Trends in Transplantation 2007;1:35-43

Valganciclovir: Dosing Strategies for Effective Cytomegalovirus Prevention

Mark D. Pescovitz

Department of Surgery and Department of Microbiology/Immunology Indiana University, Indianapolis, IN, USA

Abstract

Valganciclovir has widely become the agent of choice for the prevention of cytomegalovirus in recipients of organ transplants. Optimal dosing is needed to achieve efficacy and avoid toxicity. For subjects at high risk of cytomegalovirus, it is strongly suggested that full-dose (based on renal function) valganciclovir be used. While low-dose valganciclovir appears to be efficacious in some reports, the recommendations are based on inadequately designed trials and must be taken with caution. Unfortunately, because of the sample size needed, it is not likely that the efficacy of reduced-dose valganciclovir will be adequately tested in well-controlled trials. The duration of prophylaxis, particularly whether prophylaxis should be extended beyond three months, continues to be an important question and is the subject of a well-designed clinical trial of which we anxiously await the results. **(Trends in Transplant 2007;1:35-43)**

Corresponding author: Mark D. Pescovitz, mpescov@iupui.edu

Key words

Valganciclovir. Ganciclovir. Transplant. Cytomegalovirus. Children. Pharmacokinetics.

Correspondence to:
Mark D. Pescovitz
Indiana University Medical Center
Department of Surgery
UH 4601
550 N University Blvd
Indianapolis, IN 46202, USA
E-mail: mpescov@iupui.edu

Mark D. Pescovitz is a consultant to Roche and received honoraria for speaking and also research grants.

Introduction

Cytomegalovirus (CMV) is the cause of substantial morbidity in solid-organ transplant recipients[1,2]. Since the field of CMV is so large, this review will have a limited scope, addressing only the issues of dosing for effective prophylaxis of CMV in recipients of organ transplantation. Because of differences in pathophysiology, dosing in patients with HIV and following bone-marrow or stem-cell transplantation will not be addressed in this review.

Cytomegalovirus prophylaxis

Ganciclovir, in its several forms (oral, intravenous), or the recently approved prodrug valganciclovir, has emerged as the principle drug for CMV prophylaxis[3]. Ganciclovir, an acyclic nucleoside analog of 2'-deoxyguanosine, requires tri-phosphorylation to exert its antiviral activity, the first phosphorylation of which is mediated by the virally encoded kinase, UL97; this leads to the specificity of the drug for infected cells. Cellular enzymes complete the activation to ganciclovir triphosphate, which is then able to inhibit the CMV viral DNA polymerase (UL54). The actual antiviral activity is prolonged beyond ganciclovir contained in the blood because of the long intracellular half-life of the triphosphate (6-24 hours)[4]. Ganciclovir is excreted unchanged in the urine by both glomerular filtration and net active tubular secretion and therefore dose modifications based on renal function are required[5]. Ganciclovir shows potent antiviral activity against all known human herpes viruses[6]. For most sensitive strains of CMV the IC_{50} is in the range of 0.08-14 μM (0.02-3.58 mg/ml). Viral resistance to ganciclovir is well-documented including transplant recipients and is primarily by mutations in the UL97 gene but occasionally in the UL54 gene[7-9].

In the first large, randomized, controlled trial of ganciclovir in organ transplantation reported in 1995, CMV disease developed in only one of 124 patients (0.8%) treated with intravenous ganciclovir (6 mg/kg/d IV for 30 days after transplantation followed by 6 mg/kg/d five days per week until day 100) compared to 48 of 126 patients (38%) treated with acyclovir (10 mg/kg IV every 8 hours while hospitalized followed by 800 mg 4/d orally until day 100)[10]. Many but not all of the logistic problems with intravenous ganciclovir for prophylaxis were substantially alleviated by the development of an oral formulation[11]. In a study in liver-transplant recipients, 100 days of oral ganciclovir 1 g 3/d were better than placebo in preventing CMV disease[12]. In the high-risk group, i.e. CMV donor serology positive/recipient serology negative (D+/R–), the rate of CMV disease in the placebo-treated group was 44 vs. 14.8% in the ganciclovir-treated group. This rate of CMV disease in the placebo group is important to remember when considering the frequency of late CMV that occurs after completion of prophylaxis. While late CMV does occur after completion of prophylaxis, particularly in the high-risk group, the rate is substantially lower than if no prophylaxis were provided; therefore, while not perfect, prophylaxis does have a long-term benefit in the prevention of CMV disease.

For prophylaxis, the utility of intravenous ganciclovir is limited by the risk of line infections, and the utility of oral ganciclovir is limited by the poor oral bioavailability requiring frequent large daily doses, and the development of resistance and breakthrough CMV disease[9,12,13]. These limitations stimulated the search for an improved version of ganciclovir, the result of which was valganciclovir.

Valganciclovir

Valganciclovir is the L-valine ester of ganciclovir (Fig. 1). It was originally studied in the setting of HIV-associated CMV retinitis for which it was first approved by the FDA[14]. Only

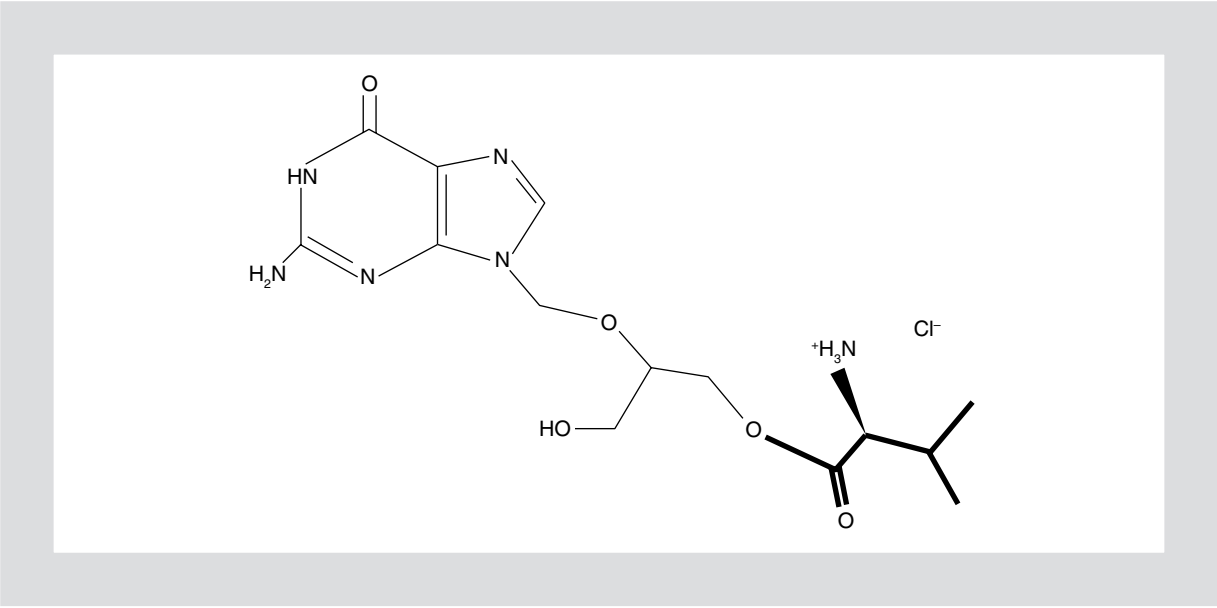

Figure 1. *Schematic diagram of valganciclovir. The bold part on the right of the molecule is the amino acid valine that is conjugated to the ganciclovir portion by an ester linkage.*

after this approval was it studied in transplant patients. Valganciclovir is rapidly converted to ganciclovir and the amino acid valine after oral absorption. There are no other metabolites. Once converted to ganciclovir, the mechanism of antiviral activity and clearance is the same as that described for ganciclovir[3,15]. Because of the long intracellular half-life of ganciclovir as noted above, there is probably little rationale to split the daily dose of valganciclovir in the hope of reducing toxicity; however, this has not been formally tested.

The 60% absorption of valganciclovir (as measured by ganciclovir blood concentrations) is linear over the normal dosing range, indicating that the absorption pathway is not saturated[16,17]. The addition of the amino acid valine to ganciclovir therefore increases the absorption from 6% as seen with the parent ganciclovir, a factor of approximately 10-fold[18,19]. Although the valine is attached to ganciclovir by an ester linkage, valganciclovir takes advantage of the peptide transport mechanism of the small intestine, similar to what occurs with valacyclovir[19-21]. Valganciclovir is then rapidly hydrolyzed to ganciclovir, such that little intact valganciclovir is detectable in the circulation[16,17,22]. Plasma concentrations of ganciclovir reach maximal concentrations within 2-3 hours after dosing. Dosing valganciclovir with food leads to an increased ganciclovir exposure of about 30% ($p < 0.001$)[16]. Mean C_{max} values of ganciclovir also increase but less so ($p = 0.079$). The manufacturer recommends that valganciclovir be given with food.

The first trial with valganciclovir in organ transplantation was a phase II pharmacokinetic study in 28 stable liver-transplant patients[17]. This open-label study was conducted to confirm dosing recommendations determined originally in HIV subjects. The subjects received a single dose/day of oral ganciclovir 1000 mg 3/d, valganciclovir 450 mg 1/d and 900 mg 1/d , and intravenous ganciclovir 5 mg/kg, in random order. The fact that these were not at steady state is important to consider when comparing actual drug exposure. The study suggested that the total drug exposure of valganciclovir 450 mg was equivalent to oral ganciclovir, and that valganciclovir 900 mg was similar to but slightly less than intravenous ganciclovir. The study set the stage

for the international, multicenter, randomized, double-blind, double-dummy phase III pivotal trial of 364 CMV-seronegative recipients of hearts, livers, or kidneys from seropositive donors (D+/R–)[23]. Based on the standard of care for duration of prophylaxis, 100 days of valganciclovir 900 mg 1/d were compared to 100 days of oral ganciclovir 1 g 3/d for the prevention of CMV disease, with the primary efficacy endpoint at six months and a secondary efficacy endpoint at one year. The results demonstrated that valganciclovir was equal (i.e. non-inferior) to oral ganciclovir at six and 12 months. Since the efficacy was demonstrated in patients prohibited from initial use of IV therapy (oral therapy had to be started within 10 days posttransplantation), it is reasonable to wait for up to ten days before starting prophylaxis, thus avoiding the need for any IV ganciclovir. These efficacy results have been confirmed in an open-label trial[24].

Because of the ease of dosing, valganciclovir has become the standard of care for those who subscribe to prophylaxis of CMV after organ transplantation. However, various dosing strategies different from those used in the pivotal trial are being promoted, with the goals of decreasing the occurrence of late CMV, reducing cost, reducing side effects, and extending the use into children. These strategies are:

1. Extended prophylaxis
2. Reduced dosing
3. Liquid formulation for children

Extended prophylaxis

The current standard duration for valganciclovir is 100 days, the duration used in the Paya, et al. study[23]. This "standard" duration is the legacy of the first placebo-controlled trial of posttransplant CMV prophylaxis; Balfour, et al. used 12 weeks of acyclovir[25]. As they stated, "Three months is a logical duration of prophylaxis because cytomegalovirus disease usually occurs during that period". Following on the success of this protocol, Winston, et al.[10] compared 100 days of intravenous ganciclovir to 100 days of acyclovir, with improved efficacy. In the placebo-controlled trial of oral ganciclovir in liver-transplant recipients, again 100 days was the selected time for prophylaxis[12]. Since this was now the indicated time for oral ganciclovir, the time of prophylaxis was set for valganciclovir. But is this sufficient prophylaxis? Is it too long? Is it not long enough?

In the study of Paya, et al. with either oral ganciclovir or valganciclovir, while there were no cases of CMV disease on treatment, after treatment stopped approximately 18% of patients developed CMV during the first year posttransplantation[23]. As noted above, in the placebo-controlled trial with oral ganciclovir the rate of CMV in absence of any prophylaxis was substantially higher. Therefore, the occurrence of late CMV after prophylaxis should not be interpreted as a lack of long-term benefit. When analyzing the time of viremia posttransplantation[26], there was a peak at six months, thus suggesting that perhaps there would be a benefit to extend prophylaxis beyond three months.

The data from Paya, et al. were analyzed post hoc in an attempt to identify markers that would predict who might benefit from such extended prophylaxis. The clinical utility of quantitative plasma viral load measurements for predicting CMV disease recurrence was tested and found to be a poor correlate[26]. Measurements of viral load by PCR were performed every two weeks until day 100 and at months 4, 4.5, 5, 6, 8 and 12 posttransplantation. Using a positive cutoff value of > 400 viral genome copies/ml, sensitivity was 38%, specificity 60%, positive predictive value 17%, and negative predictive value 82% for prediction of CMV disease. Therefore, routine monitoring would have predicted disease in only 24/64 (38%) patients. Similarly poor as a predictor in these previously CMV-naive patients,

was seroconversion[27]. The presence of CMV antibodies at the end of 100 days of prophylaxis could not distinguish patients who would recur from those who would not. While the presence of antibodies at six months did demarcate those patients less likely to recur, the numbers were so small as to be clinically insignificant[27].

There are no well-designed studies specifically addressing length of therapy, although several have used extended therapy beyond three months, particularly in high-risk patients such as lung recipients, D+/R– transplants, or those treated with depleting antibody[28-31]. Zamora, et al. found that the recurrence rate for post-lung transplant CMV was > 36% for patients who received less than six months of valganciclovir prophylaxis as opposed to < 10% for patients who received greater than six months[32]. More recently, Doyle, et al. compared the rate of CMV disease in renal-transplant recipients who received either 12 or 24 weeks of oral ganciclovir[33]. They found a rate of CMV of only 7% in patients with the extended prophylaxis compared to a 31% rate ($p < 0.01$) in those who received the shorter, standard course. A double-blind, placebo-controlled trial in D+/R– renal-transplant recipients comparing 90 vs. 180 days of valganciclovir prophylaxis sponsored by Roche is currently underway.

Reduced dosing

The appropriate dosing for valganciclovir should be based on the goal of achieving appropriate ganciclovir levels. Since absorbed ganciclovir is eliminated from the body almost entirely by renal excretion, dosing modification based on renal function is mandatory[3]. The question then becomes, what is an appropriate level of ganciclovir to target. Should the target be a maximum or minimum blood level, or some combination of both? Or should total drug exposure as measured by area under the curve (AUC) be targeted? And in fact, do the blood concentrations have any significance since the active form of ganciclovir is intracellular ganciclovir triphosphate[3]? In a study of oral ganciclovir versus intravenous ganciclovir, of which the results are unfortunately only "on file" and not published, it was demonstrated that AUC and not the raw blood levels, such as maximum concentration, drove efficacy (as referenced in Brown, et al.[16]). When a creatinine clearance (CrCl)-based dosing algorithm for oral ganciclovir was tested in a group of patients on dialysis awaiting transplantation, and in recipients of liver or kidney transplants[12,18], it was designed with AUC in mind, aiming to achieve drug exposures similar to those shown to be effective in patients with HIV[34]. While oral ganciclovir was efficacious, upon further examination of the data some interesting findings became apparent[18]. For patients with moderately to severely reduced estimated CrCl (10-24 and 25-50 ml/min) the dosing algorithm resulted in suboptimal ganciclovir exposures as determined by AUC. This may have contributed to the occurrence of CMV disease in some of these patients. Furthermore, no patient with CrCl in the range of 50-69 ml/min developed CMV disease in contrast to 6/75 (8.2%) with CrCl >70 ml/min[18]. Patients in both clearance ranges were dosed with oral ganciclovir1 gm 3/d, which when coupled with the differences in renal function, resulted in higher AUC in the group with mild renal impairment. These results indicate that for patients with excellent renal function, the dose of 1000 mg 3/d of oral ganciclovir is inadequate. However, a recommendation to increase the dose of oral ganciclovir above the 1000 mg 3/d, i.e. more than 12 pills a day, was not considered practical.

As noted above, in the phase II trial with valganciclovir in liver-transplant recipients, 450 mg/d provided similar drug exposure to the oral ganciclovir at 1000 mg 3/d[17]. However, based on the concern for suboptimal levels using 1000 mg 3/d[18], the pivotal trial of

valganciclovir used the higher dose of 900 mg 1/d[23]. Since the publication of the results of this study, many abstracts and full reports have appeared indicating excellent results using a reduced dose of 450 mg of valganciclovir 1/d (*vide infra*). Those promoting this reduced dose cite the report indicating that 450 mg provides the same drug exposure seen with 1000 mg 3/d of oral ganciclovir, and therefore they believe that the reduced dose should provide efficacy equal to 900 mg 1/d. Other reasons put forward for the reduced dose is the fear of leukopenia that was somewhat more common with valganciclovir 900 mg than oral ganciclovir[23], and a desire to both reduce drug costs and pill burden.

While studies with both liver and renal transplant recipients have shown the efficacy of reduced-dose strategies, there are significant methodologic problems with them. First, most of the studies are retrospective and none are adequately powered for non-inferiority of 450 vs. 900 mg[29,31,35,36]. Second, either the renal function of the patients in the reports is not reported[28,29,36] or at best only the serum Cr is reported[35]. In fact, Park, et al. state that the valganciclovir dose "was reduced for impaired renal function per manufacturer's guidelines"[36]. Starting at a dose of 450 mg for a patient with normal renal function obviates that statement as the manufacturer's guidelines list the dose as 900 mg. For a patient with a CrCl of < 60 ml/min, valganciclovir 450 mg (i.e. the reduced dose) would be the appropriate dose per the label. Many transplant patients early posttransplantation have clearances in this range. Recipients of living-donor renal transplants typically have excellent renal function early on, and it was in these patients that 450 mg of valganciclovir failed to prevent CMV disease while on therapy, suggesting underdosing[29]. Third, there are many causes of neutropenia other than valganciclovir, including depleting antibodies, mycophenolate mofetil, sirolimus, and the reduced use of corticosteroids, which increase the neutrophil count. Lastly, as has been recently shown using population pharmacokinetics in patients now at steady state, the drug exposure from oral ganciclovir 1000 mg 3/d is more than half that seen with valganciclovir 900 mg, thereby implying that using a reduced valganciclovir dose would provide less drug exposure than that achieved with oral ganciclovir[37].

As part of the pivotal valganciclovir trial, a population pharmacokinetic/pharmacodynamic analysis was done. These results showed that with a ganciclovir AUC (combining oral ganciclovir and valganciclovir patients) of 50 µg·hr/ml, the incidence of CMV viremia at four months posttransplantation (i.e. one month after stopping prophylaxis) was < 10%[38]. This level was achieved more often in patients on valganciclovir than oral ganciclovir. A similar analysis from this study demonstrated that the rate of neutropenia (< 1000 cells/µl) at four months increased above 20% only when the AUC increased above > 61 µg·hr/ml.

An argument however could be made that the point for dose adjustment could be at a CrCl of 70 ml/min, with those having better renal function receiving full-dose valganciclovir[37] (Fig. 2). This is similar to the earlier studies with oral ganciclovir that suggested that those subjects with CrCl > 70 ml/min were those at greatest risk of CMV and therefore would benefit most from higher doses[18].

Other issues that must be kept in mind are the variability in renal function posttransplantation as the kidney recovers from preservation injury, surgical stress, and the effect of nephrotoxic immunosuppression. Dose adjustments are therefore frequently required as renal function changes to avoid both under and over dosing. The reliability of calculated CrCl in transplant patients, particularly those who are malnourished with low muscle mass, may be questioned. Risk factors for CMV including donor/recipient CMV status and the use of depleting antibodies should be con-

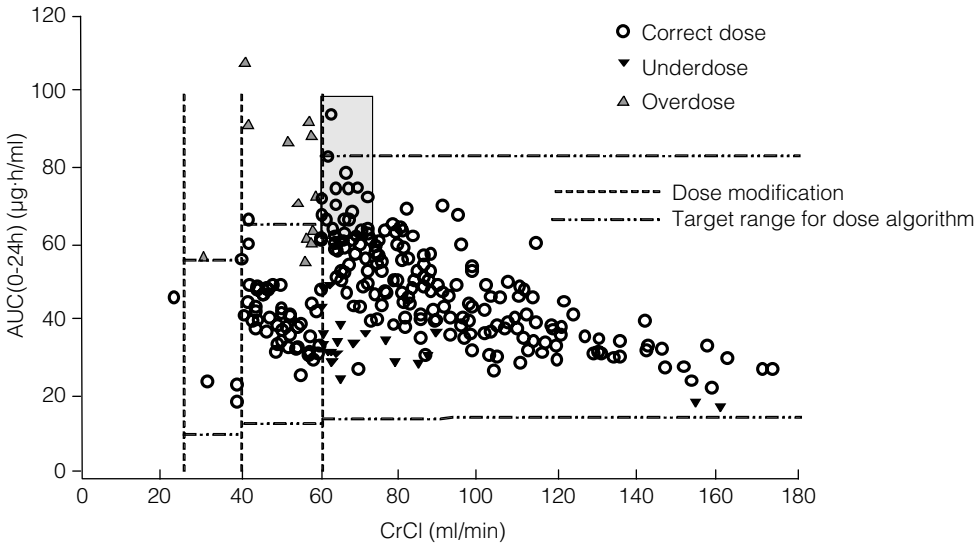

Figure 2. *Calculated individual area under the curve (AUC) versus calculated creatinine clearance (CrCl) of valganciclovir-treated patients in the pivotal trial comparing valganciclovir versus oral ganciclovir. Modified from Wiltshire, et al.[37]. The vertical lines are the protocol-mandated breakpoints for dose adjustment. The horizontal lines are the targeted exposure per the dosing algorithm. The shaded box indicates a range of drug exposure greater than 60 (a range that might be associated with increased toxicity). Several patients fall into this box, most of which have CrCl between 60 and 70 ml/hr.*

sidered when contemplating reduced-dose strategies. Subjects at low risk for CMV disease may achieve adequate benefit from reduced-dose valganciclovir[39]. Lastly, the dose recommendations are based on prophylaxis in the absence of detectable viral load; it is probably not wise to use reduced doses of valganciclovir in a preemptive strategy where the viral load would be higher[40].

A potential downside to reduced-dose valganciclovir would be the increased development of resistant strains of CMV. Valganciclovir was significantly better at preventing CMV viremia during treatment[23]. The UL97-mediated viral resistance to ganciclovir did not occur in the valganciclovir group, although resistance to ganciclovir occurred in 1.9% of patients in the oral ganciclovir group at the end of 100 days of prophylaxis and 0 and 6.1% for suspected CMV disease at 12 months[41]. Furthermore, a single case of UL54-mediated resistance was also seen in the oral ganciclovir group with no cases in the valganciclovir group[42]. It is hypothesized that the higher drug exposure provided by valganciclovir explained this reduced incidence of resistance development[41,42].

Pediatric use

There are no currently approved oral formulations of ganciclovir or valganciclovir for children, thus requiring the clinical site to prepare their own oral solution. In our and others studies with oral ganciclovir in the pediatric age group, it was noted that a dose higher than expected based on weight was needed to achieve adequate levels[43-46]. One explanation proposed was that of overall better renal function in the pediatric age group[43]. Therefore, simple extrapolation from adult dosing is ill advised.

As with oral ganciclovir previously, valganciclovir is now being used off-label for CMV prophylaxis in children. There are three main issues to be addressed regarding the use of valganciclovir in children:

1. Determination of the appropriate dosing algorithm.
2. Development of a standard liquid formulation.
3. Determination of the appropriate duration of dosing.

The first two of these deficiencies have been studied in recent (as yet unpublished) pediatric liver and kidney transplant trials. A syrup formulation prepared by Roche was tested in short pharmacokinetic studies in liver and kidney recipients (manuscript in preparation). The data show that the appropriate formula for valganciclovir dose in mg appears to be: 7 x body surface area x CrCl (using the Schwartz formula). With the dose proportional to both patient size and renal function, it is not unusual that a full adult dose (900 mg/d) could be needed in a child who has just received an adult renal transplant. Since ganciclovir is cleared essentially unchanged in the urine, it is primarily the kidney that is being dosed, not the child. A larger, safety and efficacy trial in 60 pediatric transplant patients followed, confirming the dosing paradigm in its ability to achieve appropriate target levels, safety and efficacy (manuscript in preparation). Single-center experiences with locally prepared valganciclovir formulations have indicated early efficacy and safety in 10 liver recipients[47] or surveys of lung-transplant centers[48]. Presumably the duration of prophylaxis would parallel that of the adult population, but there are no studies currently addressing this in the literature.

Conclusion

Valganciclovir has widely become the agent of choice for the prevention of CMV in recipients of organ transplants. Optimal dosing is needed to achieve efficacy and avoid toxicity. For subjects at high risk of CMV, it is strongly suggested that full-dose (based on renal function) valganciclovir be used. While low-dose valganciclovir appears to be efficacious in some reports, the recommendations are based on inadequately designed trials. Unfortunately, because of the sample size needed, it is not likely that the efficacy of reduced-dose valganciclovir will be adequately tested in well-controlled trials. The duration of prophylaxis, however, continues to be an important question and is the subject of a well-designed clinical trial of which we anxiously await the results.

References

1. Kanj SS, Sharara AI, Clavien PA, Hamilton JD. CMV infection following liver transplantation: review of the literature. Clin Infect Dis 1996;22:537-49.
2. Patel R, Snydman DR, Rubin RH, et al. CMV prophylaxis in solid organ transplant recipients. Transplantation 1996; 61:1279-89.
3. Crumpacker CS. Ganciclovir. N Engl J Med 1996;335:721-9.
4. Smee DF, Boehme R, Chernow M, Binko BP, Matthews TR. Intracellular metabolism and enzymatic phosphorylation of 9-(1,3-dihydroxy-2-propoxymethyl)guanine and acyclovir in herpes simplex virus-infected and uninfected cells. Biochem Pharmacol 1985;34:1049-56.
5. Fletcher C, Sawchuk R, Chinnock B, de Miranda P, Balfour HH Jr. Human pharmacokinetics of the antiviral drug DHPG. Clin Pharmacol Ther 1986;40:281-6.
6. Griffiths PD. Progress in the clinical management of herpesvirus infections. Antivir Chem Chemother 1995;6:191-209.
7. Drew WL, Miner R, Saleh E. Antiviral susceptibility testing of CMV: criteria for detecting resistance to antivirals. Clin Diagnost Virol 1993;1:179-85.
8. Chou S, Guentzel S, Michels KR, Miner RC, Drew WL. Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical CMV isolates. J Infect Dis 1995;172:239-42.
9. Limaye AP, Corey L, Koelle DM, Davis CL, Boeckh M. Emergence of ganciclovir-resistant CMV disease among recipients of solid-organ transplants. Lancet 2000;356:645-9.
10. Winston DJ, Winn D, Shaked A, Busuttil RW. Randomized comparison of ganciclovir and high-dose acyclovir to prevent CMV for long term-term CMV prophylaxis in liver transplant recipients. Lancet 1995;346:43-50.
11. Spector SA, Busch DF, Follansbee S, et al. Pharmacokinetic, safety, and antiviral profiles of oral ganciclovir in persons infected with HIV: a phase I/II study. J Infect Dis 1995;171:1431-7.
12. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of CMV disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group (corrected). Lancet 1997;350:1729-33.
13. Limaye AP, Raghu G, Koelle DM, Ferrenberg J, Huang ML, Boeckh M. High incidence of ganciclovir-resistant CMV infection among lung transplant recipients receiving preemptive therapy. J Infect Dis 2002;185:20-7.
14. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for CMV retinitis. N Engl J Med 2002;346:1119-26.
15. Matthews T, Boehme R. Antiviral activity and mechanism of action of ganciclovir. Rev Infect Dis 1988;10(Suppl 3):S490-4.

16. Brown F, Banken L, Saywell K, Arum I. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. Clin Pharmacokinet 1999;37:167-76.
17. Pescovitz MD, Rabkin J, Merion RM, et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrob Agents Chemother 2000; 44(10):2811-2815.
18. Pescovitz MD, Pruett TL, Gonwa T, et al. Oral ganciclovir dosing in transplant recipients and dialysis patients based on renal function. Transplantation 1998;66:1104-7.
19. Lee VH. Membrane transporters. Eur J Pharm Sci 2000; 11(Suppl 2):S41-50.
20. Ganapathy ME, Huang W, Wang H, Ganapathy V, Leibach FH. Valacyclovir: a substrate for the intestinal and renal peptide transporters PEPT1 and PEPT2. Biochem Biophys Res Commun 1998;19:470-5.
21. Sinko PJ, Balimane PV. Carrier-mediated intestinal absorption of valacyclovir, the L-valyl ester prodrug of acyclovir: 1. Interactions with peptides, organic anions and organic cations in rats. Biopharm Drug Dispos 1998;19:209-17.
22. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV- seropositive subjects. J Clin Pharmacol 1999;39:800-4.
23. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of CMV disease in solid organ transplant recipients. Am J Transplant 2004;4:611-20.
24. Ciancio G, Burke GW, Mattiazzi A, et al. CMV prophylaxis with valganciclovir in kidney, pancreas-kidney, and pancreas transplantation. Clin Transplant 2004;18:402-6.
25. Balfour J, Henry H , Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of CMV disease in recipients of renal allografts. N Engl J Med 1989;320:1381-8. ***For those interested in the history of CMV prophylaxis this is a seminal paper demonstrating for the first time that oral medication could accomplish this goal.*
26. Humar A, Paya C, Pescovitz MD, et al. Clinical utility of CMV viral load testing for predicting CMV disease in D+/R– solid organ transplant recipients. Am J Transplant 2004;4:644-9.
27. Humar A, Mazzulli T, Moussa G, et al. Clinical utility of CMV serology testing in high-risk CMV D+/R– transplant recipients. Am J Transplant 2005;5:1065-70.
28. Keven K, Basu A, Tan HP, et al. CMV prophylaxis using oral ganciclovir or valganciclovir in kidney and pancreas-kidney transplantation under antibody preconditioning. Transplant Proc 2004;36:3107-12.
29. Gabardi S, Magee CC, Baroletti SA, Powelson JA, Cina JL, Chandraker AK. Efficacy and safety of low-dose valganciclovir for prevention of CMV disease in renal transplant recipients: a single-center, retrospective analysis. Pharmacotherapy 2004;24:1323-30.
30. Taber DJ, Ashcraft E, Baillie GM, et al. Valganciclovir prophylaxis in patients at high risk for the development of CMV disease. Transpl Infect Dis 2004;6:101-9.
31. Akalin E, Sehgal V, Ames S, et al. CMV disease in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis. Am J Transplant 2003;3:731-5.
32. Zamora MR, Nicolls MR, Hodges TN, et al. Following universal prophylaxis with intravenous ganciclovir and CMV immune globulin, valganciclovir is safe and effective for prevention of CMV infection following lung transplantation. Am J Transplant 2004;4:1635-42.
33. Doyle AM, Warburton KM, Goral S, Blumberg E, Grossman RA, Bloom RD. 24-week oral ganciclovir prophylaxis in kidney recipients is associated with reduced symptomatic CMV disease compared to a 12-week course. Transplantation 2006;81:1106-11. **The best available data suggesting that longer term prophylaxis will have an added benefit for CMV prophylaxis.*
34. Spector SA, McKinley GF, Lalezari JP, et al. Oral ganciclovir for the prevention of CMV disease in persons with AIDS. N Engl J Med 1996;334:1491-7.
35. Gruber SA, Garnick J, Morawski K, et al. CMV prophylaxis with valganciclovir in African American renal allograft recipients based on donor/recipient serostatus. Clin Transplant 2005;19:273-8.
36. Park JM, Lake KD, Arenas JD, Fontana RJ. Efficacy and safety of low-dose valganciclovir in the prevention of CMV disease in adult liver transplant recipients. Liver Transpl 2006;12:112-6.
37. Wiltshire H, Hirankarn S, Farrell C, et al. Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. Clin Pharmacokinet 2005;44:495-507. ******** *This and the following paper provide the most up to date analysis of the pharmacokinetic and pharmacodynamic analysis of ganciclovir in transplant patients.*
38. Wiltshire H, Paya CV, Pescovitz MD, et al. Pharmacodynamics of oral ganciclovir and valganciclovir in solid organ transplant recipients. Transplantation 2005;79:1477-83. ***See previous comment.*
39. Cochrane AB. Antiviral dosing and efficacy for prophylaxis of CMV disease in solid organ transplant recipients. Am J Health Syst Pharm 2006;63(Suppl 5):S17-21.
40. Singh N, Wannstedt C, Keyes L, Gayowski T, Wagener MM, Cacciarelli TV. Efficacy of valganciclovir administered as preemptive therapy for CMV disease in liver transplant recipients: impact on viral load and late-onset CMV disease. Transplantation 2005;79:85-90.
41. Boivin G, Goyette N, Gilbert C, et al. Absence of CMV -resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. J Infect Dis 2004;189:1615-8.
42. Boivin G, Goyette N, Gilbert C, Covington E. Analysis of CMV DNA polymerase (UL54) mutations in solid organ transplant patients receiving valganciclovir or ganciclovir prophylaxis. J Med Virol 2005;77:425-9.
43. Pescovitz MD, Brook B, Leapman SB, Milgrom ML, Filo RS. Oral ganciclovir in pediatric transplant recipients: a pharmacokinetic study. Clin Transplant 1997;11:613-7.
44. Trang JM, Kidd L, Gruber W, et al. Linear single-dose pharmacokinetics of ganciclovir in newborns with congenital CMV infections. Clin Pharmacol Ther 1993;53:15-21.
45. Filler G, Lampe D, von Bredow MA. Prophylactic oral ganciclovir after renal transplantation-dosing and pharmacokinetics. Pediatr Nephrol 1998;1998:6-9.
46. Frenkel LM, Capparelli EV, Dankner WM, et al. Oral ganciclovir in children: pharmacokinetics, safety, tolerance, and antiviral effects. The Pediatric AIDS Clinical Trials Group. J Infect Dis 2000;182:1616-24.
47. Clark BS, Chang IF, Karpen SJ, et al. Valganciclovir for the prophylaxis of CMV disease in pediatric liver transplant recipients. Transplantation 2004;77:1480. **One of only a few publications documenting the efficacy of valganciclovir in children.*
48. Danziger-Isakov LA, Faro A, Sweet S, et al. Variability in standard care for CMV prevention and detection in pediatric lung transplantation: survey of eight pediatric lung transplant programs. Pediatr Transplant 2003;7:469-73.