was as effective in preventing CMV disease and CMV DNAemia as oral ganciclovir. Valacyclovir was associated with a significantly reduced risk of acute rejection in comparison with both ganciclovir prophylaxis and deferred therapy.

Measure of benefits used in the economic analysis
The authors did not derive a measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

Direct costs
The direct costs included were those of the hospital. These comprised all costs directly related to CMV, such as the costs of hospitalisation and treatment of CMV disease, the costs of prophylaxis, and the costs of diagnostic procedures on CMV activation and CMV monitoring post renal transplantation. The authors did not include the costs associated with the treatment of acute rejection episodes or other infections. The costs and the quantities were not reported separately. The sources of the unit costs used to value resource use were not reported. As the costs were incurred during one year, discounting was not relevant and was not performed. The study reported the average costs. The price year was not reported.

Statistical analysis of costs
The mean costs were reported alongside their standard deviations.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($). The conversion to US dollars was made using the average exchange rate over the course of the study (i.e. US$1 = 35.48 Czech crowns).

Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total 12-month direct CMV-related costs per patient were $3,072 (+/- 2,006) for patients treated with ganciclovir, $2,906 (+/- 2,433) for those receiving valacyclovir and $4,906 (+/- 5,686) for those receiving deferred therapy.

This resulted in 37% and 41% cost-reductions with ganciclovir and valacyclovir, respectively, in comparison with deferred therapy.
Synthesis of costs and benefits
The costs and benefits were not combined.

Authors’ conclusions
Three months’ treatment with valacyclovir for renal transplant recipients was as effective in preventing cytomegalovirus (CMV) disease and CMV DNAemia as oral ganciclovir. In addition, valacyclovir was associated with a significantly reduced risk of acute rejection in comparison with both ganciclovir prophylaxis and deferred therapy. The costs of both regimens were comparable, both being cost-effective and leading to an approximate reduction in CMV-related costs relative to those patients not receiving prophylaxis.

CRD COMMENTARY - Selection of comparators
The authors compared three different interventions for the prophylaxis of CMV disease after renal transplantation, all which appeared to be current practice in the authors’ settings. However, based on the results of a pilot study, after one year the trial did not enrol any further patients to the deferred therapy group because of ethical considerations. You should decide if the treatments being compared represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The study was based on an RCT. This was appropriate for the study question, as well-conducted RCTs are the ‘gold’ standard study design when comparing health technologies. The study sample appears to have been representative of the study population. In addition, the patient groups were shown to be comparable in terms of their basic demographic characteristics, immunologic parameters and immunosuppressive therapy. The authors also performed appropriate statistical analyses to test if differences in outcomes between the three groups were statistically significant. However, they acknowledged that, although an RCT was conducted, it was a single-centre study with a limited number of enrolled patients.

Validity of estimate of measure of benefit
The authors did not derive a measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. The authors, however, explicitly reported that several costs were excluded from the analysis, such as the costs associated with the treatment of acute rejection episodes. As there were statistically significant differences in acute rejections between the three groups, the results could have favoured ganciclovir and deferred therapy since they were associated with more acute rejection episodes. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The authors did not report the sources used for the unit costs, although it would appear these were derived from the authors' settings. The authors also did not report whether cost-differences between the three groups were statistically significant. Appropriate currency conversions were performed and the exchange rate was reported. However, the authors did not report the price year used, which will hamper any possible inflation exercises. As the costs were incurred during a 1-year period, discounting was irrelevant and was not performed.

Other issues
The authors made appropriate comparisons of their findings with those from other studies that had also found ganciclovir and valacyclovir to be superior to other prophylaxis interventions. The issue of generalisability to other settings was not addressed through sensitivity analyses. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, the study was carried out at a single institution.
with a limited number of enrolled patients. Second, it was unclear whether the results from the study were generalisable to patients with more favourable donor characteristics or with recipients at risk of primary CMV infection.

**Implications of the study**
The authors reported that the encouraging results of valacyclovir-based prophylaxis could have major clinical implications given the increasing incidence of ganciclovir-resistant CMV disease. Ganciclovir could thus be reserved solely for the treatment of symptomatic CMV infection.

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**Other publications of related interest**


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