Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients
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CRD summary
This review concluded that universal prophylaxis and pre-emptive therapy are beneficial in preventing cytomegalovirus organ disease in solid organ transplant recipients. Both approaches are associated with reduced allograft rejection, but only universal prophylaxis reduces bacterial and fungal infections and mortality. The authors’ conclusions are appropriate, although the review was unable to directly compare the relative effectiveness of the two approaches.

Authors’ objectives
To evaluate the efficacy of universal prophylaxis and pre-emptive approaches in preventing organ disease by cytomegalovirus (CMV) infection and other complications in solid organ transplant recipients.

Searching
MEDLINE and EMBASE (both from inception to May 2005), Evidence-Based Medicine (from 2000 to May 2005), and the Cochrane CENTRAL Register and Cochrane Database of Systematic Reviews (Issue 4, 2004) were searched for English and non-English language studies; the search terms were reported. Relevant pharmaceutical companies were contacted for unpublished studies, and abstracts from the meetings (2003 and 2004) of the Infectious Disease Society of America, Interscience Conference on Antimicrobial Agents and Chemotherapy, and American Transplantation Congress, were reviewed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Trials comparing pre-emptive or prophylaxis antiviral therapy for the prevention of CMV with non-active therapy were eligible for inclusion. Trials of universal prophylaxis that used less than 2 g of acyclovir or less than 3 g of ganciclovir per day, or gave universal prophylaxis for less than 60 days, were excluded. Trials that gave pre-emptive therapy for less than 14 days were also excluded, as were trials of immunoglobulin alone or in combination with antiviral drugs. All of the included pre-emptive therapy trials used ganciclovir antiviral therapy; the included studies of universal prophylaxis used acyclovir, ganciclovir or valacyclovir. Comparison was with placebo or no drugs. One study of universal therapy was included despite the duration of therapy being less than 60 days.

Participants included in the review
Trials of solid organ transplant recipients were eligible for inclusion. The included trials were of kidney or liver recipients, apart from one study of heart recipients. In the pre-emptive therapy trials, 11.6% of participants had donor-positive/recipient-negative CMV serostatus and 86.2% had recipient-positive serostatus. For participants receiving universal prophylaxis, the respective rates were 12.7% and 77.9% for the trials of acyclovir, 16.4% and 81.8% for the trials of ganciclovir, and 33.4% and 66.2% for the trial using valacyclovir.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The primary outcome of interest was CMV organ disease which was defined as CMV viraemia, detected by positive culture, pp65 or polymerase chain reaction, as well as clinical or histologic involvement of an organ due to the same infection. The secondary outcomes were allograft rejection, allograft loss, bacterial and fungal infections, non-CMV viral infections, time to CMV organ disease, CMV recurrence, CMV resistance and death. The median length of follow-up in the included studies was 6 months.

How were decisions on the relevance of primary studies made?

Two investigators independently assessed studies for relevance.

**Assessment of study quality**
The primary studies were assessed for method of randomisation, concealment of randomisation, blinding of the patients and investigators, and the reporting of participant drop-outs and withdrawals, using the 5-point Jadad scale. Two investigators independently assessed study quality.

**Data extraction**
Two investigators were involved in extracting the data, though it was unclear whether the extraction was conducted independently or by one investigator and checked by a second. Only patients with CMV organ disease were included in the case definition. Patients with CMV syndrome (symptomatic viraemia without end-organ involvement) were classified as being without CMV disease. The proportions of patients with CMV organ disease in the intervention and control group were extracted and the odds ratio (OR) and 95% confidence interval (CI) estimated for the primary studies. Where there were no outcome events in one group, 0.5 was added to all cells to allow the calculation of the OR.

**Methods of synthesis**
How were the studies combined?
Studies of universal prophylaxis and pre-emptive treatment were pooled separately using the Mantel-Haenszel fixed-effect model and DerSimonian and Laird random-effects model. Where there was statistically significant heterogeneity (P<0.10), only results from the latter were reported.

How were differences between studies investigated?
Several subgroup analyses, specified a priori, were conducted separately for universal prophylaxis and pre-emptive therapy. Statistical heterogeneity was assessed using the Breslow-Day method and the I-squared statistic. Post-hoc sensitivity analyses that excluded data from certain studies were conducted. Publication bias was assessed using the Egger regression approach.

**Results of the review**
Seventeen RCTs (n=1,980) were included: 11 of universal prophylaxis (n=1,582) and 6 (n=398) of pre-emptive therapy.

All the trials scored 2 or 3 on the Jadad scale. Three of the 17 trials were double-blind (all were trials of universal prophylaxis); allocation concealment was adequate in 5 (all were trials of universal prophylaxis); length of follow-up was assessed as adequate in 7 trials (3 trials of pre-emptive therapy and 4 trials of universal therapy). In general, the trials were of a modest size.

Universal prophylaxis.

There was a statistically significant reduction in the development of CMV organ disease with universal prophylaxis compared with the control group (OR 0.20, 95% CI 0.13, 0.31). There was also a statistically significant reduction in the secondary end points of rate of acute allograft rejection, bacterial and fungal infections, non-CMV viral infections and mortality, but not for graft loss. There was no evidence of statistically significant heterogeneity. The removal of individual trials from the analysis, including the trial with a treatment duration of less than 60 days, did not affect the overall efficacy.

In the subgroup analyses, there was a statistically significant decrease in CMV organ disease compared with controls for donor-positive/recipient-negative CMV serostatus patients, in immunosuppressed patients who received induction therapy with antilymphocyte antibodies, in kidney transplant and liver transplant recipients, and for acyclovir at more than 2 g/day, acyclovir 3.2 g/day and ganciclovir 3 g/day.

Pre-emptive therapy.
There was a statistically significant reduction in the development of CMV organ disease with pre-emptive therapy compared with the control group (OR 0.28, 95% CI 0.11, 0.69). There was also a statistically significant reduction in the secondary end points of rate of acute allograft rejection, but not for graft loss, bacterial and fungal infections or mortality. Non-CMV viral infections could not be assessed. There was no evidence of statistically significant heterogeneity.

In the subgroup analyses, there was no statistically significant decrease in CMV organ disease compared with controls for donor-positive/recipient-negative CMV serostatus patients, nor in immunosuppressed patients who received induction therapy with antilymphocyte antibodies, nor in liver transplant recipients. There was a statistically significant decrease in CMV organ disease for kidney transplant recipients compared with controls.

There was no evidence of publication bias as assessed by the Egger regression method.

**Authors' conclusions**

Universal prophylaxis and pre-emptive therapy are beneficial in preventing CMV organ disease in solid organ transplant recipients. Both approaches are associated with a reduction in allograft rejection, but only universal prophylaxis reduces bacterial and fungal infections and mortality. Both acyclovir and ganciclovir are effective for universal prophylaxis.

**CRD commentary**

The review addressed a clear research question using defined inclusion criteria. Relevant electronic databases were searched for studies and the search terms were reported. Attempts were made to locate unpublished studies, thereby reducing the risk of publication bias, and language restrictions were not applied. Appropriate measures were taken to reduce error and bias in the study selection, quality assessment and data extraction processes. Some relevant details of the study populations were provided. The quality of the included studies was assessed and the authors discussed their findings in the context of study quality. The statistical pooling seemed appropriate and statistical heterogeneity was assessed. The authors' conclusions follow from the evidence presented. However, most of the included studies were not blinded and were of a modest size, and may have been underpowered. No direct comparisons of the two therapies were available and indirect statistical comparisons were not made, therefore the relative benefits of the two therapies or of the different antiviral drugs used for universal prophylaxis are unclear.

**Implications of the review for practice and research**

Practice: The authors stated that the results suggest that universal prophylaxis may be the preferred method of treatment, though a trial directly comparing universal prophylaxis with preemptive therapy is required to confirm this. High-dose oral acyclovir should remain among the drugs of choice for universal prophylaxis in all liver and kidney transplant patients who are at a high risk for CMV organ disease.

Research: The authors stated that trials are required to directly compare universal prophylaxis with pre-emptive therapy and high-dose acyclovir with ganciclovir or valganciclovir.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.