

Pre-emptive treatment of Cytomegalovirus

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GUIDELINES

Pre-emptive treatment of Cytomegalovirus (CMV) infection significantly reduces the risk of CMV disease compared with placebo. (Level 1)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Valganciclovir is equally efficacious in preventing CMV disease when used as prophylaxis or as pre-emptive treatment (Level 2 evidence but not designed for this outcome)
- Pre-emptive treatment of CMV infection results in significantly less leukopenia than prophylaxis, however, there is no difference in other adverse events.
- Pre-emptive treatment with ½ dose ganciclovir and ½ dose foscarnet results in increased drug toxicity compared with full dose ganciclovir alone.
- The cost of both prophylaxis and pre-emptive treatment is substantial and depends on the costing of the diagnostic test and medications in individual units.
- Pre-emptive treatment depends on an accurate diagnostic test.
- Both CMV polymerase chain reaction (PCR) testing and pp65 antigenaemia testing appear efficacious in the detection of CMV infection when used in trials of pre-emptive therapy.
- All studies have used CMV testing at weekly or fortnightly intervals in patients treated with pre-emptive therapy.

IMPLEMENTATION AND AUDIT

Renal units undertaking pre-emptive treatment should screen patients at appropriate intervals with either pp65 antigenaemia testing or PCR. All patients undergoing a pre-emptive treatment program should be audited to determine the efficacy of the screening test in an individual unit.

BACKGROUND

Cytomegalovirus infection and disease are important causes of morbidity and mortality among renal transplant recipients. It has long been recognised that this is the most common opportunistic pathogen in renal transplant patients. Cytomegalovirus may manifest as a non-specific illness characterised by fever, mononucleosis, leukopenia and thrombocytopenia, or as a variety of clinical syndromes including pneumonitis, hepatitis, encephalitis and focal gastrointestinal disease.

A number of strategies have been developed to prevent CMV disease. One of these is prophylaxis, which can be performed universally on all transplant recipients irrespective of the risk of CMV disease or can be targeted to subsets of patients, depending on risk stratification determined by the CMV zero-status of both the donor and recipient.

Pre-emptive therapy, however, involves directing prophylaxis towards only those recipients in whom diagnostic tests have indicated early replication of CMV is occurring. This is an attempt to prevent the progression of asymptomatic infection into CMV disease. Since the initial CARI guideline, published in 2004, there have been a number of new trials and 3 meta-analyses examining the efficacy of pre-emptive therapy to prevent CMV disease in solid organ transplant recipients.

This review has undertaken to assess the following factors:

- is pre-emptive therapy effective in preventing CMV disease?
- is there any difference between the efficacy of pre-emptive treatment and prophylaxis in preventing CMV disease?
- which medications are efficacious in the pre-emptive treatment of CMV infection?
- what are the adverse affects associated with pre-emptive therapy?, and
- is there any cost difference between pre-emptive treatment and prophylaxis?

SEARCH STRATEGY

Databases searched: MeSH terms and text words for transplantation were combined with MeSH terms and text words for cytomegalovirus and combined with MeSH terms and text words for antiviral agents and diagnostic tests. The search was carried out in Medline (1966 – January Week 1, 2010). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 7 January 2009; 25 January 2011.

WHAT IS THE EVIDENCE?

There are 3 meta-analyses including a Cochrane Review examining the efficacy of pre-emptive treatment of CMV infection to prevent CMV disease. Since the publication of the meta-analyses in 2006, there has been a further randomised controlled trial which compared the efficacy of different treatment regimens for pre-emptive treatment of CMV infection. There have also been 2 RCTs comparing prophylaxis with pre-emptive treatment using oral valganciclovir.

The meta-analyses have examined pre-emptive treatment for CMV infection compared with placebo, or standard of care and compared with anti-viral prophylaxis examining the following endpoints:

1. risk of CMV disease
2. CMV organ involvement
3. acute rejection
4. all-cause mortality
5. graft loss
6. leukopenia, and
7. renal dysfunction.

The outcomes in summary are as follows:

Risk of cytomegalovirus disease

Pre-emptive treatment with IV or oral ganciclovir significantly reduces the risk of CMV disease compared with placebo or control. Other medications that have been shown to reduce the incidence of CMV disease when used pre-emptively are valganciclovir and a combination of ½ dose IV ganciclovir and ½ dose foscarnet.

In a comparison of prophylactic versus pre-emptive treatment with valganciclovir, there was significantly more CMV DNAemia with the pre-emptive approach but no difference in the development of CMV disease. [1] Similarly, in a RCT comparing pre-emptive treatment with valganciclovir to prophylaxis with valaciclovir [2], there was no difference in the incidence of CMV disease.

Cytomegalovirus organ involvement

There is no difference in the degree of organ involvement due to CMV when pre-emptive treatment is compared with placebo or standard care. This has not been specifically examined in trials comparing prophylaxis with pre-emptive treatment.

Acute rejection

There is no difference in the risk of acute rejection with pre-emptive treatment of CMV either compared with placebo or standard of care, or with prophylaxis.

Mortality

There is no difference in mortality with pre-emptive treatment of CMV either compared with placebo or standard of care, or with prophylaxis.

Graft loss

There is no difference in graft survival with pre-emptive treatment of CMV either compared with placebo or standard of care, or with prophylaxis.

Leukopenia

There is no difference in leukopenia with pre-emptive treatment of CMV compared with placebo or standard of care. There is a significantly lower risk of leukopenia using pre-emptive treatment compared with prophylaxis.

Renal dysfunction

There is no difference in the incidence of renal dysfunction with pre-emptive treatment of CMV either compared with placebo or standard of care, or with prophylaxis.

Drug toxicity

In the RCT comparing full dose IV ganciclovir with ½ dose IV ganciclovir and ½ dose foscarnet, there was a significantly greater risk of toxicity in the combination group.

Cochrane review: Strippoli et al, 2006 [3]

The aim of this review was to examine the efficacy of pre-emptive treatment to prevent CMV disease. Ten trials were included in the analysis; 6 examined pre-emptive treatment compared with placebo or treatment of symptomatic disease only; 3 compared pre-emptive treatment with prophylaxis; 1 compared different medication regimens for pre-emptive treatment.

Pre-emptive treatment compared with placebo or standard care

A total of 1393 patients were screened. Of these, 1035 were excluded largely due to the absence of development of viraemia or viraemia levels below the threshold for treatment. In total, 358 patients were included in these 6 studies. Of these, 17.8% (64) developed CMV disease between the testing for viraemia and randomisation and hence were excluded. A further 6 patients (1.7%)

were excluded due to protocol violations. Compared with placebo or standard care, pre-emptive treatment significantly reduced the risk of symptomatic CMV disease (RR 0.29; CI: 0.11 - 0.80) (see Fig 1).

There was no difference, however, in the risks of acute rejection, all-cause mortality, graft loss, leukopenia or renal dysfunction (see Fig 2).

Pre-emptive treatment compared with anti-viral prophylaxis

A total of 151 patients entered 3 trials comparing pre-emptive treatment with prophylaxis. The incidence of CMV disease did not differ significantly between pre-emptive treatment with oral or IV ganciclovir, and prophylaxis with oral acyclovir or ganciclovir (RR 0.42 CI: 0.07 - 2.65) (see Fig 3).

Similarly, there was no difference in any adverse events measured in these studies, with the exception of leukopenia (see Fig 4). Two studies reported on leukopenia as an outcome. There was a significantly lower risk of leukopenia with pre-emptive treatment compared with prophylaxis. This analysis, however, only included 117 patients.

Pre-emptive treatment with oral versus IV ganciclovir

One study in liver transplant recipients by Singh et al, 2000 compared IV with oral ganciclovir in the pre-emptive treatment of CMV viraemia. [4] There were no significant differences in the risk of CMV disease, mortality or other infections between the two treatment regimens.

Other meta-analyses

A second meta-analysis examined both prophylaxis and pre-emptive treatment for CMV. [5] This meta-analysis included 6 trials on pre-emptive treatment. These were essentially the same as those in the Strippoli review and outcomes were very similar. Results showed a reduction in the incidence of CMV disease (OR 0.28; CI: 0.11 - 0.69) with pre-emptive treatment.

A third meta-analysis compared prophylactic and pre-emptive therapies for CMV (Small et al, 2006). [6] This paper examined 9 trials of pre-emptive therapy, most of which were included in the Strippoli review, and found a similar risk reduction with pre-emptive therapy (OR 0.30, CI: 0.15 - 0.60). This paper determined that universal prophylaxis and pre-emptive treatment are equally effective in prevention of CMV disease. This was, however, on the basis of indirect comparisons of papers examining the two strategies separately rather than randomised controlled trials directly comparing pre-emptive treatment with prophylaxis.

Additional randomised controlled trials

Prophylaxis compared with pre-emptive treatment

Kliem et al undertook a RCT comparing prophylaxis with ganciclovir for 3 months (N = 74) with pre-emptive treatment (N = 74) with IV ganciclovir followed by oral ganciclovir when a CMV viral load was confirmed as ≥ 400 CMV DNA copies/mL. [7] There was a significant reduction in CMV infection with prophylaxis in all patient groups with the exception of D-/R- patients. However, there was no difference in creatinine clearance or patient survival at 12 months. This was the primary endpoint of the trial and the endpoint used to determine the sample size.

However, a greater incidence of graft loss was seen in patients who developed CMV infection at 4 years and in patients who were randomised to pre-emptive treatment compared with prophylaxis. But when censored for death, this difference was no longer significant. This study suggests that prophylaxis may result in improved graft survival but needs to be confirmed by larger trials.

There is one additional trial (Khoury et al 2006) comparing the outcomes of kidney transplant recipients randomised to prophylaxis with oral valganciclovir, with patients treated pre-emptively with oral valganciclovir. [1]

Pre-emptive treatment was commenced when CMV DNAemia (defined by >1 test with CMV DNA levels 2000 copies/mL) occurred. Polymerase chain reaction testing for CMV was performed weekly for 16 weeks and then monthly at months 5, 6, 9 and 12. Forty-nine patients were randomised to each group. Twenty-six patients (53%) in the pre-emptive group developed CMV DNAemia and were treated with valganciclovir. The primary outcome was a pharmaco-economic comparison between the groups. Secondary outcomes were: CMV infection, clearance of CMV DNAemia and adverse events including neutropenia. Over 95% of patients in each group had induction therapy with thymoglobulin and hence were at high risk for CMV disease.

There was no difference in the incidence of symptomatic CMV infection between the two groups, with only 5 patients overall developing CMV disease (4/49 prophylactic group, 1/49 pre-emptive group). There was no difference in the incidence of neutropenia with only 3 patients developing significant neutropenia.

There was no difference in the cost of pre-emptive treatment and prophylaxis (\$US7130 ± 3748 and \$US7678 ± 6486, respectively).

A further small trial by Reischig et al (2008) randomised 70 renal transplant patients to either 3 months prophylaxis with valganciclovir or pre-emptive therapy with valganciclovir. [2] In the pre-emptive group, treatment was commenced when CMV DNA levels were greater than 2000 copies/mL. There was no difference in the incidence of CMV disease. The study found an increase in the incidence of biopsy-proven acute rejection in the pre-emptive group (36%) compared with the prophylactic group (15%, P = 0.034). However, there was no difference in the incidence of presumed rejection and the study was not powered to detect a difference in rejection episodes. In this study, the costs were greater in the pre-emptive group.

Pre-emptive treatment: comparison of treatment regimens

A single study (Mattes et al 2004) [8] has compared pre-emptive treatment in solid organ or bone marrow transplant patients randomised to full dose IV ganciclovir versus ½ dose IV ganciclovir and ½ dose foscarnet. There were only 24 patients in each group. Of these, 14 patients in total had undergone renal transplantation.

The primary outcome was the resolution of CMV DNAemia at 14 days from initiation of therapy. There was no difference in the proportion of patients who became CMV DNA negative by PCR testing. There was, however, a significant increase in toxicity in the combination arm with 7/24 patients requiring dose reduction or drug switching compared with none in the IV ganciclovir alone group (P = 0.009).

SUMMARY OF THE EVIDENCE

There are still only a small number of studies examining pre-emptive therapy in CMV. However, since the last CARI guideline, there have been a number of new trials and 3 meta-analyses. It is clear that pre-emptive treatment of CMV results in a lower incidence of CMV disease. Treatment with IV or oral ganciclovir and oral valganciclovir is effective and there is insufficient evidence to suggest that any of these medications is superior in efficacy to the others.

Similarly, current evidence is conflicting regarding the incidence of CMV disease with pre-emptive treatment or prophylaxis, however, there may be cost differences, depending on the individual costs in different institutions. In addition, there is one study that showed improved 4-year graft survival in patients treated with prophylaxis compared with those randomised to pre-emptive

treatment. If this is confirmed, clear recommendations for prophylaxis compared with pre-emptive treatment may be able to be made in the future.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: December 2000.

All recipients with asymptomatic CMV infection early after renal transplantation, documented by routine screening should receive a pre-emptive treatment in order to limit spread of the virus and avoid CMV disease. This can be achieved by early use of the validated curative treatment described above (Evidence level B). [9]

International guidelines:

Kidney Disease: Improving Global Outcomes: Recommendations made regarding prophylaxis for CMV. No recommendation regarding pre-emptive treatment. [10]

International Herpes Management Forum Workshop Guidelines 2007: [11]

1. Both prophylaxis and pre-emptive therapy effectively prevent cytomegalovirus (CMV) end-organ disease and should be considered in patient groups where supported by publications.
2. There is no evidence that prophylaxis is superior to pre-emptive therapy for preventing CMV disease or vice-versa.
3. A clinical trial comparing pre-emptive therapy and prophylaxis is warranted in solid organ transplant patients.
4. The available evidence from non-randomised studies suggests that prophylaxis more clearly controls some of the indirect effects of CMV than does pre-emptive therapy.
5. The available evidence from non-randomised studies suggests that late-onset disease and anti-viral resistance are more problematic with prophylaxis than pre-emptive therapy.
6. Pre-emptive therapy for CMV disease has the potential to stimulate protective immunity but studies are required to document this.
7. Pre-emptive therapy for CMV disease is used widely in clinical practice and appears reliable enough to be used as a primary endpoint in clinical trials.
8. If a randomised comparison of CMV prophylaxis versus pre-emptive therapy is conducted, formal cost effectiveness analyses should be included.

SUGGESTIONS FOR FUTURE RESEARCH

1. The efficacy of pre-emptive treatment should be compared with prophylaxis for CMV in an adequately powered multicentre randomised controlled trial.
2. The efficacy of different treatment regimens should be examined in an adequately powered multicentre randomised controlled trial.

CONFLICT OF INTEREST

Helen Pilmore has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

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APPENDICES

Table 1. Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)
Khoury et al 2006	98	Randomised controlled clinical trial	US	Kidney transplant recipients at risk for CMV	Prophylaxis (valganciclovir)	Preemptive therapy	12
Reischig et al 2008	70	Randomised controlled clinical trial	Czech Republic	Kidney transplant recipients	Prophylaxis (valacyclovir)	Preemptive therapy (valganciclovir)	12

Table 2. Quality of included studies

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)	Quality Score
		(participants)	(investigators)	(outcome assessors)			
Khoury et al 2006	Block design stratified by CMV serostatus	No	No	No	No	0.0	∅
Reischig et al 2008	Random number generator	No	No	No	Yes	1.4	∅

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.

Quality score: How successfully do you think the study minimised bias? Very well (+), Okay (∅), Poorly (-)

Table 3. Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Khoury et al 2006	Death	0/49	0/49	Not estimable	0.00 (95%CI: -0.01, 0.04)
	Failed allograft	0/49	1/49	0.33 (95%CI: 0.01, 7.99)	-0.02 (95%CI:-0.08, 0.03)
	Rejection	1/49	4/49	0.25 (95%CI: 0.03, 2.16)	-0.06 (95%CI: -0.15, 0.03)
	CMV DNAemia	14/49	29/49	0.48 (95%CI:0.29, 0.80)	-0.31 (95%CI: -0.49, -0.12)
	Recurrent CMV	0/49	5/49	0.09 (95%CI:0.01, 1.60)	-0.10 (95%CI:-0.19, -0.01)
	Symptomatic CMV	4/49	1/49	4.00 (95%CI: 0.46, 34.52)	0.06 (95%CI:-0.03, 0.15)
	Neutropenia	2/49	1/49	2.00 (95%CI:0.19, 21.34)	0.02 (95%CI: -0.05, 0.09)
Reischig et al 2008	Death	1/34	0/36	4.29 (95%CI: 0.18, 102.17)	0.03 (95%CI: -0.05, 0.11)
	Graft Loss	3/34	1/36	3.18 (95%CI: 0.35, 29.07)	0.06 (95%CI: -0.05, 0.17)
	CMV disease	3/34	2/36	1.59 (95%CI: 0.28, 8.93)	0.03 (95%CI:-0.09, 0.15)
	CMV DNAemia	3/34	13/36	0.33 (95%CI: 0.10, 1.08)	-0.17 (95%CI:-0.46, -0.09)
	Neutropenia	10/34	5/36	2.12 (95%CI: 0.81, 5.56)	0.16 (95%CI: -0.04, 0.35)

Figure 1. Comparison pre-emptive medication for CMV viraemia versus placebo or standard care, outcome all symptomatic CMV disease

Review: Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients

Comparison: 1 Pre-emptive medication for CMV viraemia versus placebo or standard care

Outcome: 1 All symptomatic CMV disease

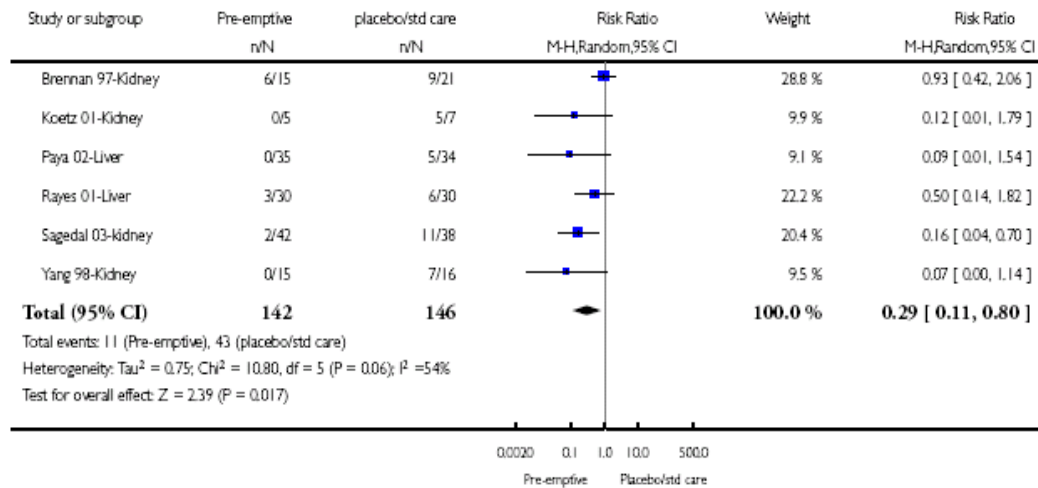


Figure 2. Comparison pre-emptive medication for CMV viraemia versus placebo or standard care, outcome 7 adverse effects

Review: Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients

Comparison: 1 Pre-emptive medication for CMV viraemia versus placebo or standard care

Outcome: 7 Adverse effects

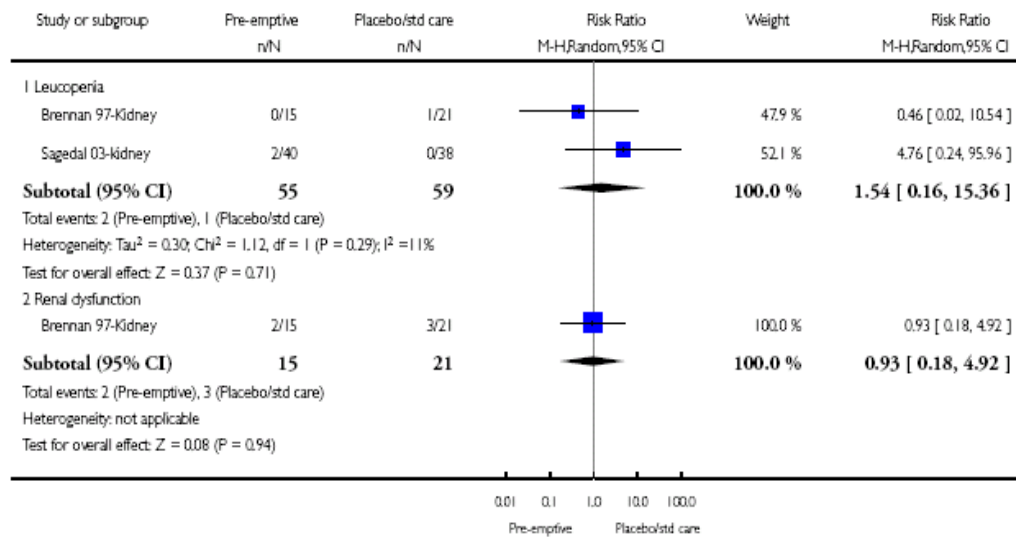


Figure 3. Comparison two pre-emptive medications versus prophylaxis, outcome all symptomatic CMV disease

Review: Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients

Comparison: 2 Pre-emptive medication versus prophylaxis

Outcome: 1 All symptomatic CMV disease

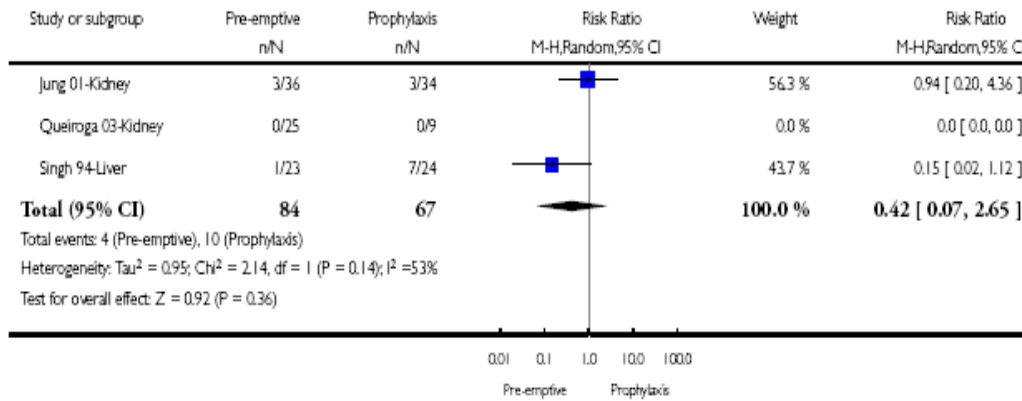


Figure 4. Comparison two pre-emptive medications versus prophylaxis, outcome 4 adverse effects

Review: Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients

Comparison: 2 Pre-emptive medication versus prophylaxis

Outcome: 4 Adverse effects

