Trends in Transplant. 2008;2:92-100

# Optimal Length of Valganciclovir Prophylaxis after Solid Organ Transplantation

*Albert J. Eid[1,4], Carlos V. Paya[2] and Raymund R. Razonable[1-3]*

*[1]Division of Infectious Diseases, [2]Department of Medicine and [3]William J. von Liebig Transplant Center, Mayo Clinic College of Medicine, Rochester, MN, USA; [4]Division of Infectious Diseases, University of Kansas Medical Center, Kansas City, KS, USA*

## Abstract

**Purpose:** ***Valganciclovir is the most commonly used drug for prophylaxis against cytomegalovirus after solid organ transplantation. In this article, we review the contemporary experience and clinical trial data that support the use of valganciclovir prophylaxis among solid organ transplantation populations.***

**Methods:** ***Review of clinical trials, observational studies, review articles, consensus statements, and guidelines on the use of valganciclovir prophylaxis after solid organ transplantation.***

**Results:** ***Three months of valganciclovir prophylaxis is recommended to all cytomegalovirus donor-positive/recipient-negative kidney, pancreas, heart, and liver transplant recipients. Based on an expert panel consensus, valganciclovir prophylaxis may be prolonged to ≥ 6 months in cytomegalovirus recipient-positive and cytomegalovirus donor-positive/recipient-negative lung transplant recipients. As an alternative to preemptive therapy, three months of valganciclovir prophylaxis is also recommended to cytomegalovirus recipient-positive kidney, pancreas, heart, and liver transplant recipients; this approach has resulted in an almost complete prevention of cytomegalovirus disease in cytomegalovirus recipient-positive solid organ transplant recipients. In contrast, cytomegalovirus donor-positive/recipient-negative solid organ transplant recipients remain at increased risk of primary cytomegalovirus disease, albeit at a delayed onset after transplantation. The emergence of delayed-onset cytomegalovirus disease in roughly 25% of cytomegalovirus donor-positive/recipient-negative solid organ transplant recipients raises the question on the optimal duration of prophylaxis in high-risk transplant populations. Preliminary data from single-center studies suggest that prolonging the duration to six months further reduces the incidence of cytomegalovirus disease in cytomegalovirus donor-positive/recipient-negative kidney recipients, although the safety of this approach in terms of drug toxicity and resistance is yet to be prospectively evaluated. In this regard, there is an ongoing clinical trial comparing 100 versus 200 days of***

**Correspondence to:**
Raymund R. Razonable
Division of Infectious Diseases
Mayo Clinic College of Medicine
200 First Street SW
Rochester, MN, 55905 USA
E-mail: razonable.raymund@mayo.edu

***valganciclovir prophylaxis in cytomegalovirus donor-positive/recipient-negative kidney transplant recipients and this is anticipated to provide guidance as to the optimal duration of valganciclovir prophylaxis in this high-risk population.***

**Conclusions:** ***The optimal duration of valganciclovir prophylaxis is variable, depending on the cytomegalovirus donor/recipient status, type of organ transplanted, risk of allograft rejection, and intensity of immunosuppression. Our continued effort to redefine the optimal duration of valganciclovir prophylaxis is anticipated to lead to better management and outcome of solid organ transplant recipients.*** **(Trends in Transplant. 2008;2:92-100)**

*Corresponding author: Raymund R. Razonable, razonable.raymund@mayo.edu*

## Key words

***Valganciclovir. Antiviral prophylaxis. Solid organ transplantation. Outcome. Cytomegalovirus.***

## Introduction

Since the advent of transplantation, cytomegalovirus (CMV) has remained as the single most common pathogen that has influenced clinical outcome[1]. Cytomegalovirus causes direct clinical illness, manifested as fever, myelosuppression, and tissue-invasive disease. In the absence of antiviral prophylaxis, these direct CMV effects occur most commonly during the first three months after solid organ transplantation. Through indirect and immunomodulatory mechanisms, CMV also increases the risk of allograft dysfunction and other opportunistic infections. The risk of developing the direct and indirect effects of CMV is highest among CMV-seronegative recipients of solid allografts from CMV-seropositive donors (CMV $D^+/R^-$) and among CMV-seropositive transplant recipients receiving lymphocyte-depleting drugs such as muromonab-CD3[1].

The two major strategies for preventing CMV disease after solid organ transplantation are: (i) antiviral prophylaxis, which provides antiviral drugs to all patients at risk of CMV disease; and (ii) preemptive therapy, which entails the administration of antiviral drugs when CMV is detected on routine surveillance using polymerase chain reaction or phosphoprotein 65 antigenemia. Several meta-analyses have demonstrated that both strategies are highly effective in preventing CMV disease[2-4]. However, antiviral prophylaxis is currently the preferred method of CMV prevention, particularly among CMV $D^+/R^-$ solid organ transplant recipients who have the highest risk of developing CMV disease. Antiviral prophylaxis also provides the added benefits of lower mortality rates and lower incidence of opportunistic infections[3].

In this review, we provide an overview of the contemporary practice of anti-CMV prophylaxis in solid organ transplantation, with particular emphasis on the most commonly used drug – valganciclovir. In the process, we highlight the evolving need to re-define the optimal duration of valganciclovir prophylaxis in solid organ transplant recipients.

## The evolution of cytomegalovirus prophylaxis: searching for the optimal drug and duration

The practice of antiviral prophylaxis after solid organ transplantation has evolved over the years. Acyclovir, a guanosine analog inhibitor of viral DNA polymerase, was the first antiviral drug used for anti-CMV prophylaxis after kidney[5,6], pancreas[5,6], heart[7], and liver[8] transplantation, with modest and inconsistent efficacy. While some studies showed that oral acyclovir was efficacious for CMV prevention after kidney transplantation[5,6],

other studies did not show any beneficial effect[9]. In general, oral acyclovir lacked efficacy for CMV prevention after liver transplantation[8,10], especially in CMV $D^+/R^-$ patients. The modest efficacy of acyclovir seemed related to systemic drug exposure[11]. Hence, its prodrug valacyclovir, which provides higher bioavailability, was demonstrated to be highly efficacious for preventing CMV disease after kidney transplantation[12]. Some studies even demonstrated comparable efficacy between valacyclovir and ganciclovir after kidney (but not after liver, heart, and lung) transplantation[13,14].

Ganciclovir, a guanosine analog inhibitor of viral DNA polymerase, is highly active against CMV *in vitro*[15] and generally provides better efficacy when compared to acyclovir in the prevention of CMV disease after solid organ transplantation[16,17]. However, when given for only 14 days, intravenous (IV) ganciclovir was not effective in reducing the incidence of CMV disease in a cohort of CMV $D^+/R^-$ kidney transplant recipients[18,19]. Prolonging the duration of IV ganciclovir prophylaxis to 28 days resulted in better efficacy among CMV $R^+$ heart recipients, but not CMV $D^+/R^-$ heart/lung recipients and CMV $R^+$ lung recipients[20]. The results of these studies suggested that prophylaxis for longer than 28 days may be necessary for preventing CMV disease, at least among high-risk CMV $D^+/R^-$ solid organ transplant populations. These clinical observations reflect the natural history of CMV disease, which traditionally occurs during the first three months after transplantation[12].

Subsequent clinical trials have therefore extended the duration of prophylaxis to three months after solid organ transplantation[21-23]. The administration of IV ganciclovir for 90-100 days reduced the incidence of CMV disease in CMV $D^+/R^-$ liver transplant recipients to 5.4% (compared to 40% in patients who received < 7 weeks of prophylaxis)[24]. The major drawback to IV ganciclovir, however, was the need for long-term vascular access and the associated risks of thrombosis, phlebitis, and line-associated infections. When the oral formulation of ganciclovir became available, it was demonstrated that when given for three months, it reduced the incidence of CMV infection (75 vs. 45%; $p < 0.05$) and disease (60 vs. 29%; $p < 0.05$) among CMV $D^+/R^-$ kidney recipients[23]. Compared to placebo, oral ganciclovir given for 98 days reduced the six-month incidence of CMV infection (51.5 vs. 24.5%; $p < 0.001$) and CMV disease (19 vs. 5%; $p < 0.001$) in liver recipients[21], including CMV $D^+/R^-$ patients (44 vs. 15%; $p = 0.02$) and patients who received antilymphocyte antibodies (33 vs. 5%; $p = 0.002$)[21]. Among the lower-risk CMV $R^+$ liver recipients, oral ganciclovir for 12 weeks reduced the incidence of CMV disease to 1% (compared to 7% among patients who received acyclovir)[25].

The poor bioavailability of oral ganciclovir, however, results in low systemic levels that have been postulated to facilitate the emergence of drug-resistant CMV. Its L-valyl ester, valganciclovir, circumvents this by providing 60% bioavailability[26]. Pharmacokinetic studies indicate that standard valganciclovir dosing achieves a similar daily area under the concentration time curve ($AUC_{24}$) as the standard dose of IV ganciclovir[27]. In a landmark randomized, prospective, multicenter study that compared valganciclovir (900 mg daily) and oral ganciclovir (1 gm three-times daily) prophylaxis for 100 days in a cohort of 364 solid organ transplant recipients (referred to as the PV16000 trial), the incidences of CMV disease at six months (12.1 vs. 15.2%) and 12 months (17.2 vs. 18.2%) were comparable between valganciclovir or oral ganciclovir, respectively[22]. Moreover, there was a lower incidence of viremia during prophylaxis, longer time-to-viremia, and lower peak viral load in the valganciclovir group[22]. Supported by this clinical data and its pharmacokinetic profile, valganciclovir has emerged as the most commonly used drug for antiviral prophylaxis after solid organ transplantation[28].

The evolution of antiviral prophylaxis after solid organ transplantation has also seen the use of CMV hyperimmune globulin, alone or in combination with antiviral drugs. A recent meta-analysis, however, failed to show significant benefit in terms of CMV disease prevention, although it was associated with reduced mortality[29]. Foscarnet and cidofovir, both acting as inhibitors of viral DNA polymerase, are highly active *in vitro* against

**Table 1. Estimated incidence of CMV disease in various solid organ transplant recipients**

| | CMV $D^+/R^-$ | | CMV $R^+$ | |
|---|---|---|---|---|
| **Type of transplant** | **No prophylaxis** | **With prophylaxis*** | **No prophylaxis** | **With prophylaxis*** |
| Kidney and/or pancreas | 45-65% | 6-29% | 8-10% | 1-2% |
| Liver | 45-65% | 6-29% | 8-19% | 4-13% |
| Heart | 29-74% | 19-30% | 20-40% | 2% |
| Lung and lung/heart | 50-91% | 36-40%*<br>10%† | 35-59% | 10%*<br>< 5%† |

CMV: cytomegalovirus; $D^+/R^-$: donor positive, recipient negative; $R^+$, recipient positive. Data were estimated based on clinical trials and retrospective and observational studies, as discussed in the text[22,32,35,38,42,53,55].
*Prophylaxis given for a duration of 3 months unless otherwise indicated (†indicates 6 months of prophylaxis after lung transplantation). CMV disease in patients who received prophylaxis generally occurs after the completion of antiviral prophylaxis (delayed-onset CMV disease).

CMV, but the risk of associated nephrotoxicity has limited their use in solid organ transplantation. Antiviral prophylaxis continues to evolve, as illustrated by the ongoing clinical trial of maribavir, a novel anti-CMV drug that acts as a UL97 kinase inhibitor, for the prevention of primary CMV disease after liver transplantation.

## Valganciclovir prophylaxis after kidney and pancreas transplantation

In the absence of antiviral prophylaxis, it is estimated that 8-32% of all kidney recipients and up to 50% of all pancreas recipients will develop CMV infection and disease after transplantation[30]. With three months of valganciclovir prophylaxis, the estimated incidence has been reduced to 2.9-17% (Table 1)[31,32].

The risk of CMV disease is primarily dependent on the CMV donor and recipient serologic status. In the absence of antiviral prophylaxis, the incidence of CMV disease among CMV $R^+$ kidney/pancreas recipients is estimated at 10%. This incidence has been reduced to 1% among CMV $R^+$ kidney recipients who received three months of antiviral (valacyclovir) prophylaxis[12]. Valganciclovir has not been rigorously studied in CMV $R^+$ kidney/pancreas recipients; however, it is believed to be highly effective in preventing CMV disease in this population. Currently, as an alternative to preemptive therapy, valganciclovir prophylaxis for three months is recommended for the prevention of CMV disease in CMV $R^+$ kidney/pancreas recipients.

In the absence of anti-CMV prophylaxis, CMV $D^+/R^-$ kidney/pancreas recipients have a higher estimated incidence of CMV disease (45-65%)[5,12]. Because of this high risk of CMV disease, it is recommended that CMV $D^+/R^-$ kidney/pancreas recipients receive valganciclovir prophylaxis for three months after transplantation[33]. This recommendation is supported by findings of the PV16000 trial, which included 132 kidney and/or pancreas recipients[22]. In subgroup analysis, kidney and pancreas recipients who received valganciclovir for three months had a lower six-month incidence of CMV disease compared to those who received oral ganciclovir prophylaxis (6 vs. 23% for kidney recipients, and 0 vs. 17% for kidney/pancreas recipients, respectively)[22].

Several retrospective studies have confirmed that valganciclovir prophylaxis for three months reduced the incidence of CMV disease in CMV $D^+/R^-$ kidney/pancreas recipients, although not to the same extent as demonstrated in the PV16000 trial[34]. Most retrospective studies have reported that 25-30% of CMV $D^+/R^-$ kidney/pancreas recipients who received three months of valganciclovir prophylaxis develop delayed-onset primary CMV disease[35,36]. Allograft rejection, presence of medical comorbidities, and the occurrence of bacterial and fungal infections predispose to the development of delayed-onset

primary CMV disease[35]. Moreover, delayed-onset CMV disease has been associated with allograft loss and mortality after kidney transplantation[35].

To this end, an important question is raised: What is the optimal length of valganciclovir prophylaxis to prevent CMV disease? Will prolongation of valganciclovir prophylaxis beyond the standard three months duration result in further reduction in CMV disease incidence without a corresponding increase in associated risk? To address this issue, a randomized clinical trial is being conducted to evaluate the efficacy and safety of 100 vs. 200 days of valganciclovir prophylaxis in CMV $D^+/R^-$ kidney recipients. While the results of this clinical trial are eagerly awaited, the findings of recent single-center trials may foreshadow the anticipated outcome. In one of these studies, the incidence of CMV disease was significantly further reduced among CMV $D^+/R^-$ kidney recipients who received 24 weeks compared to 12 weeks of oral ganciclovir prophylaxis (6.5 vs. 31%, respectively)[37]. In another study, prolonging valganciclovir prophylaxis from three to six months led to a further decline in incidence of CMV disease from 25 to 5% among thymoglobulin-treated kidney recipients[38]. However, as some transplant centers are now adapting a more prolonged prophylactic approach in high-risk CMV $D^+/R^-$ kidney and pancreas recipients[37-38], one should be cautious as to its potential risks such as the adverse effects of bone marrow suppression and the possible emergence of difficult-to-manage and sometimes fatal drug-resistant CMV[39,40].

## Valganciclovir prophylaxis after liver transplantation

In the absence of anti-CMV prophylaxis, the overall estimated incidence of CMV disease after liver transplantation is 22-29%[21,30]. However, the incidence can be as high as 45-65% among CMV $D^+/R^-$ liver recipients, or as low as 8-19% among CMV $R^+$ liver recipients who are not receiving antiviral prophylaxis[21]. Valganciclovir and oral ganciclovir prophylaxis have significantly reduced the incidence of CMV disease in all CMV $D^+/R^-$ and CMV $D/R^+$ serogroups. However, based on the results of the PV16000 trial[22], the efficacy of valganciclovir prophylaxis in liver recipients appears to be significantly less compared to kidney, pancreas, and heart recipients[22]. Additionally, there is an ongoing debate as to which of the drugs (valganciclovir or oral ganciclovir) is more effective for CMV disease prevention among CMV $D^+/R^-$ liver recipients. Among 177 CMV $D^+/R^-$ liver recipients who participated in the PV16000 trial, the six-month incidence of CMV disease was 19% in the valganciclovir group compared to 12% in the oral ganciclovir group[22]. As a result, the U.S. Food and Drug Administration (FDA) did not approve of the use of valganciclovir prophylaxis in CMV $D^+/R^-$ liver recipients. Nonetheless, a survey of transplant centers across the USA and Canada showed that valganciclovir is the most common drug used for CMV prophylaxis after liver transplantation[28].

Several single-center studies have estimated that CMV disease occurs in up to 30% of CMV $D^+/R^-$ liver recipients after they complete three months of valganciclovir prophylaxis (i.e. delayed-onset CMV disease) (Table 1)[41,42]. In one retrospective study, CMV disease was observed in 14 of 54 (26%) CMV $D^+/R^-$ liver recipients who received at least three months of valganciclovir prophylaxis[43]. Our clinical experience also suggests that, while no breakthrough CMV disease occurred during valganciclovir prophylaxis, about 29% of CMV $D^+/R^-$ liver recipients will eventually develop CMV disease at a delayed onset (between 3-6 months) after liver transplantation[42]. Studies have reported that age, female gender, renal dysfunction, and allograft rejection predisposes to the development of delayed-onset primary CMV disease (Table 2)[41,42,44,45]. Delayed-onset CMV disease has also been significantly associated with mortality after liver transplantation[46]. Hence, a better strategy for CMV prevention is warranted.

Among CMV $R^+$ liver recipients, oral ganciclovir prophylaxis has reduced the incidence of CMV disease from 8-19% to less than 4%[21], suggesting that a three-month duration of oral

ganciclovir prophylaxis is likely sufficient in CMV $R^+$ liver recipients. However, clinical data suggest that the efficacy of valganciclovir in preventing CMV disease in CMV $R^+$ liver recipients is also possibly less when compared to oral ganciclovir. While valganciclovir has not been subjected to rigorous controlled clinical trials in CMV $R^+$ liver recipients, one observational study demonstrated that 13% of CMV $R^+$ liver recipients, especially the CMV $D^+/R^+$ group, developed CMV infection and disease, despite three months of valganciclovir prophylaxis[43].

## Valganciclovir prophylaxis after heart and lung transplantation

The risk of CMV infection and disease after thoracic organ transplantation varies, depending on the organ transplanted and the CMV D/R serostatus. In the absence of antiviral prophylaxis, it is estimated that up to 75% of lung recipients[47] and 21-50% of heart recipients develop CMV disease[30]. As in other solid organ transplant groups, the risk of CMV disease is highest among CMV $D^+/R^-$ patients (Table 1), and the use of valganciclovir or oral and IV ganciclovir has significantly reduced the incidence of CMV disease among thoracic organ transplant recipients.

The current guidelines recommend three months of valganciclovir to all CMV $D^+/R^-$ patients and, as an alternative to preemptive therapy, to CMV $R^+$ heart recipients. In a subgroup analysis of the 56 CMV $D^+/R^-$ heart recipients that participated in the PV16000 trial, the six-month incidence of CMV disease was 6% in the valganciclovir group and 10% in the ganciclovir group[22]. However, as with other CMV $D^+/R^-$ solid organ transplant groups, the incidence of delayed-onset primary CMV disease that is seen in clinical practice (i.e. outside of the controlled clinical trial setting) is estimated at 30% of all CMV $D^+/R^-$ heart recipients, with almost all cases occurring after the completion of three months of valganciclovir prophylaxis (i.e. delayed-onset CMV disease)[48]. Acute rejection enhances the risk of developing CMV disease, despite valganciclovir prophylaxis (Table 2)[48].

**Table 2. Risk factors for delayed onset cytomegalovirus disease in solid organ transplant recipients**

| |
|---|
| 1. CMV $D^+/R^-$ serostatus |
| 2. Acute allograft rejection |
| 3. Over-immunosuppression |
| 4. Female gender |
| 5. Comorbidity |
| 6. Renal insufficiency |
| 7. Bacterial infection |
| 8. Fungal infection |

CMV: cytomegalovirus; $D^+/R^-$: donor positive and recipient negative serostatus.

In contrast to the other solid organ transplant populations, clinical studies suggest that a longer period of valganciclovir prophylaxis is necessary for the prevention of CMV disease in CMV $D^+/R^-$ and CMV $R^+$ lung and heart/lung transplant recipients[47,49-52]. Indeed, despite 12 weeks of valganciclovir or oral and IV ganciclovir prophylaxis, the incidence of CMV infection and disease remains high among lung recipients. In one study of CMV $D^+/R^-$ and $R^+$ lung recipients that compared valganciclovir vs. IV ganciclovir (CMV $D^+/R^-$) or oral ganciclovir (CMV $R^+$) prophylaxis for 12 weeks, there was a comparable incidence of CMV infection (40% with valganciclovir vs. 45% with IV or oral ganciclovir) and disease (20% with valganciclovir vs. 17.5% with IV or oral ganciclovir)[53]. The high rates of CMV disease despite three months of valganciclovir prophylaxis has led other transplant centers, including ours, to prolong valganciclovir prophylaxis, especially among CMV $D^+/R^-$ lung recipients[54]. In one single-center study that assessed the optimal duration of valganciclovir prophylaxis in CMV $D^+/R^-$ and $R^+$ lung recipients, it was demonstrated that at least 180 days of valganciclovir prophylaxis was necessary to remarkably reduce the incidence of CMV infection and disease after lung transplantation[55]. Following an initial prophylaxis using a combination of CMV immunoglobulin and IV ganciclovir (for 90 days in CMV $D^+/R^-$ or 30 days in $R^+$ lung recipients), valganciclovir prophylaxis was administered for 180, 270, and 365 days.

Freedom from CMV infection and disease was significantly higher among patients who received 180 (90%), 270 (95%), or 365 (90%) days of valganciclovir prophylaxis, compared to those who received only 100-179 days (64%) or < 100 days (59%) of valganciclovir prophylaxis[55]. However, our anecdotal experience suggests that, regardless of the duration of antiviral prophylaxis, lung recipients will remain at high risk of CMV disease so long as they remain CMV-seronegative, as illustrated by a patient who developed primary CMV disease despite five years of antiviral prophylaxis[56].

## Optimal length of valganciclovir prophylaxis: balancing benefits and risks

As illustrated above, a multitude of clinical factors influence the length of valganciclovir prophylaxis after solid organ transplantation, and hence the dictum of "one size fits all" does not necessarily apply. Indeed, an individualized approach is needed to define the optimal length for each transplant recipient. The clinical factors that could influence the optimal duration of valganciclovir prophylaxis are CMV D/R serostatus, allograft rejection, use of antilymphocyte antibodies, and the net state of immunosuppression.

Based on available clinical data, CMV $R^+$ kidney, pancreas, liver, and heart recipients may be managed either with preemptive valganciclovir therapy (if the tools necessary for optimal CMV surveillance are available) or three months of valganciclovir prophylaxis. In some patients, such as those with acute rejection and those receiving lymphocyte-depleting immunosuppressive drugs, one may prolong the duration of prophylaxis on a case-by-case basis, at least until the intensity of pharmacologic immunodeficiency has been remarkably reduced. In the vast majority of CMV $R^+$ kidney, pancreas, liver, and heart recipients, three months of valganciclovir is likely sufficient to prevent CMV disease.

In contrast, the emergence of delayed-onset primary CMV disease has challenged the optimal duration of valganciclovir prophylaxis among CMV $D^+/R^-$ solid organ transplant recipients. Currently, CMV $D^+/R^-$ kidney, pancreas, liver, and heart recipients are recommended to receive at least three months of valganciclovir prophylaxis, while CMV $R^+$ and CMV $D^+/R^-$ lung recipients should receive at least six months of valganciclovir. Despite this approach, however, CMV $D^+/R^-$ solid organ transplant recipients remain at high risk of delayed-onset primary CMV disease after completion of valganciclovir prophylaxis, particularly when they remain CMV-seronegative or they are severely immunosuppressed as a result of therapy for allograft rejection. Clinical states associated with "cytokine storm", such as allograft rejection and bacterial and fungal infections, have also been associated with delayed-onset CMV disease.

Because delayed-onset CMV disease is associated with poor allograft and patient survival, one may argue to re-define the strategy for CMV prevention in this high-risk cohort. Whether this is best approached by prolonging valganciclovir prophylaxis to all at-risk patients or by a targeted approach (given only to those with defined clinical risks such as allograft rejection) remains to be evaluated. A list of known clinical factors associated with increased risk of delayed-onset CMV disease is listed in table 2. To illustrate the potential benefit of this approach, we have shown that since we have re-initiated 1-3 additional months of valganciclovir prophylaxis to CMV $D^+/R^-$ liver, kidney, and heart recipients who developed acute allograft rejection, the incidence of CMV disease has been reduced in this group. Using this example, one may find it reasonable to extend the duration of valganciclovir prophylaxis to a period of less intense immunosuppression.

Currently, the randomized clinical trial comparing standard (100 days) vs. prolonged (200 days) duration of valganciclovir prophylaxis in CMV $D^+/R^-$ kidney recipients is about to be completed. It is anticipated that this trial will advance clinical practice by defining better strategies for CMV prevention. We anticipate that this prolonged prophylaxis approach will lead to further reduction of CMV disease. However, this will not likely lead to complete protection against CMV disease since CMV $D^+/R^-$ solid organ transplant recipients and those

who have absent or deficient CMV-specific T-cell immunity[57] will remain at risk of CMV disease during the posttransplant period as long as they remain CMV-seronegative or severely immunosuppressed. Importantly, it will be important to assess the additional risks associated with prolonging valganciclovir prophylaxis, in terms of drug resistance[40] and adverse effects such as leucopenia and neutropenia[39].

## Conclusion

Valganciclovir prophylaxis is the most common method for the prevention of CMV disease after solid organ transplantation. Clinical evidence suggests that three months of valganciclovir prophylaxis is highly efficacious in CMV disease prevention, especially among CMV $R^+$ kidney, pancreas, liver, and heart recipients. However, CMV $D^+/R^-$ solid organ transplant recipients remain at high risk of delayed-onset primary CMV disease despite three months of valganciclovir prophylaxis. This emergence of delayed-onset CMV disease challenges the current clinical practice and raises the important question: What is the optimal length of valganciclovir prophylaxis? Prolonging the duration of valganciclovir prophylaxis to a period of less intense (i.e. minimal) immunosuppression could theoretically protect patients from delayed-onset CMV disease. In this regard, one should consider the CMV D/R status, the type of organ transplanted, the ongoing risk of rejection, and the intensity of immunosuppression in defining the optimal duration of valganciclovir prophylaxis. It is anticipated that our ongoing search for the optimal length of valganciclovir prophylaxis will lead to better management and outcome of our most vulnerable solid organ transplant recipients.

## Acknowledgements

Research support to Raymund R Razonable from Department of Medicine, and the William J von Liebig Transplant Center.

## References

1. Razonable RR, Paya CV. Herpesvirus infections in transplant recipients: current challenges in the clinical management of CMV and Epstein-Barr virus infections. Herpes. 2003;10:60-5.
2. Hodson EM, Jones CA, Webster AC, et al. Antiviral medications to prevent CMV disease and early death in recipients of solid-organ transplants: a systematic review of randomized controlled trials. Lancet. 2005;365:2105-15. **This meta-analysis of randomized clinical trials demonstrated the benefits of antiviral drugs for prophylaxis against CMV disease in solid organ transplant recipients. A reduction in all-cause mortality was also demonstrated in patients receiving antiviral prophylaxis.*
3. Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by CMV in solid organ transplant recipients. Ann Intern Med. 2005;143:870-80. **This meta-analysis of randomized clinical trials demonstrated the benefits of antiviral drugs for prophylaxis against CMV disease in solid organ transplant recipients.*
4. Small LN, Lau J, Snydman DR. Preventing post-organ transplantation CMV disease with ganciclovir: a meta-analysis comparing prophylactic and preemptive therapies. Clin Infect Dis. 2006;43:869-80. **This meta-analysis of randomized clinical trials demonstrated the benefits of antiviral drugs for prophylaxis against CMV disease in solid organ transplant recipients.*
5. Vila A, Guirado LL, Balius A, et al. Acyclovir prophylaxis of CMV disease in kidney transplant recipients. Transplant Proc. 1999; 31:2335-6.
6. Balfour HH, 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;320:1381-7.
7. Egan JJ, Carroll KB, Yonan N, Woodcock A, Crisp A. Valacyclovir prevention of CMV reactivation after heart transplantation: a randomized trial. J Heart Lung Transplant. 2002;21:460-6.
8. Martin M, Manez R, Linden P, et al. A prospective randomized trial comparing sequential ganciclovir-high dose acyclovir to high dose acyclovir for prevention of CMV disease in adult liver transplant recipients. Transplantation. 1994;58:779-85.
9. Wong T, Lavaud S, Toupance O, et al. Failure of acyclovir to prevent CMV infection in renal allograft recipients. Transpl Int. 1993;6:285-9.
10. Badley AD, Seaberg EC, Porayko MK, et al. Prophylaxis of CMV infection in liver transplantation: a randomized trial comparing a combination of ganciclovir and acyclovir to acyclovir. NIDDK Liver Transplantation Database. Transplantation. 1997;64:66-73.
11. Fiddian P, Sabin CA, Griffiths PD. Valacyclovir provides optimum acyclovir exposure for prevention of CMV and related outcomes after organ transplantation. J Infect Dis. 2002;186(Suppl 1):S110-5.
12. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of CMV disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. N Engl J Med. 1999;340:1462-70.
13. Reischig T, Opatrny K, Bouda M, Treska V, Jindra P, Svecova M. A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of CMV disease after renal transplantation. Transpl Int. 2002;15:615-22.
14. 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.
15. Keating MR. Antiviral agents. Mayo Clin Proc. 1992;67:160-78.
16. Somerville T, Hurst G, Alloway R, Gaber A, Shokouh-Amiri MH, Stratta R. Superior efficacy of oral ganciclovir over oral acyclovir for CMV prophylaxis in kidney-pancreas and pancreas alone recipients. Transplant Proc. 1998;30:1546-8.
17. Flechner SM, Avery RK, Fisher R, et al. A randomized prospective controlled trial of oral acyclovir versus oral ganciclovir for CMV prophylaxis in high-risk kidney transplant recipients. Transplantation. 1998;66:1682-8.
18. Rondeau E, Bourgeon B, Peraldi MN, et al. Effect of prophylactic ganciclovir on CMV infection in renal transplant recipients. Nephrol Dial Transplant. 1993;8:858-62.
19. Dunn DL, Gillingham KJ, Kramer MA, et al. A prospective randomized study of acyclovir versus ganciclovir plus human immune globulin prophylaxis of CMV infection after solid organ transplantation. Transplantation. 1994;57:876-84.
20. Merigan TC, Renlund DG, Keay S, et al. A controlled trial of ganciclovir to prevent CMV disease after heart transplantation. N Engl J Med. 1992;326:1182-6.
21. Gane E, Saliba F, Valdecasas GJ, et al. Randomized 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.

22. 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. **This landmark clinical trial demonstrated the safety and efficacy of valganciclovir for the prevention of CMV disease in CMV $D^+/R^-$ liver, kidney, pancreas and heart transplant recipients. There was also benefit in terms of reduced viremia in patients receiving valganciclovir.*
23. Kletzmayr J, Kreuzwieser E, Watkins-Riedel T, Berlakovich G, Kovarik J, Klauser R. Long-term oral ganciclovir prophylaxis for prevention of CMV infection and disease in CMV high-risk renal transplant recipients. Transplantation. 2000;70:1174-80.
24. Seu P, Winston DJ, Holt CD, Kaldas F, Busuttil RW. Long-term ganciclovir prophylaxis for successful prevention of primary CMV disease in CMV-seronegative liver transplant recipients with CMV-seropositive donors. Transplantation. 1997;64:1614-7.
25. Winston DJ, Busuttil RW. Randomized controlled trial of oral ganciclovir versus oral acyclovir after induction with IV ganciclovir for long-term prophylaxis of CMV disease in CMV-seropositive liver transplant recipients. Transplantation. 2003;75:229-33.
26. Razonable RR, Paya CV. Valganciclovir for the prevention and treatment of CMV disease in immunocompromised hosts. Expert Rev Anti Infect Ther. 2004;2:27-41.
27. Pescovitz MD, Rabkin J, Merion RM, et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrob Agents Chemother. 2000;44:2811-5.
28. Levitsky J, Singh N, Wagener MM, Stosor V, Abecassis M, Ison MG. A survey of CMV prevention strategies after liver transplantation. Am J Transplant. 2008;8:158-61.
29. Hodson EM, Jones CA, Strippoli GF, Webster AC, Craig JC. Immunoglobulins, vaccines or interferon for preventing CMV disease in solid organ transplant recipients. Cochrane Database Syst Rev. 2007:CD005129.
30. Patel R, Paya CV. Infections in solid-organ transplant recipients. Clin Microbiol Rev. 1997;10:86-124.
31. Weng FL, Patel AM, Wanchoo R, et al. Oral ganciclovir versus low-dose valganciclovir for prevention of CMV disease in recipients of kidney and pancreas transplants. Transplantation. 2007;83:290-6.
32. Akalin E, Sehgal V, Ames S, et al. Cytomegalovirus disease in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis. Am J Transplant. 2003;3:731-5
33. Cytomegalovirus. Am J Transplant. 2004;4(Suppl 10):51-8. **This article presents the consensus for CMV diagnosis, prevention, and treatment, as recommended by the American Society of Transplantation Infectious Diseases Community of Practice.*
34. 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.
35. Arthurs SK, Eid AJ, Kremers W, et al. Delayed-onset primary CMV disease and the risk of allograft failure after kidney transplantation. Clin Infect Dis. 2008;46:840-6. **This study demonstrated that CMV disease, even at a delayed onset, is associated with allograft failure and mortality after kidney transplantation. Similar studies have also shown this negative impact after liver transplantation, thereby implying the need to further redefine the optimal length of valganciclovir prophylaxis.*
36. Manuel O, Venetz J, Fellay J, et al. Efficacy and safety of universal valganciclovir prophylaxis combined with a tacrolimus/mycophenolate-based regimen in kidney transplantation. Swiss Med Wkly. 2007;137:669-76.
37. 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. **Foreshadowing what may be anticipated in the ongoing clinical trial of 100 vs. 200 days of valganciclovir in CMV $D^+/R^-$ kidney recipients, this single-center study demonstrated further reduction in the incidence of CMV disease after prolonged compared to standard prophylaxis.*
38. Akalin E, Bromberg JS, Sehgal V, Ames S, Murphy B. Decreased incidence of CMV infection in thymoglobulin-treated transplant patients with 6 months of valganciclovir prophylaxis. Am J Transplant. 2004;4:148-9. **This study demonstrated that prolonging the duration of valganciclovir prophylaxis to 6 months further reduces the incidence of CMV disease in high-risk transplant recipients.*
39. Eid AJ, Razonable RR. Cytomegalovirus disease after solid organ transplantation: Advances lead to challenges and opportunities. Curr Opin Organ Transplant. 2008;12:610-17.
40. Eid AJ, Arthurs SK, Deziel P, Wilhelm MP, Razonable RR. Emergence of drug-resistant cytomegalovirus in the era of valganciclovir prophylaxis. Clin Transplant. 2008 [in press].
41. Razonable RR, Rivero A, Rodriguez A, et al. Allograft rejection predicts the occurrence of late-onset CMV disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. J Infect Dis. 2001;184:1461-4.
42. Arthurs SK, Eid AJ, Pedersen RA, et al. Delayed-onset primary CMV disease after liver transplantation. Liver Transpl. 2007;13:1703-9.
43. Jain A, Orloff M, Kashyap R, et al. Does valganciclovir hydrochloride (valcyte) provide effective prophylaxis against CMV infection in liver transplant recipients? Transplant Proc. 2005; 37:3182-6.
44. Freeman RB, Paya C, Pescovitz MD, et al. Risk factors for CMV viremia and disease developing after prophylaxis in high-risk solid-organ transplant recipients. Transplantation. 2004;78: 1765-73.
45. Limaye AP, Bakthavatsalam R, Kim HW, et al. Late-onset CMV disease in liver transplant recipients despite antiviral prophylaxis. Transplantation. 2004;78:1390-6.
46. Limaye AP, Bakthavatsalam R, Kim HW, et al. Impact of CMV in organ transplant recipients in the era of antiviral prophylaxis. Transplantation. 2006;81:1645-52.
47. Speich R, Thurnheer R, Gaspert A, Weder W, Boehler A. Efficacy and cost effectiveness of oral ganciclovir in the prevention of CMV disease after lung transplantation. Transplantation. 1999;67:315-20.
48. Kijpittayarit-Arthurs S, Eid AJ, Kremers WK, et al. Clinical features and outcomes of delayed-onset primary CMV disease in cardiac transplant recipients. J Heart Lung Transplant. 2007; 26:1019-24.
49. Perreas KG, McNeil K, Charman S, Sharples LD, Wreghitt T, Wallwork J. Extended ganciclovir prophylaxis in lung transplantation. J Heart Lung Transplant. 2005;24:583-7.
50. Gutierrez CA, Chaparro C, Krajden M, Winton T, Kesten S. Cytomegalovirus viremia in lung transplant recipients receiving ganciclovir and immune globulin. Chest. 1998;113:924-32.
51. Valantine HA, Luikart H, Doyle R, et al. Impact of CMV hyperimmune globulin on outcome after cardiothoracic transplantation: a comparative study of combined prophylaxis with CMV hyperimmune globulin plus ganciclovir versus ganciclovir alone. Transplantation. 2001;72:1647-52.
52. Weill D, Lock BJ, Wewers DL, et al. Combination prophylaxis with ganciclovir and CMV immune globulin after lung transplantation: effective CMV prevention following daclizumab induction. Am J Transplant. 2003;3:492-6.
53. Humar A, Kumar D, Preiksaitis J, et al. A trial of valganciclovir prophylaxis for CMV prevention in lung transplant recipients. Am J Transplant. 2005;5:1462-8. **This multicenter study from Canada demonstrated that valganciclovir is as effective as IV or oral ganciclovir for the prevention of CMV disease in lung transplant recipients.*
54. Zamora MR, Davis RD, Leonard C. Management of CMV infection in lung transplant recipients: evidence-based recommendations. Transplantation. 2005;80:157-63. **This is the consensus statement from a panel of experts. The experts recommended, based on evaluation of clinical trials and data, that valganciclovir for 6 months is needed for the prevention of CMV disease in at-risk lung transplant recipients.*
55. 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. **This single-center study from Colorado demonstrated that valganciclovir prophylaxis is effective for the prevention of CMV disease in lung transplant recipients so long as it is administered for at least 180 days (6 months).*
56. Kijpittayarit S, Deziel P, Eid AJ, Razonable RR. Primary CMV disease after five years of antiviral prophylaxis. Transplantation. 2006;81:137-8.
57. Sester M, Sester U, Gartner B, et al. Levels of virus-specific CD4 T cells correlate with CMV control and predict virus-induced disease after renal transplantation. Transplantation. 2001;71:1287-94.