

3. Pre-emptive treatment of Cytomegalovirus

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Guidelines

(Include recommendations based on level I or II evidence)

Pre-emptive treatment with ganciclovir of asymptomatic CMV infection based on appropriate diagnostic laboratory tests reduces CMV disease compared with placebo. (Level II evidence based on liver transplant)

Suggestions for clinical care

(Suggestions are based on Level III and IV evidence)

- Pre-emptive therapy for CMV requires a rapid, sensitive and specific assay to detect CMV reactivation sufficiently in advance of disease symptoms.
- Pre-emptive therapy has only been examined using screening tests performed at weekly or fortnightly intervals.
- pp65 antigenaemia-negativity is usually associated with no development of CMV disease.

Background

Cytomegalovirus (CMV) 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.

CMV 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 serostatus 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.

There have now been a number of papers 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?
- are currently available tests for the diagnosis of CMV infection reliable enough to guide who should have pre-emptive therapy?, and
- what are the adverse affects associated with pre-emptive therapy?

Search strategy

Databases searched: MeSH terms and text words for CMV were combined with MeSH terms and text words for solid organ transplantation, including kidney transplantation, then combined with MeSH terms and text words for interventions for CMV, and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – June Week 1 2002). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search/es: 28 June 2002.

What is the evidence?

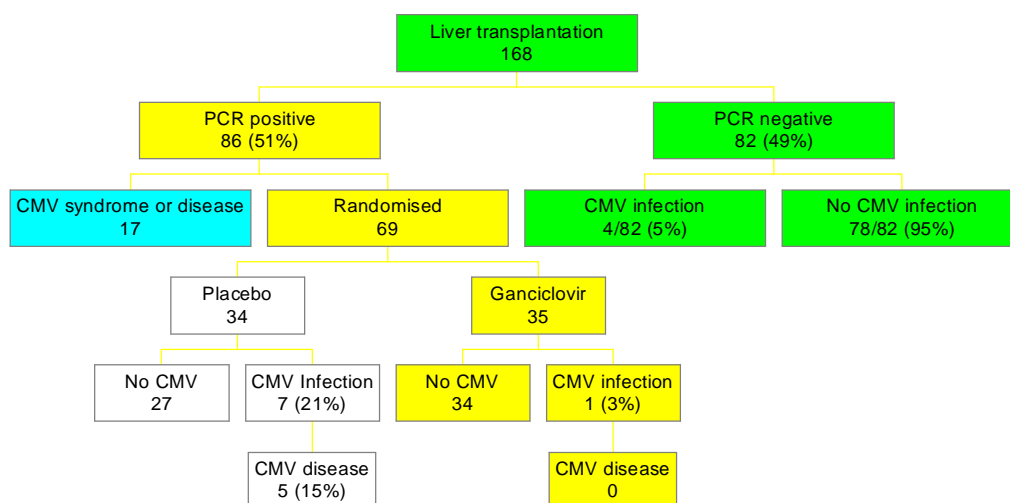
Only five randomised controlled trials (RCTs) have been undertaken examining the efficacy of pre-emptive therapy. One of these was excluded due to very small numbers and inadequate powering. In addition, there are a number of cohort studies and case series, most of which were excluded due to very small numbers. Most studies are in liver transplant recipients and it is noteworthy that the incidence of CMV disease is higher in liver than renal transplant recipients and liver transplant patients have a tendency to get more severe disease.

The trials showed that pre-emptive treatment with ganciclovir in the setting of positive diagnostic tests in asymptomatic patients reduced the incidence of CMV disease compared with placebo. Fewer patients are treated with ganciclovir using pre-emptive therapy than if universal prophylaxis is used. Diagnostic tests used were pp65 antigenaemia testing or PCR testing for CMV. Patients who had persistently negative pp65 antigenaemia testing had a very low risk of developing CMV disease. Unfortunately, a minority of patients developed evidence of CMV disease at the same time as the diagnostic test became positive, necessitating treatment for CMV disease rather than pre-emptive treatment. The optimal time intervals for screening are not clear with most studies performing diagnostic testing at weekly or fortnightly intervals.

Paya et al (2002)

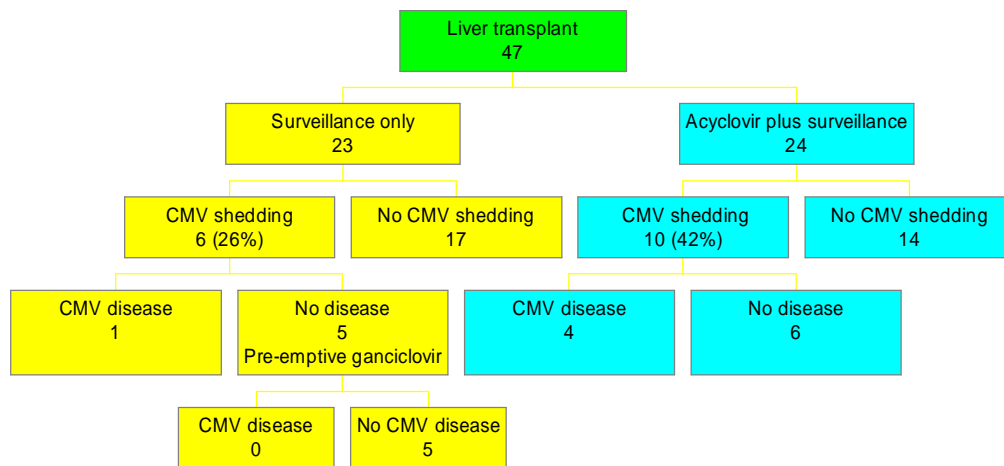
- RCT (Level II evidence)
- 168 consecutive liver transplant recipients
- Surveillance PCR of peripheral blood leukocytes weekly for weeks 0-8
- Patients followed for 16 weeks
- Randomised to placebo vs oral ganciclovir if PCR positive

- Amplified PCR products detected using Roche PCR ELISA kit
- 86/168 patients PCR positive
- 17/86 thought to have CMV syndrome or disease at time of positive PCR were excluded
- 69 patients randomised to placebo vs oral ganciclovir
- No difference between the proportion of D+/R– patients in the placebo and treatment groups; $p = 0.54$
- In the placebo group ($n = 34$), 7 patients (21%) developed CMV infection (definition: positive shell vial culture or histology) compared with 1/35 (3%) of the ganciclovir group; $p = 0.02$
- 5/34 patients (15%) in the placebo group developed CMV disease (definition: positive shell vial culture plus histology/immunostaining plus symptoms) compared with 0/35 in the ganciclovir group; $p = 0.003$
- Of the 8 patients who developed evidence of CMV infection, 7 were D+/R–
- The negative predictive value of the test was 90%.



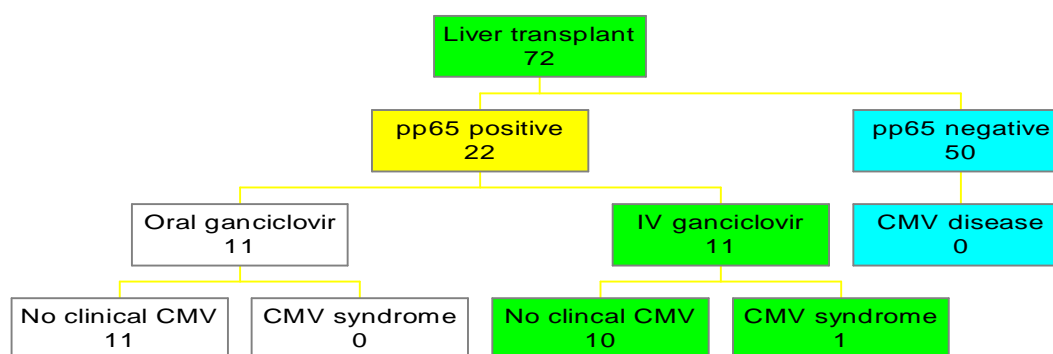
Singh et al (1994)

- RCT
- 47 consecutive liver transplant recipients
- Surveillance cultures for CMV (buffy coat and urine) each performed 2-4 weeks for 24 weeks
- Randomised to acyclovir vs no treatment
- No treatment group received oral ganciclovir if cultures were positive and no clinical evidence of disease
- 23/47 patients had surveillance only, 6/23 (26%) had evidence of CMV shedding – 1/6 developed CMV disease while 5 had no evidence of CMV disease and were treated with ganciclovir. Of these 5, no patients developed CMV disease. In the acyclovir group (n = 24), 42% had evidence of CMV shedding. Of these (n = 10), 4/10 (40%) developed CMV disease
- This is a poor study for pre-emptive treatment as only 5 patients had pre-emptive treatment. In addition, the pre-emptive treatment was not randomised.



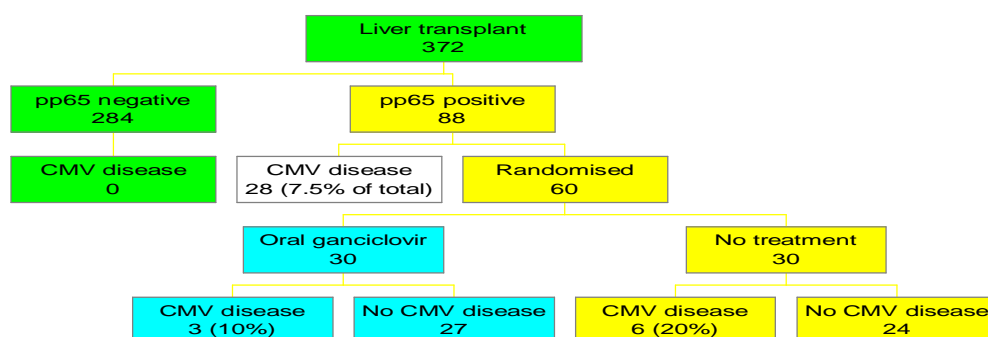
Singh et al (2000)

- RCT
- Aim to compare oral with IV ganciclovir as pre-emptive treatment for CMV
- 72 consecutive liver transplant patients
- Surveillance for CMV pp65 antigenaemia performed at weeks 2,4,6,8,12 and 16
- 22/72 (31%) patients developed positive pp65 antigenaemia (1 or more wbc with characteristic fluorescence/ 2×10^5 pbl) on surveillance. These patients were randomised to oral ganciclovir for 6 weeks or IV ganciclovir for 1 week
- Only 5/22 were D+/R-
- Block randomisation in groups of 4 using stratification for CMV status of recipient and donor
- Outcomes were CMV syndrome and disease
- CMV syndrome = mononucleosis-like syndrome with fever and antigenaemia and presence of either leukopenia, thrombocytopenia or atypical lymphocytes
- No patient who was persistently pp65 antigenaemia-negative developed CMV syndrome or disease
- Patients treated with oral or IV ganciclovir did not develop clinical CMV disease. 1/11 (9%) patients treated with IV ganciclovir developed a subsequent CMV syndrome (ns).



Rayes et al (2001)

- RCT
- 372 consecutive liver transplant patients
- Surveillance performed by weekly pp65 antigenaemia from weeks 1-16
- If positive antigenaemia, randomised to either oral ganciclovir for 14 days or no treatment
- Endpoints were development of CMV syndrome or disease
- 284/372 patients were persistently pp65 antigenaemia-negative and none of these developed CMV syndrome or disease (donor / recipient serostatus not defined in this group)
- 88 patients were pp65 antigenaemia-positive and of these, 60 were randomised to oral ganciclovir versus no treatment
- D+/R– patient numbers equal in each group (20%)
- 3/30 (10%) patients on oral ganciclovir developed CMV disease and 6/30 (20%) developed CMV disease in no treatment group (ns).



Summary of the evidence

There are a small number of studies examining pre-emptive therapy in CMV. Only studies examining this in solid organ transplant patients have been analysed. Many of the studies are small and most are in liver transplant recipients.

Pre-emptive therapy has only been examined using ganciclovir. No recommendation can be made for pre-emptive therapy with other anti-viral agents at this time.

For pre-emptive therapy to be successful, appropriate diagnostic blood tests must be used. Diagnostic blood tests that have shown the efficacy of pre-emptive therapy include CMV PCR testing and pp65 antigenaemia testing. Patients who are persistently PCR negative or pp65 antigenaemia-negative have a very low risk of developing clinical CMV disease.

Unfortunately, most studies show that the diagnostic test positivity does not always precede clinical evidence of infection or disease for the time intervals over which surveillance is undertaken.

Patients who are donor-positive, recipient-negative, have a higher risk of developing CMV disease. Pre-emptive therapy has been studied in this group of patients. It has been shown that most of these patients do develop evidence of CMV infection on laboratory testing and there is a high chance of patients being pre-emptively treated for CMV.

Pre-emptive therapy will result in fewer patients requiring anti-viral agents in the recipient-positive group than would happen if universal prophylaxis were used. One advantage of pre-emptive therapy is the avoidance of unnecessary exposure to a drug in patients who are not at increased risk of developing CMV disease or CMV-associated death as determined by diagnostic laboratory testing.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

British Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

INTERNATIONAL GUIDELINES: International Herpes Management Forum (IHMF): Intravenous GCV pre-emptive therapy guided by the shell vial assay is more effective than prophylaxis with high-dose oral acyclovir in liver transplant recipients for the prevention of CMV infection or disease.

Implementation and audit

Renal units undertaking pre-emptive treatment should screen patients at appropriate intervals and with either pp65 antigenaemia testing or PCR. PCR testing varies and the level at which pre-emptive treatment should be undertaken has not been determined. All patients undergoing a pre-emptive treatment program should be audited to determine the efficacy of the screening test in an individual unit.

Suggestions for future research

1. The efficacy of pre-emptive treatment should be compared with prophylaxis for CMV in an adequately powered multicentre RCT in renal transplant recipients. An economic analysis of such a study would be an important adjunct.
2. The efficacy of diagnostic tests other than pp65 antigenaemia need to be examined in RCTs.

References

Paya CV, Wilson JA, Espy MJ et al. Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002; 185: 854-60.

Rayes N, Seehofer D, Schmidt CA et al. Prospective randomized trial to assess the value of preemptive oral therapy for CMV infection following liver transplantation. *Transplantation* 2001; 72(5): 881-85.

Singh N, Paterson DL, Gayowski T et al. Cytomegalovirus antigenemia directed preemptive prophylaxis with oral versus I.V. ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, controlled trial. *Transplantation* 2000; 70(5): 717-22.

Singh N, Yu VL, Mieles L et al. High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. A randomized trial. *Ann Intern Med* 1994; 120: 375-81.

Appendices

Table 1 Characteristics of randomised controlled trial evidence

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Paya et al 2002	69	Randomised controlled clinical trial	Teaching hospital	Liver transplant recipients	Ganciclovir p.o. 3000 mg/day x 56 days	Placebo	4	
Raves et al 2001	60	Randomised controlled clinical trial	Teaching hospital	Liver transplant recipients	Ganciclovir p.o. 3000 mg/day x 14 days	No treatment	4	
Singh et al 2000	22	Randomised controlled clinical trial	University	Liver transplant recipients	Ganciclovir p.o. 6000 mg/day x 14 days, then 3000 mg/day x 28 days	Ganciclovir i.v. 10 mg/kg/day x 7 days	3	
Singh et al 1994	47	Randomised controlled clinical trial	University	Liver transplant recipients	Ganciclovir i.v. 10 mg/kg/day x 7 days	Acyclovir p.o. 3200 mg/day x 168 days	6	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Paya et al 2002	Adequate	Yes	Yes	NA*	Yes	NA
Rayes et al 2001	Unclear	No	No	NA	Yes	0
Singh et al 2000	Unclear	No	No	NA	NA	0
Singh et al 1994	Unclear	No	No	NA	NA	0

* NA = not available

Table 3 Results of 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]
Paya et al 2002	All symptomatic CMV disease	0/35	5/34	0.09 (0.01 to 1.54)	-0.15 (-0.27 to -0.02)
	Acute rejection	0/35	1/34	0.32 (0.01 to 7.69)	-0.03 (-0.11 to 0.05)
Rayes et al 2001	All symptomatic CMV disease	3/30	6/30	0.50 (0.14 to 1.82)	-0.10 (-0.28 to 0.08)
	All-cause mortality	4/30	3/30	1.33 (0.33 to 5.45)	0.03 (-0.13 to 0.20)
Singh et al 2000	All symptomatic CMV disease	0/11	1/11	0.33 (0.02 to 7.39)	-0.09 (-0.31 to 0.13)
Singh et al 1994	All symptomatic CMV disease	1/23	7/24	0.15 (0.02 to 1.12)	-0.25 (-0.45 to -0.04)
	All-cause mortality	3/23	3/24	1.04 (0.23 to 4.65)	0.01 (-0.19 to 0.20)