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Original Article

Low-dose valaciclovir and cytomegalovirus immunoglobulin to prevent cytomegalovirus disease in high-risk renal transplant recipients

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SUMMARY AT A GLANCE

This retrospective review assessed the efficacy of a combination of low-dose valaciclovir and intravenous CMV immunoglobulin to prevent CMV disease in CMV-negative recipients of kidneys from CMV-positive donors (D+/R–) showing that low-dose valaciclovir with CMVIg was as efficacious in preventing CMV disease as other published regimens, including those with full-dose valaciclovir and valganciclovir.

ABSTRACT:

Background: **Cytomegalovirus (CMV) remains an important cause of disease in renal transplant recipients. Prophylaxis is effective in reducing disease; however, the optimal regimen remains uncertain. We assessed the efficacy of low-dose valaciclovir (3 months) and intravenous CMV immunoglobulin in the prevention of CMV disease in CMV-negative recipients of kidneys from CMV-positive donors (D+/R–).**

Methods: **A single-centre, retrospective study examining the incidence of CMV disease and patient and graft survival in all patients transplanted between October 2000 and November 2004.**

Results: **Among 203 renal transplant recipients, 46 were D+/R– (22.7%) and received prophylaxis. Of the 203 recipients, 21 (10.3%) developed CMV disease over a four-year follow-up period. Within the D+/R– group, CMV disease occurred in 15.2% of patients at 6 months (7/46), and 21.7% at 4 years (10/46). Of the 10 D+/R– patients who developed CMV disease, six were inadvertently on a dose of valaciclovir below that dictated by protocol arising from a failure to increase dosage in parallel with improving recipient renal function. In the D+/R– recipients where the protocol was adhered to, the incidence of CMV disease was 5% (2/40) at 6 months, and 10% (4/40) at 4 years.**

Conclusion: **Low-dose valaciclovir with CMV immunoglobulin was as efficacious in preventing CMV disease as other published regimens, including those with full-dose valaciclovir and valganciclovir. There was a low incidence of CMV disease beyond 6 months. Outcomes could be improved by ensuring appropriate dose adjustment following changes in renal function.**

INTRODUCTION

Cytomegalovirus (CMV) disease remains a feared complication of solid organ transplantation (SOT) with potential for significant morbidity and mortality. The reported incidence of CMV disease varies widely because of differences in methods of viral detection, immunosuppressive regimens and CMV prophylaxis. CMV seronegative recipients of organs from CMV seropositive donors (D+/R–) are the most susceptible to infection. In the absence of prophylaxis, CMV disease occurs in up to two-thirds of D+/R– SOT recipients varying from a mild febrile illness to potentially fatal organ involvement (predominantly gastrointestinal tract and lungs), usually presenting within the first 6 months post transplantation.[1] Prophylaxis with antiviral medications reduces CMV disease and CMV-associated mortality in SOT recipients.[2–4] Studies using oral valaciclovir,[5] ganciclovir[6,7] and valganciclovir[7–9] report a reduction in CMV disease for the duration of prophylaxis, but an overall incidence of 20 to 30% within the first year of transplantation (especially after cessation of prophylaxis).[4–7]

In previous studies, prophylaxis with oral ganciclovir was superior to oral aciclovir in the prevention of CMV disease,

while outcomes with valaciclovir are comparable to those with oral ganciclovir and valganciclovir.[5,6,10–13] One randomized placebo-controlled trial of valaciclovir also reported a reduction in acute rejection in D+/R− renal transplant patients receiving prophylactic valaciclovir (8000 mg/day).[5] Small uncontrolled series of renal transplant recipients suggest that low-dose valaciclovir (3000 mg/day) may be as effective as higher doses but with fewer adverse events.[14,15] All antiviral agents for CMV prevention are costly and associated with toxicity, and the optimal prophylactic regimen (agent, dose and duration) is not yet determined.

Cytomegalovirus immunoglobulin (CMVIg), prepared from sera of individuals with high titre anti-CMV antibodies, has been licensed for the prophylactic therapy of CMV disease in SOT recipients since 1987.[16,17] In a randomized placebo-controlled trial involving 59 renal transplant recipients, prophylaxis with CMVIg reduced the incidence of CMV disease from 60% to 21% in D+/R− recipients.[16] In another randomized controlled trial of 146 CMV D+/R− liver transplant recipients, severe CMV disease was reduced from 26% to 12% with administration of CMVIg compared with placebo, although there was no statistically significant reduction in the incidence of CMV disease overall.[18] Improved graft survival and a reduction in the incidence of asymptomatic viraemia have also been reported among recipients of CMVIg.[19] In the paediatric renal transplant population, prophylaxis with CMVIg has been reported to significantly reduce the rate of hospitalizations attributed to CMV infection.[20] CMVIg also has other potential benefits, being widely used in the prevention and treatment of antibody-mediated rejection associated with blood group incompatibility or anti-HLA antibodies in sensitized patients;[21–23] however, it still remains unclear whether the addition of CMVIg to antiviral drugs for the prevention of CMV will improve clinical outcomes in SOT.

The desire to minimize pill burden, the incidence of delayed CMV disease and concerns with toxicity of antiviral agents led us to consider a regimen of low-dose valaciclovir (3000 mg/day or reduced according to glomerular filtration rate (GFR)) combined with intravenous (IV) infusions of CMVIg for D+/R− patients. We report the first study assessing outcomes of renal transplant recipients at high-risk of CMV disease receiving this regimen.

METHODS

The records of all renal transplant recipients at The Royal Melbourne Hospital (Victoria, Australia) transplanted between October 2000 and November 2004 were reviewed. During this period, CMV prophylaxis was restricted to D+/R− patients and comprised oral valaciclovir 1500 mg twice daily (*bid*) for 3 months and CMVIg (CSL Limited Australia), 1.8 g IV weekly, for 8 weeks. Prophylaxis was commenced within the first 24 h of immunosuppression. The dose of valaciclovir was adjusted for GFR, based on the Cockroft–Gault formula (Table 1). Patients with other CMV serostatus (D+/R+, D−/R+, D−/R−) did not routinely receive prophylaxis. However, if lymphocyte-depleting antibody was used for the treatment of rejection, patients were commenced on oral valaciclovir monotherapy for 3 months.

Table 1 Valaciclovir dosing based on glomerular filtration rate (GFR)†

GFR	<30 mL/min	30–60 mL/min	>60 mL/min
Valaciclovir dose	500 mg *bid*	1000 mg *bid*	1500 mg *bid*

†GFR calculated by Cockroft–Gault formula.

Cytomegalovirus disease was defined as presentation with a febrile illness accompanied by detection of CMV DNA in the serum by polymerase chain reaction and/or evidence of infection on biopsy of the affected organ. Patients with CMV disease were treated with at least 2 weeks IV ganciclovir.

Medical records of 209 consecutive renal transplant recipients were reviewed. Six patients were excluded as they were enrolled in a trial investigating alternative CMV prophylaxis. A total of 199 patients received a combination of prednisolone, mycophenolate mofetil (MMF) and either tacrolimus (Tac) or cyclosporine (CsA). The remaining four patients were enrolled in a trial using sirolimus instead of a calcineurin inhibitor. Tac levels were targeted between 10 and 15 ng/mL for the first 2–4 weeks, 6 and 10 ng/mL to the end of 3 months, 5 and 8 ng/mL to 1 year, and 3 and 5 ng/mL beyond this. CsA levels were targeted between 1200 and 1600 μg/L for the first 2–4 weeks, 800 and 1200 μg/L to the end of 3 months, 600 and 1000 μg/L to 1 year, and 400 and 800 μg/L beyond this. MMF dosing was 1000 mg twice daily for patients receiving CyA and 500 mg twice daily for patients receiving Tac. Trimethoprim/sulfamethoxazole (80 mg/400 mg thrice weekly) was routinely administered for 6 months as prophylaxis for *Pneumocystis jeroveci* infection.

RESULTS

Data for all 203 transplant recipients from October 2000 to November 2004 are presented in Table 2. Forty-six were D+/R− recipients. There was no difference in the demographic characteristics of this group in comparison to the remaining patients, of whom 135 were D+/R+ or D−/R+, and 22 were D−/R−. Oral valaciclovir and CMVIg were administered to the 46 D+/R− recipients as per protocol.

The incidence of CMV disease among the 203 patients was 6.4% at 6 months, 10.1% at 12 months and 10.3% at 4 years. The median time to presentation of CMV disease was 125 days. In the D+/R− group, the incidence of CMV disease was 15.2% at 6 months (7/46), and 21.7% at 4 years (10/46). Of the seven D+/R− patients who developed CMV disease, six patients did not receive prophylaxis according to the protocol, with valaciclovir administered below the recommended dose (Table 3). Two patients began with valaciclovir 500 mg *bid* adjusted for a GFR of 13 and 16 mL/min, respectively, at 1 week post transplant, with no adjustment made as GFR improved to 53 and 58 mL/min, respectively, at 1 month post transplant. Two other patients received inappropriately reduced doses of valaciclovir (500 mg *bid*) for their respective GFR (between 60 and 79 mL/min) at 1 week following transplantation. These four patients developed

Table 2 Demographic characteristics of patients

Patient demographics	All patients ($n = 203$)		Patients with CMV disease ($n = 21$)	
	n	%	*n*	%
Age, mean in years (range)	43.7	17–70	41.4	19–62
Gender				
Female	65	32	7	33
Male	138	68	14	67
Indication for transplantation				
Chronic glomerulonephritis	76	37	9	43
Reflux nephropathy	35	17	7	33
Diabetic nephrosclerosis	18	9	2	10
Polycystic kidney disease	18	9		
Interstitial nephritis	7	3		
Vasculitis/SLE	10	5		
Obstructive nephropathy			1	5
Other†	39	19	2	10
Previous renal transplant	25	12	5	24
Donor source				
Deceased donor	111	55	12	57
Living related	56	28	6	29
Living unrelated	36	18	3	14
Cases of CMV and D/R status				
D+/R+	103	51	9	43
D+/R–	46	23	10	48
D–/R+	32	16	1	5
D–/R–	22	11	1	5

†Other indications included hypertensive nephropathy, obstructive nephropathy, amyloid nephropathy, familial diseases (Alport's, Fabry's, medullary cystic kidney disease) and idiopathic disease. CMV, cytomegalovirus; SLE, systemic lupus erythematosus.

Table 3 Recipients who developed CMV infection on non-protocol prophylaxis

Patient	Valaciclovir dose	Serum creatinine, μmol/L (GFR†)			
		Day 7		Day 30	
1	500 mg bid (3 months)	800	13	190	53
2	500 mg bid (2 months)‡	750	16	210	58
3	500 mg bid (10 weeks)‡	200	60	150	78
4	500 mg bid (10 weeks)‡	90	79	90	79
5	500 mg tid (3 months)	170	60	210	48
6	Ceased at 1 week‡§	1240	6	250	36

†GFR: glomerular filtration rate in mL/min, calculated by Cockroft–Gault formula. ‡Patients who developed CMV infection within 90 days post transplant. §Patient developed psychosis attributed to valaciclovir. CMV, cytomegalovirus.

CMV disease within 90 days of receiving their grafts (i.e. whilst on prophylaxis). A fifth patient had a creatinine of 170 μmol/L (estimated GFR 45 mL/min) and received 3 months of valaciclovir 500 mg *tid* when the appropriate dose for that level of renal function was approximately 30% higher. A sixth patient had valaciclovir ceased in the first post-transplant week following the development of an acute brain syndrome, and received CMVIg alone. For the 40 D+/R– patients who received prophylaxis as per protocol, the incidence of CMV disease was 5% ($n = 2$) at 6 months and 10% ($n = 4$) at 4 years.

Among those not receiving prophylaxis, the incidence of CMV disease was 8.7% in the D+/R+ group (9/103) and 3% in the D–/R+ group (1/32). In the D–/R– group ($n = 22$), one patient developed CMV disease 12 months post transplantation following exposure to pulse methylprednisolone and OKT3 (Muromonab-CD3) for treatment of rejection.

Ten patients had biopsy-proven organ involvement with CMV – six had colitis and four had gastritis or oesophagitis. One patient with CMV disease had associated abnormal liver function test as the only sign of infection and 10 other patients had CMV disease characterized by fever, constitutional symptoms, and a positive serum CMV polymerase chain reaction. All the patients diagnosed with CMV disease received treatment with IV ganciclovir.

During the four-year period of observation, patient survival was 94.9% among the entire cohort with a graft survival of 89.4%. Among the 21 patients who developed CMV disease, patient survival was 95.2% (20/21), and graft survival was 90.5% over the same period.

DISCUSSION

We report a study assessing the administration of valaciclovir with CMVIg as prophylaxis for CMV disease in high-risk renal transplant recipients. CMV remains the commonest life-threatening opportunistic infection following renal transplantation and those at greatest risk are CMV-negative recipients of organs from CMV-positive donors, where an incidence of up to 60% has been noted in the absence of prophylaxis.[5–8,17,19,24–27] A meta-analysis evaluating prophylaxis with either oral aciclovir, valaciclovir or ganciclovir in SOT recipients reported a 60% reduction in CMV disease and 40% reduction in all-cause mortality among those receiving antiviral prophylaxis.[3]

With an attempt to reduce pill burden and toxicity of antiviral agents we introduced low-dose valaciclovir and CMVIg as CMV prophylaxis and report this regimen to be as efficacious in preventing CMV disease as other published regimens, including those with full-dose valaciclovir and valganciclovir. The efficacy of low-dose valaciclovir (3000 mg/day) was suggested by two small retrospective renal transplant studies, where the incidence of CMV disease was 8.5% at 6 months[14] and 24% at 3 years,[15] respectively. CMVIg, administered as monotherapy or in combination with antiviral agents, also reduces the incidence of CMV disease by up to 75% in renal transplant recipients[16–19,27–29] and a meta-analysis of CMVIg in SOT showed a significant reduction in CMV disease, CMV-related deaths and all-cause mortality.[17]

In our study, the incidence of CMV disease among the entire patient population was 10.3%. However, only the high-risk D+/R– patients received prophylaxis, and within

this group there was a 15.2% incidence of CMV disease 6 months post transplantation. This is similar to the incidence reported in patients receiving ganciclovir (oral or IV) or high-dose valaciclovir; in these studies the incidence of CMV disease ranged from 11% to 50%.[5,8,10–12,30] In our study, the majority of D+/R− patients who developed CMV disease were receiving valaciclovir at a dose below that recommended by our protocol for their level of renal function. Where patients had a significant delay in attaining nadir creatinine, the valaciclovir dose was not increased appropriately when renal function ultimately improved. The incidence of CMV disease among D+/R− recipients in whom prophylaxis was administered as per protocol was 5% at 6 months, and 10% at 4 years. This compares favourably with the incidence of CMV disease reported with other regimens, including two retrospective studies with similarly low-dose valaciclovir.[5,8,10–12,14,15,30]

In a recent randomized controlled trial, comparing 100 days of oral ganciclovir and valganciclovir, Paya *et al*.[7] reported CMV disease in 23% of renal transplant patients receiving oral ganciclovir and 6% of patients receiving valganciclovir at 6 months; by 12 months, up to 31% of SOT recipients required therapy for CMV disease. This is consistent with the findings of Arthurs *et al*.,[31] where 3 months of prophylaxis with oral ganciclovir or valganciclovir was followed by a cumulative incidence of CMV disease of 18% at 3 months, 27% at 6 months and 30% at 21 months post prophylaxis. Interestingly, the recipients of low-dose valaciclovir and CMVIg in our study had a low rate of late CMV disease; while the incidence was 15.2% at 6 months, it had only risen to 21.7% at 4 years.

Although there is debate about the use of prophylaxis compared with pre-emptive therapy for prevention of CMV disease, a meta-analysis reported that only prophylaxis reduced the incidence of CMV end-organ disease in subgroups of patients at highest risk of infection and in those who received induction therapy with anti-lymphocyte antibodies.[32] One recent study of renal transplant recipients compared valaciclovir prophylaxis therapy (8000 mg/day for 3 months) with pre-emptive valganciclovir therapy (900 mg *bid* when they developed viraemia) reporting no difference in the incidence of CMV disease, although a significantly higher rate of transplant rejection in the pre-emptive therapy arm.[11]

The low valaciclovir dosage in our protocol resulted in only 2.2% of patients experiencing neurotoxicity. This is slightly lower than the rate reported by Reddy *et al*. using low-dose valaciclovir alone,[14] and compares favourably with an incidence of between 16%[5] and 38%[14] in studies using conventional valaciclovir dosing. None of our patients reported any ill effects from the infusions of CMVIg, although an adverse event rate of 8% has been reported elsewhere, the commonest symptoms being back pain, long bone pain, chills, flushing and itch.[16]

In our study, 9% of D+/R+ patients and 5% of D−/R+ patients, who did not receive prophylaxis, developed CMV disease, indicating a number needed to treat of 11 and 20, respectively. Given the morbidity associated with CMV disease and associations with other adverse post transplant outcomes,[33] we have now extended prophylaxis to all renal transplant recipients in our unit except D−/R−.

Cytomegalovirus disease has been associated with inferior transplant and patient outcomes. However, among the 21 patients in our study who developed CMV disease, patient survival and graft survival at 4 years was 95.2% and 90.5%, respectively; no different from the other patients transplanted in this period. A study by Opelz *et al*.,[27] showed that CMV prophylaxis (with aciclovir, ganciclovir or CMVIg) improved graft survival and reduced rejection in D+/R− patients. Other reported benefits of CMV prophylaxis include a reduction in opportunistic infections including *Pneumocystis jeroveci* pneumonia.[3,28,30] One retrospective multicentre analysis also showed that CMVIg was associated with a decrease in the incidence of post-transplant lymphoproliferative disease in the first year post transplant.[27]

Despite the efficacy of valaciclovir, the use of valganciclovir for CMV prophylaxis is increasing.[4,7,34] It is often associated with troublesome neutropenia especially in combination with MMF.[35,36] The use of reduced dose valganciclovir in combination with CMVIg may overcome this complication while maintaining protection from CMV.

Notwithstanding retrospectivity and lack of randomization, this study shows the ability of low-dose valaciclovir and CMVIg to prevent CMV disease in CMV seronegative recipients of renal transplants from CMV-positive donors with efficacy equivalent to other published regimens. It results in lower toxicity compared with prophylaxis with standard dose valaciclovir, and is associated with a low incidence of late-onset disease. Outcomes may be further enhanced by ensuring appropriate dose adjustment is made in association with changes in renal function, or by delaying commencement of valaciclovir until the nadir creatinine is reached.

REFERENCES

1. Brennan DC. Cytomegalovirus in renal transplantation. *J. Am. Soc. Nephrol.* 2001; **12**: 848–55.
2. Opelz G, Döhler B, Ruhenstroth A. Cytomegalovirus prophylaxis and graft outcome in solid organ transplantation: A collaborative transplant study report. *Am. J. Transplant.* 2004; **4**: 928–36.
3. Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: The efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann. Intern. Med.* 2005; **143**: 870–80.
4. Hodson EM, Craig JC, Strippoli GF, Webster AC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst. Rev.* 2008; **2**: CD003774.
5. 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.
6. Flechner SM, Avery RK, Fisher R *et al*. A randomized prospective controlled trial of oral acyclovir versus oral ganciclovir for

cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998; **66**: 1682–8.
7. Paya C, Humar A, Dominguez E *et al*. Efficacy and safety of valganciclovir versus oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am. J. Transplant.* 2004; **4**: 611–20.
8. Avidan YP, Paul M, Rahamimov R *et al*. Selective low-dose valganciclovir for prevention of cytomegalovirus disease following kidney transplantation. *J. Infect.* 2008; **57**: 236–40.
9. Sun H-Y, Wagener MM, Singh N. Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: A systematic review. *Am. J. Transplant.* 2008; **8**: 2111–8.
10. Kletzmayr J, Kreuzwieser E, Watkins-Riedel T *et al*. Long-term oral ganciclovir prophylaxis for prevention of cytomegalovirus infection and disease in cytomegalovirus high-risk renal transplant recipients. *Transplantation* 2000; **70**: 1174–80.
11. Reischig T, Jindra P, Hes O *et al*. Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. *Am. J. Transplant.* 2008; **8**: 69–77.
12. Yango A, Morrissey P, Zanabli A *et al*. Comparative study of prophylactic oral ganciclovir and valacyclovir in high-risk kidney transplant recipients. *Nephrol. Dial. Transplant.* 2003; **18**: 809–13.
13. Pavlopoulou ID, Syriopoulou VP, Chelioti H *et al*. A comparative randomised study of valacyclovir versus oral ganciclovir for cytomegalovirus prophylaxis in renal transplant recipients. *Clin. Microbiol. Infect.* 2005; **11**: 736–43.
14. Reddy SP, Handa A, Tan L *et al*. Low-dose valaciclovir prophylaxis against cytomegalovirus disease in renal transplant recipients. *Transpl. Int.* 2003; **16**: 726–9.
15. Sund F, Wahlberg J, Eriksson BM. CMV disease in CMV-mismatched renal transplant recipients with prophylactic low dose valaciclovir. *J. Clin. Virol.* 2001; **23**: 107–11.
16. 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.
17. Bonaros N, Mayer B, Schachner T *et al*. CMV-hyperimmune globulin for preventing cytomegalovirus infection and disease in solid organ transplant recipients: A meta-analysis. *Clin. Transplant.* 2008; **22**: 89–97.
18. Snydman DR, Werner BG, Dougherty NN *et al*. Cytomegalovirus immune globulin prophylaxis in liver transplantation: A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* 1993; **119**: 984–91.
19. Snydman DR. Historical overview of the use of cytomegalovirus hyperimmune globulin in organ transplantation. *Transpl. Infect. Dis.* 2001; **3** (Suppl 2): 6–13.
20. Bock GH, Sullivan EK, Miller D *et al*. Cytomegalovirus infections following renal transplantation – effects on antiviral prophylaxis: A report of the North American pediatric renal transplant cooperative study. *Pediatr. Nephrol.* 1997; **11**: 665–71.
21. Jordan SC, Vo AA, Peng A, Toyoda M, Tyan D. Intravenous gammaglobulin (IVIG): A novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. *Am. J. Transplant.* 2006; **6**: 459–66.
22. Segev D, Simpkins C, Warren D *et al*. ABO incompatible high-titer renal transplantation without splenectomy or anti-CD20 treatment. *Am. J. Transplant.* 2005; **5**: 2570–75.
23. Stegall MD, Gloor J, Winters JL, Moore SB, Degoey S. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. *Am. J. Transplant.* 2006; **6**: 346–51.
24. Hodson EM, Jones CA, Webster AC *et al*. Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: A systematic review of randomised controlled trials. *Lancet* 2005; **365**: 2105–15.
25. Eid AJ, Razonable RR. Cytomegalovirus disease in solid organ transplant recipients: Advances lead to new challenges and opportunities. *Curr. Opin. Organ. Transpl.* 2007; **12**: 610–7.
26. Limaye AP, Bakthavatsalam R, Kim HW *et al*. Impact of cytomegalovirus in organ transplant recipients in the era of antiviral prophylaxis. *Transplantation* 2006; **81**: 1645–52.
27. Opelz G, Daniel V, Naujokat C *et al*. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: A multicentre retrospective analysis. *Lancet Oncol.* 2007; **8**: 212–8.
28. Rostaing L, Martinet O, Cisterne JM *et al*. CMV prophylaxis in high-risk renal transplant patients (D+/R–) by acyclovir with or without hyperimmune (CMV) immunoglobulins: A prospective study. *Am. J. Nephrol.* 1997; **17**: 489–94.
29. Leroy F, Sechet A, Abou Ayache R *et al*. Cytomegalovirus prophylaxis with intravenous polyvalent immunoglobulin in high-risk renal transplant recipients. *Transplant. Proc.* 2006; **38**: 2324–6.
30. Pascual J, Alarcon MC, Marcen R *et al*. Cytomegalovirus infection after renal transplantation: Selective prophylaxis and treatment. *Transplant. Proc.* 2003; **35**: 1756–7.
31. Arthurs SK, Eid AJ, Pedersen RA *et al*. Delayed-onset primary cytomegalovirus disease and the risk of allograft failure and mortality after kidney transplantation. *Clin. Infect. Dis.* 2008; **46**: 840–6.
32. Strippoli GF, Hodson EM, Jones CJ, Craig JC. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst. Rev.* 2006; **1**: CD005133.
33. Bailey TC, Ettinger NA, Storch GA *et al*. Failure of high-dose oral acyclovir with or without immune globulin to prevent primary cytomegalovirus disease in recipients of solid organ transplants. *Am. J. Med.* 1993; **95**: 273–8.
34. Weng FL, Patel AM, Wanchoo R *et al*. Oral ganciclovir versus low-dose valganciclovir for prevention of cytomegalovirus disease in recipients of kidney and pancreas transplants. *Transplantation* 2007; **83**: 290–6.
35. Brum S, Nolasco F, Sousa J *et al*. Leukopenia in kidney transplant patients with the association of valganciclovir and mycophenolate mofetil. *Transplant. Proc.* 2008; **40**: 752–4.
36. Hartmann EL, Gatesman M, Roskopf-Somerville J *et al*. Management of leukopenia in kidney and pancreas transplant recipients. *Clin. Transplant.* 2008; **22**: 822–8.