

2. Prophylaxis for Cytomegalovirus infection in patients following renal transplantation

Date written: February 2003

Final submission: June 2004

Guidelines

(Include recommendations based on level I or II evidence)

- a. **Prophylactic treatment for CMV is recommended in solid organ transplantation as it is associated with a significant decrease in CMV disease compared with placebo or no treatment (approximately a 50% decrease in relative risk). (Level I evidence)**
- b. **Prophylactic treatment for CMV is recommended in solid organ transplantation as it is associated with a significant decrease in CMV infection compared with placebo or no treatment (approximately a 40% decrease in relative risk). (Level I evidence)**
- c. **The use of the antiviral agents, oral valaciclovir, intravenous or oral ganciclovir and oral valganciclovir, give comparable results for prophylaxis in solid organ transplantation. (Level II evidence)**
- d. **In donor/recipient subgroups, prophylactic treatment for CMV disease is indicated when the donor is positive and the recipient is positive or negative on the pre-transplant CMV antibody assay. (Level II evidence)**

Suggestions for clinical care

(Suggestions are based on Level III and IV evidence)

- Duration of therapy: Most trials had a duration of prophylaxis of 90 days. There were no controlled trials that looked at duration.
- Antiviral agents or CMV immune globulin: Antiviral agents are superior to CMV immune globulin in preventing CMV disease.
- Dosing: In the reported studies, total daily doses of antiviral agents used were as follows and were reduced for impaired renal function:
 - oral acyclovir 3200 mg
 - oral valaciclovir 8000 mg
 - oral valganciclovir 900 mg, and
 - intravenous ganciclovir 5-10 mg/kg for an average of 14 days.

Note: Oral ganciclovir is no longer available in Australia

Background

Cytomegalovirus (CMV) belongs to the group of herpesviruses and is a common infection in the community, with about 80% of adults showing seropositivity to the virus (Rubin 1993). CMV is the most frequent viral infection following renal transplantation with evidence of infection found in at least two thirds of patients. The major determinants of infection are the presence of latency (seropositivity) in the recipient and the type of immunosuppressive regimen administered. It is usual to make a distinction between infection and disease where disease is characterised by evidence of organ damage and infection is detection of virus with or without disease.

CMV disease is associated with increased morbidity and mortality, whereas infection alone may be associated with an increased risk of transplant rejection and bacterial and fungal infection (Dickenmann et al 2001, Tong et al 2002, McLaughlin et al 2002). These consequences have led to interventions for prophylaxis, early diagnosis and treatment.

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?

Cochrane review: August 2002 saw the publication of a Cochrane review of CMV prophylaxis with anti-viral agents for solid organ transplantation (Couchoud 2002). This meta-analysis included 13 randomised trials with 1138 patients split between a treatment group of 585 and a control group of 553. These trials consisted of all solid organ transplants.

The objectives of the review were to:

- assess the efficacy of anti-viral agents in the prevention of CMV infection
- assess the efficacy of anti-viral agents in the prevention of symptomatic CMV disease, and
- assess the efficacy of anti-viral agents in decreasing the incidence of acute rejection graft loss and death.

This Cochrane analysis did not separate different prophylactic treatments (oral or intravenous ganciclovir and acyclovir) and excluded trials using other interventions

such as immunoglobulins, interferons and vaccination. The Cochrane review searched the usual databases between January 1982 and September 1996.

The results show that prophylactic treatment is associated with a significant reduction in CMV disease and infection (RR 0.51, CI: 0.41-0.64; $p < 0.001$ for disease and RR 0.62, CI: 0.53-0.73; $p < 0.001$ for infection). Although there was no reduction in acute rejection rates (RR 0.92, CI: 0.79-1.07), graft loss or death, a 20% reduction in both graft loss and death was observed but these did not reach statistical significance with the confidence intervals crossing 1. Subgroup analysis of pretransplant antibody status (donor: D + or – and recipient: R + or –) showed significant reduction in disease in D + and R + or – groups. In D – R + groups, a reduction in disease was observed but this did not reach significance. There was no significant reduction in infection in any subgroup. However, numbers were small, with less than 100 in each group. Although subgroup analysis between ganciclovir and acyclovir did not show any difference in disease, there was a significant difference in infection with ganciclovir (RR 0.52; CI: 0.42-0.64 for ganciclovir and RR 0.80; CI: 0.60-1.05 for acyclovir).

Other reports: Randomised controlled trials (RCTs) performed since the Cochrane review include additional trials that have compared various agents. Oral acyclovir versus oral ganciclovir trials (Flechner et al 1998, Rubin et al 2000) show ganciclovir to be a superior agent for the prevention of disease. Valaciclovir versus placebo (Lowance et al 1999) shows similar results to the Cochrane review. Another RCT comparing oral ganciclovir and valaciclovir with controls on no therapy showed no significant differences with both treatment arms being superior to controls for CMV disease, infection and treatment failure (death, graft loss, disease or withdrawal) (Reischig et al 2002).

In 2004, Paya et al reported a double blind, double dummy, clinical study comparing oral ganciclovir and oral valganciclovir in 301 high risk (D+/R-) recipients of solid organ transplants. The results showed that the agents were equivalent in terms of CMV disease, viraemia, acute rejection, graft loss and acute rejection after CMV disease. Valganciclovir had a slight increase in neutropaenia (8.2% vs 3.2%). The time to onset of CMV disease was delayed in the valganciclovir group at six months but they were equal at 12 months. The pharmacokinetic study showed that valganciclovir patients achieved a higher area under the curve (AUC) by 1.7%.

The use of CMV immune globulin was excluded from the Cochrane review. However, an RCT of immune globulin versus no treatment reported by Snyderman et al (1987) in D +/R – renal transplant recipients shows reduction in CMV disease from 60% to 21% ($p < 0.01$) but no reduction in CMV infection as measured by virus isolation or seroconversion. Most evidence for CMV immune globulin comes from recipients of bone marrow transplantation.

There are no RCTs that compare duration of therapy. One RCT comparing acyclovir and ganciclovir in liver transplant recipients, with 3 months prophylaxis, shows that protection against CMV disease lasts up to 1 year (Winston & Busuttill 2003). These authors mention that their regimen was not associated with ganciclovir resistance.

Non-randomised studies:

- In a separate report of the study by Paya et al (2004), Boivin et al (2004) prospectively screened for ganciclovir resistance by UL97 and UL54 gene sequencing on CMV DNA positive sera (these sequences would detect most reported resistance mutations). CMV resistance did not emerge with valganciclovir and of three patients in the ganciclovir group with gene sequence positivity, there were no clinical consequences and all three cleared the virus.
- A retrospective study in a single centre by Akalin et al (2003) of 129 kidney and kidney/pancreas recipients also showed equivalence between oral valganciclovir and ganciclovir.

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 for Renal Transplantation:

CMV prophylaxis is recommended for the seronegative recipients of a seropositive donor kidney and for seropositive recipients receiving antibody treatment as induction or therapy for acute rejection. Prophylaxis must be selected from the following five validated modalities:

- Weekly intravenous infusions of hyperimmune globulin for 6 weeks (at high dose) or 16 weeks (low dose)
- Oral acyclovir for 12 weeks at a daily dose of 3200 mg adjusted for renal function
- Oral valaciclovir for 90 days at a daily dose of 8000 mg adjusted for renal function
- Ganciclovir administered intravenously for 14 days at a dose of 10 mg/kg/day adjusted for renal function, or
- Oral ganciclovir for 12 weeks at a daily dose of 300 mg adjusted for renal function (Berthoux et al 2000).

Clinical Practice Guidelines of the American Society of Transplantation:

Recommendations for prophylaxis are based on donor/recipient antibody status pre-transplantation. Prophylaxis with antiviral agents is recommended for:

- Donor + or – and recipient + scenario with the use of anti-lymphocyte products
- D +/R – scenario, and
- is discretionary for D –/R + scenario with the use of conventional immunosuppression.

There was no definite recommendation as to choice of antiviral agent as no comparative studies between agents had been performed in renal transplants at the time. However, ganciclovir was cited because of trials in liver transplant recipients (Kasiske et al 2000, Jassal et al 1998).

Implementation and audit

No recommendation.

Suggestions for future research

1. Perform more studies on the donor/recipient CMV antibody mismatch in renal transplant recipients.
2. Conduct larger studies to confirm the trend toward reduction of graft loss and death with CMV prophylaxis in renal transplant recipients.
3. Perform studies on the development of ganciclovir resistance following prophylaxis.
4. Determine the optimal duration of therapy of anti-viral agents.

References

Akalin E, Sehgal V, Ames S et al. Cytomegalovirus disease in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis. *Am J Transplant* 2003; 3: 731-35.

Berthoux F, Abramowicz D, Bradley B et al. European best practice guidelines for renal transplantation (Part 1). *Nephrol Dial Transplant* 2000; 15(Suppl 7): S71-S74.

Boivin G, Goyette N, Gilbert C et al. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. *J Infect Dis* 2004; 189: 1615-18.

Couchoud C. Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation (Cochrane Review). In: *The Cochrane Library, Issue 2, 2002*. Oxford: Update Software.

Dickenmann MJ, Cathomas G, Steiger J et al. Cytomegalovirus infection and graft rejection in renal transplantation. *Transplantation* 2001; 71(6): 764-67.

Flechner SM, Avery RK, Fisher R et al. A randomised, prospective, controlled trial of oral acyclovir versus oral ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998; 66: 1682-88.

Jassal SV, Roscoe JM, Zaltzman JS et al. Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation. *J Am Soc Nephrol* 1998; 9(9): 1697-708.

Kasiske BL, Vazquez MA, Harmon WE et al. Clinical practice guidelines of the American Society of Transplantation: Recommendations for the outpatient surveillance of renal transplant recipients. *J Am Soc Nephrol* 2000; 11(Suppl 1): S1-S86.

Lowance D, Neumayer HH, Legendre CM et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med* 1999; 340: 1462-70.

McLaughlin K, Wu C, Fick G et al. Cytomegalovirus seromismatching increases the risk of acute renal allograft rejection. *Transplantation* 2002; 74(6): 813-16.

Paya C, Humar A, Dominguez E et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; 4: 611-20.

Reischig T, Opatrny K Jr, Bouda M et al. A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation. *Transpl Int* 2002; 15: 615-22.

Rubin RH, Kemmerly SA, Conti D et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transpl Infect Dis* 2000; 2: 112-17.

Rubin RH. Infectious disease complications of renal transplantation. *Kidney Int* 1993; 44(1): 221-36.

Snydman DR, Werner BG, Heinze-Lacey B et al. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal transplant recipients. *N Engl J Med* 1987; 317: 1049-54.

Tong CY, Bakran A, Peiris JS et al. The association of viral infection and chronic allograft nephropathy with graft dysfunction after renal transplantation. *Transplantation* 2002; 74(4): 576-78.

Winston DJ and Busuttil RW. Randomized controlled trial of oral ganciclovir versus oral acyclovir after induction with intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in cytomegalovirus-seropositive liver transplant recipients. *Transplantation* 2003; 75(2): 229-33.

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
Flechner et al 1998	101	Randomised controlled clinical trial	Teaching hospital	Kidney transplant recipients	Oral ganciclovir 1000 mg tds x 84 days	Oral acyclovir 800 mg qds x 84 days	14.4	
Lowance et al 1999	408	Randomised controlled clinical trial	University	Kidney transplant recipients	Oral valaciclovir 2 g qds x 90 days	Placebo	12	
Paya et al 2004	364	Randomised controlled clinical trial	University	Kidney, heart and liver transplant recipients	Oral valganciclovir 900 mg qd x 100 days	Oral ganciclovir 1000 mg tds x 100 days	12	
Reischig et al 2002	38	Randomised controlled clinical trial	Multicentre	Kidney transplant recipients	Oral valaciclovir 2 g qid x 12 weeks	Oral ganciclovir 1 g tds x 12 weeks	6	
Rubin et al 2000	155	Randomised controlled clinical trial	Multicentre	Kidney, heart and liver transplant recipients	Oral ganciclovir 1000 mg tds x 12 weeks	Oral acyclovir 400 mg tds x 12 weeks	12	
Snydman et al 1987	99	Randomised controlled clinical trial	University	Kidney transplant recipients	Intravenous CMV immunoglobulin prophylaxis 150 mg/kg of bodyweight within 72 hours of transplant, then 100 mg/kg ² at 2 and 4 weeks after transplant, then 50 mg/kg at 6, 8, 12 and 16 weeks after transplant	Placebo	12	
Winston & Busuttill 2003	64	Randomised controlled clinical trial	University	Liver transplant recipients	Oral ganciclovir 1000 mg tds x 86 days	Intravenous ganciclovir 6 mg/kg/day of bodyweight x 86 days	12	

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)		
Flechner et al 1998	Adequate	No	No	NA*	Yes	0
Lowance et al 1999	Unclear	Yes	Yes	NA	Yes	0
Paya et al 2004	Adequate	Yes	Yes	Yes	No	0
Reischig et al 2002	Adequate	No	No	NA	No	0
Rubin et al 2000	Adequate	No	No	NA	No	0
Snydman et al 1987	Unclear	Yes	Yes	NA	No	NA
Winston & Busuttil 2003	Unclear	No	No	NA	Yes	0

* NA = not available

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]
Flechner et al 1998	CMV disease	1/40	9/39	0.11 (0.01 to 0.82)	-0.21 (-0.35 to -0.06)
Lowance et al 1999	CMV disease	18/306	60/310	0.30 (0.18 to 0.50)	-0.13 (-0.19 to -0.08)
Paya et al 2004	CMV disease	41/239	23/125	0.93 (0.59 to 1.48)	-0.01 (-0.10 to 0.07)
Reischig et al 2002	CMV disease	1/12	2/13	0.54 (0.06 to 5.24)	-0.07 (-0.32 to 0.18)
Rubin et al 2000	CMV disease	15/77	21/78	0.72 (0.40 to 1.30)	-0.07 (-0.21 to 0.06)
Snydman et al 1987	Virologically- confirmed CMV syndrome	5/24	21/35	0.35 (0.15 to 0.79)	-0.39 (-0.62 to -0.16)
Winston & Busuttil 2003	CMV disease	3/32	4/32	0.75 (0.18 to 3.09)	-0.03 (-0.18 to 0.12)