

# Valganciclovir for the prophylaxis and treatment of cytomegalovirus infection in solid organ transplantation

Erin Wade Ticehurst<sup>1</sup>

Jennifer Trofe-Clark<sup>1,2</sup>

Emily Blumberg<sup>3</sup>

Roy D Bloom<sup>2</sup>

<sup>1</sup>Department of Pharmacy Services, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; <sup>2</sup>Renal Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; <sup>3</sup>Infectious Diseases Division, University of Pennsylvania, Philadelphia, Pennsylvania, USA

**Abstract:** Cytomegalovirus (CMV) can be a problematic virus for solid organ transplant recipients affecting both morbidity and mortality. Valganciclovir (VGC) is a commonly utilized antiviral agent for the prevention of this virus post-transplantation and recently it has been evaluated for the treatment of CMV. It is a pro-drug of ganciclovir (GCV) and has increased bioavailability compared to GCV. It is unclear whether VGC is superior to intravenous or oral GCV in terms of efficacy and safety in the prevention of CMV particularly in the liver transplant population as there have been studies reporting inferiority while other studies have not. Despite this, VGC has been reported to be the most commonly utilized agent for CMV prophylaxis in the liver transplant population in the United States and Canada. This article reviews CMV and VGC in the context of solid organ transplant, describes and assesses selected studies that have been conducted using this agent in this patient population, and summarizes VGC's advantages and disadvantages. Additional studies are needed to further define VGC's role in the treatment of CMV in the solid organ transplantation population as there are an insufficient number of studies pertaining to CMV treatment and no studies have been performed to assess its role in the treatment of life-threatening CMV disease. VGC is non-inferior to GCV for CMV prevention in the solid organ transplant population with the exception of liver transplant recipients.

**Keywords:** transplant, antiviral therapy, valganciclovir

## Introduction

Cytomegalovirus (CMV), a commonly occurring virus in the general population, can have a negative impact on morbidity and mortality following solid organ transplantation.<sup>1,2</sup> Although CMV infection is usually asymptomatic in the general population,<sup>3</sup> the effects on the solid organ transplant recipient can be variable, ranging from asymptomatic viral shedding to fever and malaise, or symptomatic tissue-invasive disease. Indirect effects result from viral promotion of enhanced immunosuppression with subsequent development of other infections and post-transplant lymphoproliferative disorder and allograft rejection.<sup>1,4-7</sup> This paper will review the use of valganciclovir (VGC) in the solid organ transplant population for the prevention and treatment of CMV infection and disease.

CMV is a member of the human herpesvirus family and the beta subfamily.<sup>8</sup> The various modes of transmission include blood transfusions, sexual contact, transplacental, and direct contact with bodily secretions such as urine, breast milk, and saliva.<sup>3,9,10</sup> Transplanted organs can transmit the virus from the donor to the recipient.<sup>10,11</sup> Both the organ donor and the recipient of the transplanted organ are tested to determine

Correspondence: Erin Wade Ticehurst  
Department of Pharmacy Services,  
Hospital of the University of Pennsylvania,  
3400 Spruce Street, Philadelphia,  
Pennsylvania 19104, USA  
Tel +1 215-615-8022  
Fax +1 215-615-3814  
Email erin.ticehurst@uphs.upenn.edu

CMV serostatus prior to transplantation by determining the presence of immunoglobulin G and M antibody to CMV which is consistent with prior infection.<sup>3,5</sup>

The course of CMV infection following transmission is largely affected by the level of competency of the host immune system. In the immunocompetent host, clinical infection or disease is rare following transmission however the virus typically remains latent in the host cells.<sup>6,12,13</sup> This is not the case in the solid organ transplant recipient however. As reported by Paya and colleagues, nearly half of all recipients who were seronegative prior to transplant and who received an organ from a seropositive donor will develop CMV viremia within 12 months of the transplant and in the majority of cases the onset of viremia occurs after antiviral prophylaxis is discontinued.<sup>14</sup>

CMV infection in the solid organ transplant recipient can be classified as primary infection, reactivation or superinfection. Primary infection refers to new transmission of the virus to a seronegative organ recipient (R–), either from a

seropositive organ donor (D+), a blood transfusion, or a source within the community such as any of the modes of transmission described previously. Reactivation refers to a seropositive organ recipient's latent virus becoming active. Superinfection refers to a seropositive organ recipient becoming infected with a strain of CMV from the donor that is different than the strain they were latently infected with prior to transplant.<sup>5,15</sup> Unfortunately, there are no standardized definitions for CMV infection or disease. Therefore, various definitions as well as terminology have been applied across clinical trials. In an effort to resolve this issue, in 2006 the American Society of Transplantation published proposed definitions for CMV infection and disease in organ transplant recipients for use in reporting infectious complications in immunosuppression clinical trials.<sup>16</sup> The definitions are summarized in Table 1, and were modified from several sources<sup>5,15,17</sup> including the American Society of Transplantation Infectious Disease Guidelines<sup>5</sup> and the Canadian Society of Transplantation consensus conference on CMV.<sup>15</sup>

**Table 1** American Society of Transplantation proposed definitions of CMV infection and disease in solid organ transplant recipients<sup>16</sup>

Terminology	Definition
CMV active infection	Replicative infection that can be diagnosed by growing the virus in vitro, finding evidence of viral infection by intra-cytoplasmic or intra-nuclear inclusions or by antibody-based staining techniques for CMV in histopathologic sections or finding evidence of replication using nucleic acid based assays or antigenemia studies.
CMV disease	Evidence of CMV infection with attributable symptoms. Sub-divided into probable and definite CMV viral syndrome and tissue invasive disease, respectively.
Probable CMV syndrome	Characterized by one or more of the following: 1) Fever >38 °C for at least 2 days 2) New or increased malaise 3) Leukopenia 4) ≥5% atypical lymphocytes 5) Thrombocytopenia (threshold not defined) 6) Elevation of hepatic transaminases (ALT or AST) to 2 times the upper limit of normal (applicable to nonliver transplant recipients) Plus Evidence of CMV in blood by viral culture, antigenemia or a DNA/RNA based assay.
Definite CMV syndrome	Clinical and laboratory findings associated with probable CMV viral syndrome and no other cause of symptoms/signs identified.
Probable CMV tissue invasive disease	The occurrence of pneumonia, gastrointestinal disease, hepatitis, central nervous system disease, or other sites (such as nephritis, cystitis, myocarditis and pancreatitis) Plus Evidence of CMV in the blood and/or tissue (detected by viral culture, antigenemia, or a DNA/RNA based assay), often in the absence of other documented causes.
Definite CMV tissue invasive disease	Clinical and laboratory findings associated with probable CMV tissue invasive disease Plus Detection of CMV in tissue by culture, immunohistochemical analysis or in situ hybridization. In addition the presence of typical cytomegalovirus inclusions should be considered evidence of definite disease.

**Note:** CMV retinitis was not included as an applicable probable tissue invasive disease, but was classified as definitive disease if the lesions typical of CMV retinitis are confirmed by an ophthalmologist.

**Abbreviations:** AST, aspartate aminotransferase; ALT, alanine aminotransferase; CMV, cytomegalovirus.

The rate of CMV disease in organ recipients is influenced by many factors, including the pre-transplant donor/recipient serostatus, the immunosuppressive burden as well as the dose and duration of antiviral prophylaxis. In the era prior to routine prophylaxis, CMV disease occurred in 61% of renal transplant recipients.<sup>18</sup> In the more contemporary era, rates of CMV disease of up to 50% have been reported following pancreas or kidney-pancreas transplantation and 25% following heart, liver, and kidney transplantation.<sup>7,19</sup> The incidence of CMV disease following lung transplantation has been reported to be as high as 75%.<sup>20</sup> Rates of CMV infection and disease following solid organ transplantation vary per transplant center and this may be due to differences in immunosuppression management practices, viral monitoring and prophylaxis strategies.<sup>21</sup>

There are several risk factors for the development of CMV infection and disease in organ transplant recipients. Recipients who are CMV seronegative at the time of transplant and receive an organ from a seropositive donor are at higher risk for CMV infection than recipients who are CMV seropositive going into transplant. Other risk factors include blood transfusions, level of immunosuppression, and other host co-morbidities.<sup>5</sup>

The major purpose of antiviral prophylaxis therapy is to prevent viral reactivation and disease. It also shifts the onset of infection to later in the post-transplant period. This delay typically coincides with lower levels of immunosuppression at the time of infection for some patients, making the infection less severe and easier to treat because the host immune system is more active. Two types of CMV prevention strategies exist: pre-emptive therapy and universal prophylaxis. Preemptive therapy refers to initiating anti-CMV therapy when the viral load rises beyond a threshold value;<sup>5,15,22</sup> this method relies on regular CMV viral load monitoring. Universal prophylaxis refers to giving antiviral therapy to all patients who are at risk of CMV regardless of the degree of risk.<sup>5,15,23</sup>

There are several methods that can be utilized for CMV surveillance. Two commonly used assays are nucleic acid testing (NAT) and CMV antigenemia. NAT may be reported as positive or negative (qualitative assay) or the viral deoxyribonucleic acid (DNA) can be quantified (quantitative assay). This assay offers both high specificity and high sensitivity and is useful in assessing the level of viral activity as well as response to therapy.<sup>22,24</sup> Another test that can be helpful in identifying when a patient may require pre-emptive antiviral therapy is the antigenemia assay, an immunoassay that quantifies the amount of virus by measuring the number of white blood cells containing viral particles and offers moderate sensitivity and specificity.<sup>22</sup>

The antigenemia assay is less sensitive in patients with severe leukopenia as it requires the collection of a sufficient amount of peripheral blood neutrophils.<sup>25</sup>

## Valganciclovir

### Pharmacology

VGC is a L-valyl ester prodrug of ganciclovir (GCV) that came to market in 2001 for CMV retinitis and in 2003 was approved in the United States by the Food and Drug Administration (FDA) for CMV disease prophylaxis in seronegative heart, kidney, and kidney-pancreas transplant recipients of organs from seropositive donors.<sup>26</sup> VGC is hydrolyzed into the active drug GCV and valine.<sup>2</sup>

To exert its anti-CMV effects, GCV must enter CMV-infected cells and be phosphorylated by the viral protein UL97 kinase. The product of this reaction is GCV monophosphate which is then phosphorylated by cellular kinases thus producing GCV diphosphate and finally GCV triphosphate which is an active inhibitor of DNA polymerase.<sup>2,8,27</sup>

UL97 kinase and/or viral DNA polymerase gene (UL54) mutations can impart GCV-resistance to CMV strains.<sup>28,29</sup> Patient non-adherence and prolonged sub therapeutic ganciclovir exposure may contribute to the development of GCV-resistance.<sup>30</sup> Two other antiviral agents (cidofovir and foscarnet) are options for treating UL97 kinase mutation driven GCV-resistant CMV disease as cross-resistance to these agents would not be expected. However, it should be noted that these two agents share an unfavorable adverse effect of nephrotoxicity.<sup>5,31</sup>

### Pharmacokinetics

GCV is the only known metabolite of VGC.<sup>23</sup> Following oral administration with food the bioavailability of GCV from VGC is approximately 60% and systemic exposure to (VGC) is minimal.<sup>26,30,32</sup> The GCV area under the curve (AUC) and the maximum concentration are increased when VGC is taken with food. An increased AUC has been associated with a decreased rate of infection; therefore VGC should be administered with meals.<sup>26,33</sup>

### Dosing

The FDA-approved dose of VGC for the prevention of CMV disease in adult kidney, heart and kidney-pancreas transplant recipients with normal kidney function (creatinine clearance >60 mL/min) is 900 mg orally once daily which should be continued until 100 days post-transplant.

**Table 2** VGC dosing guidelines for patients with renal impairment<sup>26</sup>

Creatinine clearance (mL/min)	VGC dosing
40–59	450 mg orally daily
25–39	450 mg orally every two days
10–24	450 mg orally twice weekly
<10 or dialysis dependent	Not recommended

**Abbreviation:** VGC, oral valganciclovir.

VGC's metabolite (GCV) is excreted via the kidneys with a terminal half-life of  $6.48 \pm 1.38$  hours in heart, kidney, kidney-pancreas and liver transplant recipients with normal renal function.<sup>26</sup> Impaired renal function lengthens the half-life of GCV considerably. Therefore, VGC should be avoided in patients with a creatinine clearance <10 mL/minute or those undergoing hemodialysis or peritoneal dialysis since appropriate dosage amounts and dose frequency have not been well-defined.<sup>26,34</sup> Dosage adjustments are recommended for patients whose creatinine clearance is less than 60 mL/minute and the doses are described in Table 2. These doses are the FDA-approved doses for heart, kidney and kidney-pancreas recipients with renal insufficiency. A pharmacokinetic study conducted by Chamberlain and colleagues found that in the kidney transplant population a dose of VGC 450 mg orally once daily provides similar systemic exposure to oral GCV 1000 mg orally every 8 hours which was one of the more commonly used prophylaxis regimens prior to the availability of VGC but the exposure with a dose of 450 mg of VGC is less than the exposure with 900 mg of VGC.<sup>35</sup>

## Adverse effects

The main adverse effects that affect the use of VGC in the solid organ transplant population are hematologic toxicities. These toxicities appear to be dose- and/or concentration dependent but may also be heightened by concomitant medications that solid organ transplant recipients commonly receive such as antiproliferative agents. The hematologic toxicities include anemia, thrombocytopenia, leukopenia, agranulocytosis and neutropenia.<sup>2,26,33</sup>

## Clinical trials

Several prospective, randomized trials have evaluated VGC for CMV prophylaxis in solid organ transplant recipients, and one trial has evaluated VGC for treatment of non-life threatening CMV disease in this population. For the sake of brevity, only select clinical trials will herein be discussed in further detail.<sup>14,36–38</sup> For a more comprehensive overview of VGC prophylaxis trials, the reader is referred to a systematic review which provides

a review of all published studies up to April 2008 which assessed VGC as preemptive or prophylactic therapy in organ transplant recipients.<sup>39</sup>

## Pivotal trial of VGC for CMV prophylaxis in organ transplantation

The pivotal trial supporting the FDA's approval of VGC as CMV prophylaxis in the organ transplant population compared VGC to oral GCV. GCV was the active comparator in this pivotal trial since it was already FDA approved for CMV prophylaxis in organ transplant recipients, and was considered the standard of care for CMV prophylaxis.<sup>14</sup> Although the GCV pivotal trial<sup>40</sup> had a matching placebo comparator when it was performed, due to the now proven efficacy of GCV, this design would have been unethical for the current VGC trial.

## Study design

The study was designed as a prospective, multicenter, double-blind, and double-dummy study of CMV prophylaxis for high risk (CMV D+/R–) organ transplant recipients. Patients were stratified by allograft (kidney, liver, heart, kidney-pancreas) and randomly assigned in a 2:1 ratio at each center to receive VGC 900 mg orally daily or oral GCV 1000 mg three times a day within 10 days of transplant and through day 100 post-transplant. Quantitative CMV blood polymerase chain reaction (PCR) was monitored for up to 12 months post-transplant, and whenever CMV disease was suspected. Systemic exposure to GCV from either VGC or oral GCV was also assessed. The primary endpoint assessed the proportion of patients developing CMV disease (CMV syndrome and/or tissue invasive during the first six months post-transplant) as adjudicated by an independent (of both sponsor and study) blinded Endpoint Committee.

## Definitions of CMV disease

Definitions of CMV syndrome and tissue invasive disease were similar to those summarized in Table 1. CMV syndrome was defined as fever  $\geq 38^\circ\text{C}$  on  $\geq$  two occasions  $\geq 24$  hours apart within a 7 day period, positive central laboratory results for CMV (measured by quantitative CMV PCR), and at least one of the following: new or increased malaise, two successive measurements of leukopenia (defined as white blood cell count of  $<3500 \mu\text{L}$  or a white blood cell count decrease of 20% if the cell count prior to the development of clinical symptoms was  $<4000 \mu\text{L}$ )  $\geq 24$  hours apart, atypical lymphocytosis  $\geq 5\%$ , thrombocytopenia, or



elevation of hepatic transaminases to  $\geq$ twice the upper limit of normal (nonliver transplant recipients). Tissue invasive CMV was defined as symptoms or signs of organ dysfunction (excluding acute rejection in the grafted organ) and evidence of localized CMV infection in a biopsy or other appropriate specimen.

### Study results

The intent to treat population consisted of 364 patients (239 received VGC and 125 received oral GCV), and were comparable in terms of demographics. The proportions of VGC versus oral GCV patients meeting the endpoint committee CMV disease definition were also comparable for each group (12.1% versus 15.2% at 6 months and 17.2% versus 18.4% at 12 months respectively). VGC was associated with a 1.7 fold higher systemic exposure than oral GCV, and was consistent across allograft groups. Similar to what is observed in clinical practice, the majority of the cases of CMV disease occurred after discontinuation of prophylaxis. Adverse event profiles for both drugs were similar, though a non-significant higher incidence of neutropenia was seen with VGC (8.2%) compared to oral GCV (3.2%). Additionally, no GCV-resistant mutations were associated with VGC treated patients up to 1 year post-transplant. Although the overall incidence of CMV disease was comparable between the two treatment groups, statistical differences were noted in organ types, with liver transplant recipients treated with VGC experiencing a higher incidence of CMV disease.

In a subsequent FDA analysis of the liver transplant recipients in this study, there was both a higher rate of CMV disease (19% versus 12%) and tissue invasive disease (14% versus 3%) in the VGC group compared to GCV. This finding resulted in the FDA denying approval for VGC for use in liver transplant recipients.<sup>41</sup>

### Study significance and limitations

This trial is distinguished as the pivotal trial that led to the FDA approval of VGC for CMV disease prophylaxis in CMV D+/R- heart, kidney and kidney-pancreas transplant recipients. Unlike the pivotal CMV prophylaxis trial with GCV,<sup>40</sup> the VGC trial compared two active comparators for CMV prophylaxis. Limitations of the study are that it did not include lung transplant recipients or all CMV serostatus combinations, and was designed as a non-inferiority study. It was also not powered to determine if improved bioavailability and efficacy of VGC would translate into better control of indirect CMV effects such as rejection, or

improved compliance with once daily VGC dosing versus three times daily oral GCV dosing. Nevertheless, this trial represents the first clinical trial to demonstrate that VGC, a once daily dosed oral antiviral agent, has greater systemic exposure and similar efficacy and adverse event profile to GCV for CMV prophylaxis, with the exception of liver transplant recipients.

## VGC prophylaxis versus pre-emptive therapy in kidney transplantation

Although VGC prophylaxis has been shown to decrease the incidence of CMV infection and disease, it is associated with significant drug costs as well as drug-toxicities.<sup>21</sup> Therefore, a trial was performed to evaluate VGC prophylaxis compared to a pre-emptive approach for prevention of CMV infection and disease in kidney transplant recipients.<sup>36</sup> The primary purpose of the study was to compare outcomes and cost associated with each method, which had not been previously done in a prospective, randomized fashion.

### Study design

The study population consisted of adult kidney transplant recipients from a single center, and with all CMV donor/recipient combinations except D-/R-. Patients were randomized in a prospective 1:1 fashion and stratified by CMV status in an open label design to VGC 900 mg orally daily for 100 days or preemptive treatment. Preemptive treatment consisted of initiating VGC 900 mg orally twice daily for at least 21 days with the detection of CMV DNAemia (defined as  $>2000$  copies/mL by blood PCR) and continued until CMV DNAemia was negative. Patients in either group who developed CMV infection received additional maintenance VGC 900 mg daily for 3 months regardless of group assignment.

### Definition of CMV disease

Published definitions of CMV infection were used.<sup>42</sup> Of note, this same author's previously published work on CMV definitions<sup>17</sup> contributed to the formation of the American Society of Transplantation CMV infection and disease definitions<sup>16</sup> summarized in Table 1. CMV viremia was defined as the isolation of CMV by culture that involves the use of either standard or shell vial techniques. In contrast, CMV DNAemia was defined as the detection of DNA (qualitatively or quantitatively) in samples of plasma, whole blood, and isolated peripheral blood leukocytes or in buffy-coat specimens via PCR-based techniques, hybrid capture, and branched-chain DNA analysis. Asymptomatic CMV infection was

defined as the detection of CMV DNAemia in the absence of symptoms. Symptomatic CMV infection was further divided into CMV syndrome and CMV target-organ diseases. The minimum requirements for CMV syndrome were defined as the documented presence of fever (temperature  $> 38^{\circ}\text{C}$ ) for at least 2 days within a 4-day period, the presence of neutropenia or thrombocytopenia, and the detection of CMV in blood. (Note: quantitative values for neutropenia and thrombocytopenia were not given.) CMV target organ diseases were defined as the detection of CMV infection by culture, immunohistochemical analysis, or in situ hybridization together with histologic features of CMV on organ specific-biopsy.

### Study results

Forty-nine patients were enrolled in each group respectively. CMV DNAemia occurred in 29% of patients in the prophylaxis group and 59% of patients in the pre-emptive group ( $P = 0.004$ ). Median time of onset to CMV DNAemia was shorter for the pre-emptive group compared to the prophylaxis group [39 (range 14–81 days) versus 160.5 (range 10–307 days),  $P = 0.0002$ ]. Development of symptomatic CMV was similar between the groups, and was associated with mean higher peak levels of CMV DNAemia (388,133 copies/mL) versus asymptomatic infections (27,957 copies/mL,  $P = 0.001$ ). Time to clearance did not differ between groups, but CMV serostatus was found to be an independent predictor of time to clearance. No clinical or virologic failure of VGC was evident to suggest resistance in patients with recurrent CMV DNAemia. Adverse event profiles, including leukopenia, were similar between groups. Overall costs were also similar between the groups. Using a cost of \$200 per CMV PCR test and \$24 per 450 mg VGC tablet, the mean total cost per patient was  $\$7130 \pm 3748$  for the preemptive group versus  $\$7678 \pm 6486$  for the prophylaxis group ( $P = 0.611$ ).

### Study significance and limitations

Prior to this trial, prospective randomized trials to compare VGC prophylaxis with preemptive therapy for prevention of CMV infection and disease had not been performed. This study demonstrated that both prophylactic and preemptive therapies with VGC were associated with acceptable outcomes for CMV prevention. Moreover, it demonstrated that a preemptive approach to CMV prevention can also be safely utilized in a CMV D+/R– kidney transplant recipients. Overall costs were similar between strategies, though individual sub-costs varied significantly between approaches. Limitations to this study are that it was open-label and only performed in a

single center in a small number of kidney transplant recipients. It is unknown if these results are applicable to other organ transplant populations. The authors also hypothesized that there would be a 90% rate of CMV reactivation in the CMV D+/R– pre-emptive group. However, the overall incidences of CMV disease and CMV DNAemia in this subset were much lower than expected at (7.7% and 53.8% at 12 months respectively), and was not entirely explained, though late onset disease CMV disease is less common with pre-emptive therapy.<sup>21</sup> Finally, pre-emptive monitoring may not be as feasible for larger transplant centers and laboratory and drug costs will vary in different transplant practices.

## Meta-analysis of VGC versus other CMV prophylaxis regimens in organ transplantation

Previous meta-analyses<sup>43,44</sup> were unable to assess VGC to other CMV prophylaxis modalities, beyond the data from the prophylaxis pivotal trial.<sup>14</sup> A recently published meta-analysis re-evaluated all experimental (randomized) and analytical (cohort and case control) studies that compared VGC with other therapies for CMV prophylaxis after all types of organ transplant until May 2008.<sup>45</sup>

### Study methods

Nine studies (3 randomized, 3 cohort and 3 case control) consisting of 1831 patients met inclusion criteria. Seven trials comparing the efficacy of VGC to oral or intravenous GCV as prophylaxis in 1410 patients were included in the meta-analysis.<sup>14,46–51</sup> It was determined that 624 patients would be needed to provide a 90% power with a 2-tailed alpha of 0.05% to detect a 7% reduction in CMV disease, and the meta-analysis was adequately powered. VGC comparator prophylaxis groups consisted of: IV GCV alone (5 mg/kg/day) in one study<sup>50</sup> and GCV (3 g/day oral) in the other 6 studies<sup>14,46–49,51</sup> Six trials also assessed the occurrence of neutropenia (defined as absolute neutrophil count  $< 1500/\text{mm}^3$ ).<sup>14,36,46,47,49,52</sup> When comparing all included studies, prophylaxis ranged from 14 to 180 days and follow-up ranged from 6 to 12 months post-transplant.

### Definitions of CMV disease

CMV disease was defined as the presence of CMV syndrome (viral detection with fever, malaise, or cytopenia) and/or end-organ disease involvement with CMV. CMV tissue-invasive disease was defined by the presence of end organ involvement by CMV. These definitions were based on the criteria defined by Ljungman et al,<sup>42</sup> which were also used in

the previous study reviewed<sup>36</sup> and whose work contributed to American Society of Transplantation CMV infection and disease definitions<sup>16</sup> summarized in Table 1. Late onset CMV disease was defined by the occurrence of CMV disease after completion of universal prophylaxis.

### Study results

The overall risk for CMV disease did not differ significantly between the VGC and oral and IV GCV groups [odds ratio (OR) 0.98 (95% confidence interval (CI) 0.67–1.43;  $P = 0.92$ ;  $I^2 = 0\%$ )]. There was also no difference in the overall risk for late onset CMV disease (95% CI 0.67–1.64,  $P = 0.84$ ;  $I^2 = 0\%$ ). However, a separate analysis of two trials that compared VGC prophylaxis to acyclovir prophylaxis<sup>52</sup> or pre-emptive therapy<sup>36</sup> instead of GCV prophylaxis, found a statistically significant 795% higher rate of late onset CMV disease with VGC compared to acyclovir prophylaxis or preemptive therapy [OR 8.95 (95% CI 1.07–74.83,  $P = 0.04$ ;  $I^2 = 0\%$ )].

VGC increased the risk of neutropenia by 263% when compared to other preventative strategies [OR 3.63, (95% CI 1.75–7.53;  $P = 0.001$ ;  $I^2 = 0\%$ )], even in trials not using mycophenolate mofetil or induction therapy with T cell depleting therapies. Similar to the findings in the pivotal trial<sup>14</sup> and subsequent analysis<sup>41</sup> this meta-analysis also found that in liver transplant recipients, the risk of CMV tissue invasive disease with VGC prophylaxis (14%) was 4.5 times higher than with GCV (3%) (95% CI 1–20.14;  $P = 0.04$ ) at 6 months, and 3.2 times higher with VGC (14%) than with GCV (5%) (95% CI 0.99–11.19,  $P = 0.05$ ) at 12 months. However, in the overall analysis, VGC was not found to be significantly associated with poorer survival.

### Study significance and limitations

This study represents the first meta-analysis to compare VGC trials to other CMV preventative therapy, beyond the pivotal trial data.<sup>14</sup> The analysis was adequately powered, found no publication bias, and showed no greater efficacy of VGC over IV and oral GCV. Similar to findings in previous studies, CMV tissue invasive disease was found to be significantly higher in liver transplant recipients. VGC was also associated with a significantly higher risk of absolute neutropenia. Additionally, it was noted that there was a higher incidence of late CMV disease with VGC compared to acyclovir or preemptive prophylaxis, but not when compared to GCV prophylaxis. Reasons for these findings are not completely understood, and the results were not limited to CMV D+/R– recipients. A limitation of this meta-analysis was that it was not able to address the impact of the above

mentioned adverse event on the post-transplant course. Other limitations outside of those inherent with this meta-analysis study design include the lack of data able to be presented on other opportunistic infections or patterns of CMV resistance to GCV. There were also no cost data analyzed among the various preventative strategies. Future studies may help to further delineate these issues.

## Treatment with VGC for CMV disease in organ transplantation

To date, only one prospective randomized study has evaluated treatment of CMV disease in solid organ transplant recipients with VGC.<sup>37</sup> The primary outcome of the trial was treatment success defined as eradication of CMV viremia (eradication of CMV viremia was defined as  $\leq 600$  copies/mL of blood by CMV PCR) at day 21 post-treatment.

### Study methods

The trial was a prospective, randomized 1:1, open-label, multicenter trial of adult solid organ transplant recipients with both virological and clinical evidence of non-life threatening CMV disease (regardless of CMV serostatus). Patients previously received anti-CMV therapy for prophylaxis, pre-emptive treatment or treatment of disease. In the intent to treat analysis, 164 patients were randomized to 900 mg of VGC twice a day for 21 days, and 157 patients were randomized to IV GCV at a dose of 5 mg/kg twice a day for 21 days. Both groups received VGC 900 mg orally once a day for days 22–49 and CMV blood PCR was monitored by a centrally blinded lab up to day 49.

### Definition of CMV disease

CMV disease was defined as the presence of CMV in the blood by a local assay including shell vial assay, antigenemia assay, or accredited nucleic acid detection assay, plus the presence of compatible symptoms. For viral syndrome the definition was consistent with current American Society of Transplantation recommendations for use in clinical trials (Table 1).<sup>16</sup> Tissue invasive disease was defined as evidence of localized CMV infection in a biopsy or other appropriate specimen (such as bronchoalveolar lavage or cerebrospinal fluid) and/or relevant symptoms of organ dysfunction unlikely to be due to other causes.

### Study results

Demographic and baseline characteristics were similar between the two groups, including the number of patients in each group. Clinical presentations, including the incidence of tissue invasive disease, baseline viral loads and patterns of

decline in viral loads were also similar between the groups. Viral eradication was achieved in 45.1% of VGC and 48.4% of IV GCV patients at day 21 (95% CI -14%–8%) fulfilling non-inferiority criteria and at day 49 (67.1% versus 70.1% respectively,  $P = \text{ns}$ ). The mean time to a clinically relevant drop ( $\geq 0.3$  natural log units) was  $6.1 \pm 4.5$  days ( $n = 120$ ) for VGC and  $6.6 \pm 4.7$  days ( $n = 116$ ) for IV GCV, ( $P = \text{ns}$ ). The median viral load half life and the median slope of viral load decay were comparable in both arms. Clinical resolution, as assessed by the investigators, occurred at a mean of 15.1 days for both groups ( $P = \text{ns}$ ). During the first 21 days, treatment discontinuations and frequency of adverse events were also similar between the groups. The only factor found to be predictive of viral eradication was the baseline viral load. The investigators noted that patients with a baseline viral load of  $< 10,000$  copies/mL had a univariate relative chance for eradication of viremia at day 21 of 6.41 (95% CI 3.61–11.36,  $P < 0.001$ ) and at day 49 of 2.56 (95% CI 1.29–5.08,  $P = 0.001$ ) compared to those with a viral load  $\geq 10,000$  copies/mL. Despite clinical resolution, viral eradication was only achieved in approximately 58% of patients by day 21. Therefore, the investigators recommend extension of therapy beyond 21 days, and individualization therapy based on viral load measurements.

### Study significance and limitations

This study was the first prospective, randomized study to evaluate VGC for the treatment of CMV disease. There are several limitations to this study. The treatment arms compared oral to IV therapy and were not blinded; therefore, investigator bias may have been introduced. The study results can also only be applied to a subset of patients with CMV disease, as patients with life-threatening CMV illness were excluded. Moreover, no patient had extremely high viral loads (typically  $> 10^6$ ). The majority of patients (over 70%) enrolled were kidney transplant recipients, and therefore it is not known if these results are applicable to other organ populations. Cost analysis, compliance with IV versus oral treatment regimens, and the impact of concurrent reduction of immunosuppression (not mandated for this study), were not assessed. Although this study represents the first randomized prospective trial to assess VGC as a treatment option for CMV disease, it was designed as a non-inferiority study. Future trials are necessary to further address these limitations.

### Long-term outcomes of CMV disease treatment with VGC versus IV GCV

A subsequent 12-month follow-up study of the above mentioned study has also been published.<sup>38</sup>

### Study methods

Patients assessed in this study were those from the above described study,<sup>37</sup> who developed a positive CMV viral load measurement (central analysis) at the start of the study.

### Definition of CMV disease

CMV disease recurrence was defined as CMV viral load  $\geq 600$  copies/mL occurring after the end of treatment, either at the scheduled (month 3 and 6) visits or upon evidence of clinical recurrence, in patients who had previously had two negative CMV viral loads by day 49.

### Study results

This study found that clinical and viral eradication as well as clinical and viral recurrences for CMV disease were similar between the groups. Opportunistic infections were also found to be similar between the groups. Additionally, during the treatment phase no differences in GCV resistant mutations were identified. In a multivariate analysis, the only independent predictor for recurrent CMV disease was viral eradication at day 21 ( $P < 0.0001$ ). Therefore, weekly monitoring of viral loads until eradication is achieved is recommended.<sup>38</sup>

### Study significance and limitations

This trial represents the long-term results of the first randomized trial comparing VGC to IV GCV for the treatment of CMV disease in organ transplant recipients. It further supports the findings of the initial report, showing that VGC is non inferior to IV GCV for the treatment of non-life-threatening CMV disease. It also helped us to gain more insight into the viral kinetics of CMV disease. Limitations to this trial are as previously stated in the first half of the trial. Moreover, no patient treated had life-threatening CMV disease, and hence it is unknown if the results would be applicable in this patient subset. Although this study represents the best evidence to date to assess VGC as a treatment option for CMV disease, future trials are necessary to further define its role in this setting.

### Discussion

VGC has become a valuable treatment option in the prevention of CMV disease after organ transplant. Its therapeutic advantages and disadvantages in clinical practice are summarized below.

### Therapeutic advantages

VGC is an accepted option for the prevention of CMV disease in the solid organ transplant population. Due to its increased



bioavailability compared to oral GCV, VGC offers more convenient dosing (once daily compared to three times daily for prophylaxis). Its efficacy for CMV prophylaxis in many solid organ transplant populations is non-inferior to IV GCV so VGC offers the advantage of avoiding IV administration and the costs and risks associated with it (ie, line infections). The increased bioavailability may also lower the risk of the development of GCV-resistant CMV strains as it has the potential to decrease patient non-adherence while also increasing the drug level that the virus is exposed to compared to oral GCV.

## Therapeutic disadvantages

VGC is still patent-protected so its cost for most institutions is likely higher than oral GCV which is not patent-protected. The necessity of dosage adjustments for patients with renal insufficiency is not ideal from a safety standpoint. There are potential drug interactions with VGC including that when used concomitantly with mycophenolate in patients with renal insufficiency exposure to both GCV and a metabolite of mycophenolate (mycophenolic acid glucuronide) may be increased.<sup>53</sup> Other potential medications VGC may interact with include zidovudine, probenecid and didanosine.<sup>26</sup>

The hematologic toxicities associated with VGC are similar to several immunosuppressive medications commonly used in the solid organ transplant population and this can make the toxicities difficult to manage. Reducing the dosage of VGC to minimize the toxicity may increase the risk of developing GCV-resistant CMV strains.

The appropriateness of VGC use in the liver transplant population has been debated as various studies have reported clinical inferiority and non-inferiority compared to oral and IV GCV in this population.<sup>14,54,55</sup> The FDA has not approved VGC for use in liver transplant recipients.<sup>26,41</sup> Despite this, Levitsky and colleagues recently reported that VGC is commonly used in this patient population in the United States and Canada.<sup>56</sup> Additional studies will be required to determine the efficacy of VGC for prevention and treatment of CMV in liver transplant recipients.

## Place in therapy

The American Society of Transplantation and the Canadian Society of Transplantation both have published evidence based recommendations for CMV prevention and treatment.<sup>5,15</sup> Briefly, these documents recommend oral VGC, oral GCV, or IV GCV for CMV prophylaxis in all solid organ transplant recipients at risk for CMV. When using VGC for CMV prophylaxis the recommended duration of therapy is

three months. However, preliminary data in CMV high risk patients (CMV D+/R-) presented by Humar and colleagues at the 2009 American Transplant Congress suggests that these patients may benefit from a longer duration of prophylaxis.<sup>57</sup>

Likewise, the findings of Kalil and colleagues' meta-analysis support the American Society of Transplantation's recommendations.<sup>45</sup> They report that the risk of CMV disease and overall efficacy are similar between VGC, oral and IV GCV despite the increased risk of CMV tissue invasive disease in liver transplant recipients and late onset CMV disease with VGC. Future studies are necessary to address the limitations identified from current clinical trials, and to further define the role of VGC as prophylaxis and treatment for CMV in solid organ transplant recipients.

## Disclosure

Emily Blumberg receives research support and is a consultant for Roche and she also receives support from Viropharma.

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