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Comparison of standard versus low-dose valganciclovir regimens for cytomegalovirus prophylaxis in high-risk liver transplant recipients

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Alexandra Bixby was a pharmacy resident at Michigan Medicine at the time this research was conducted.

Abstract

Purpose: The purpose of this study was to compare the safety and efficacy of two valganciclovir (VGCV) institutional dosing protocols for cytomegalovirus (CMV) prophylaxis in liver transplant (LT) recipients with CMV serotype donor +/recipient- (D+/R−).

Methods: This was a single-center review of CMV D+/R− adult LT recipients who received VGCV 450 mg/day for 90 days (low-dose) or VGCV 900 mg/day for 180 days (standard-dose). The primary outcome was incidence of CMV disease at 1 year. Secondary outcomes included rates of CMV syndrome, end-organ disease, breakthrough infection, and resistance. Neutropenia, early discontinuation of VGCV, growth colony stimulating factors use (G-CSF), biopsy-proven rejection (BPAR), graft loss, and death at 1 year were analyzed.

Results: Ninety-six CMV D+/R− LT recipients were included. Although no difference in CMV disease was observed (low-dose 26% vs. standard-dose 23%, $p = 0.71$), 75% of CMV infections in the low-dose group presented with end-organ disease. Ganciclovir (GCV) resistance was observed only in the low-dose group ($n = 2$). Significantly more patients in the standard-dose group developed neutropenia (low-dose 10% vs 60% standard-dose, $p < 0.001$). In the standard-dose group, 29% required early discontinuation of VGCV (vs. 5% in the low-dose group, $p < 0.001$), and 20% were treated with G-CSF. Both cohorts had similar rates of BPAR, graft loss, and death at 1 year.

Conclusions: VGCV 900 mg/day for 180 days had higher rates of hematologic adverse effects resulting in frequent treatment interruptions. However, the occurrence of two cases of GCV-resistant CMV disease raises concerns about routinely using low-dose VGCV prophylaxis.

KEYWORDS
cytomegalovirus, liver transplantation, neutropenia, valganciclovir

1 | INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous herpes virus that infects 30%–97% of humans.[1] In solid organ transplant recipients, CMV can cause primary infection or reactivation of latent infection and can lead to unwanted consequences, such as organ dysfunction, infection, acute rejection, and mortality.[2] Therefore, it is imperative to manage CMV in transplant recipients, especially for the high-risk seronegative recipients (R−) of organs from seropositive donors (D+). In the absence of antiviral prophylaxis, there is a 92% incidence of CMV viremia and 50%–65% rate of symptomatic infection within 90 days of transplantation in CMV D+/R− transplant recipients.[3] CMV high-risk (D+/R−) patients comprise 13%–20% of all liver transplant (LT) recipients.[4]

Valganciclovir (VGCV) 900 mg by mouth (PO) once daily was approved by the United States Food and Drug Administration (FDA) for the prevention of CMV in high-risk kidney, kidney-pancreas, and heart transplant recipients based on the study by Paya et al.[5,6] In this randomized, prospective, double-blind study VGCV 900 mg once daily was compared to ganciclovir (GCV) 1000 mg oral three times daily for 100 days. CMV disease at 6 and 12 months was similar between the groups, and there was no significant difference in leukopenia and neutropenia. However, VGCV did not gain FDA approval for LT recipients based on a 19% and 12% incidence of CMV disease in the VGCV and GCV groups, respectively. Although lacking FDA approval, current guidelines recommend VGCV for 3–6 months following transplantation.[2]

Severe cytopenias, including neutropenia, are listed as a black box warning on the VGCV labeling. Guidelines provide a strong recommendation to only adjust the dose of VGCV for renal function because suboptimal doses have been associated with clinical failure and resistance.[7] For significant leukopenia, granulocyte colony-stimulating factor is often considered before dose reduction or cessation of antiviral therapy.[2]

At our institution, CMV prophylaxis protocols for CMV D+/R− LT recipients have been amended throughout the years with different VGCV doses and duration utilized. Prior to May 2014, CMV D+/R− LT recipients at University of Michigan Transplant Center received VGCV 450 mg daily for 90 days based on data that it delivers similar drug-concentrations as GCV 1000 mg PO three times daily.[8] However, due to concerns for breakthrough CMV infection, development of CMV resistance, and high rates of CMV disease occurring in the first 180 days following transplant, this protocol was changed in 2014 to recommend that high-risk LT recipients receive VGCV 900 mg daily for 180 days.[9] The goal of this study was to evaluate the safety and efficacy of VCGV 450 mg daily for 90 days versus VGCV 900 mg daily for 180 days in CMV D+/R− LT recipients.

2 | PATIENTS AND METHODS

This single-center retrospective review included adult CMV D+/R− LT recipients from University of Michigan Transplant Center who were given VGCV 450 mg daily between January 2010 and December 2013 (low-dose) or VGCV 900 mg daily from August 1, 2014 to July 31, 2017 (standard-dose). Patients were excluded if they underwent multi-organ transplant or had less than 30 days of follow-up. This study was approved by the institutional Investigational Review Board.

TABLE 1 Valganciclovir renal dose adjustments

CrCl (ml/min)	Full dose 450 mg daily (Low-dose)	Full dose 900 mg daily (High-dose)
≥60	450 mg daily	900 mg daily
40–59	450 mg every 2 days	450 mg once daily
25–39	450 mg every 2 days	450 mg every 2 days
10–24	450 mg twice weekly	450 mg twice weekly
<10 or HD/CRRT	450 mg three times weekly or after HD	450 mg three times weekly or after HD

Abbreviations: CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; HD, hemodialysis.

The primary outcome was incidence of CMV disease within 1 year of LT. Secondary outcomes included rates of neutropenia during VGCV use, breakthrough and ganciclovir resistant infections, and usage of granulocyte-colony stimulating factor (G-CSF). Additionally, incidence of biopsy-proven acute rejection, graft loss, and all-cause mortality at 1 year following transplant were reported.

2.1 | Study definitions

Quantitative CMV DNAemia testing was performed on plasma using a laboratory-developed PCR assay (lower limit of quantification 300 copies/ml). CMV disease was defined as evidence of CMV infection with attributable symptoms and was further categorized as CMV syndrome or CMV end-organ disease.[2] Patients were analyzed in an intention-to-treat fashion. Therefore, patients that stopped VGCV early due to intolerance were still evaluated for CMV disease at 1 year. CMV syndrome was defined as detection of CMV in the blood with at least one of the following: fever, malaise, leukopenia, and/or thrombocytopenia.[2,10] CMV end-organ disease was defined as presence of CMV viremia and symptoms of end-organ disease, or evidence of end-organ disease on biopsy (CMV in tissue specimen). Breakthrough infection was classified by the development of CMV infection while on VGCV prophylaxis. Unless otherwise specified, neutropenia was defined as an absolute neutrophil count (ANC) less than 1000/mm^3 and leukopenia as a white blood cell count less than 3500 cells/mm^3. VGCV renal dose adjustments per institutional protocol can be found in Table 1. Patients were considered inappropriately dosed if they were outside of the creatinine clearance range (± 5 ml/min). Ideal body weight was used to calculate creatinine clearance using the Cockcroft-Gault equation.

2.2 | Immunosuppression

Liver transplant recipients at Michigan Medicine received triple immunosuppression with tacrolimus, mycophenolate mofetil, and

corticosteroids. Induction with basiliximab was permitted for patients with evidence of renal dysfunction. Tacrolimus was adjusted to reach a goal trough of 6–10 ng/ml in the first 3 months posttransplant and 4–8 ng/ml thereafter. Corticosteroids were tapered to a prednisone dose of 5 mg daily by 30 days posttransplant. Mycophenolate mofetil 1000 mg twice daily was initiated within 24 h of transplantation and continued for the first 3 months. In patients without autoimmune indications for transplantation, the mycophenolate dose was reduced and tapered off by month 6 and prednisone could be discontinued by week 5 per the discretion of the transplant attending. Rejection was managed by intensifying maintenance immunosuppression and/or adding pulse dose steroids depending on the severity of rejection.

LT recipients who were CMV D+/R− at University of Michigan Transplant Center received VGCV 450 mg daily for 90 days prior to May 2014. This protocol was amended in June 2014 so that CMV D+/R− LT recipients received 900 mg daily for 180 days. LT recipients who were CMV D-/R+ or CMV D+/R+ received VGCV 450 mg for 90 days. Those that were CMV D−/R− received 30 days of acyclovir. CMV disease was typically treated with standard-dose VGCV (900 mg twice daily, renally adjusted). Per institutional protocol, in setting of severe neutropenia (ANC < 1000 /mm^3), VGCV should be held and weekly CMV-PCR surveillance monitoring should be initiated. Quantitative CMV PCRs were obtained prior to rejection treatment to rule out CMV viremia. CMV resistance panels were ordered based on clinical discretion. CMV prophylaxis was only resumed following a rejection episode if the patient was CMV D+/R− with plans to receive prednisone greater than 20 mg daily for more than 30 days.

2.3 | Statistical analysis

Data analysis was performed using SPSS software (version 23, SPSS, Armonk, NY, USA). Descriptive statistics were used to determine baseline and clinical characteristics. Categorical variables were reported as the number (percentage) and continuous variables as the mean plus standard deviation or median plus standard error of the mean. Categorical variables were compared utilizing a chi-square or Fisher's exact test, and normal distributed variables were compared using a two-tailed Student's *t*-test. Continuous variables not normally distributed were compared using a Mann–Whitney *U* test. Time-to-event data were analyzed using Kaplan–Meier analysis.

3 | RESULTS

3.1 | Patient characteristics

One hundred one CMV D+/R− LT recipients were screened, and 96 were included (low-dose $n = 61$ vs. standard-dose $n = 35$). Four patients were excluded due to multi-organ transplant (simultaneous liver-kidney transplant), and one patient was excluded due to death within 30 days of transplant. Baseline demographics are summarized in Table 2.

TABLE 2 Baseline Characteristics

Outcome	450 mg/day for 90 days ($n = 61$)	900 mg/day for 180 days ($n = 35$)
Age, Mean ± SD	52 ± 11	54 ± 10
Male	45 (74%)	23 (66%)
Race		
Caucasian	57 (93%)	34 (97%)
Black	4 (7%)	0 (0%)
Other	0 (0%)	1 (3%)
Second transplant	4 (7%)	1 (3%)
Reason for transplant		
HCV	21 (34%)	7 (20%)
AIH, PBC, PSC	15 (25%)	5 (14%)
NASH	7 (11%)	10 (29%)
Alcohol	7 (11%)	4 (11%)
Alpha-1 antitrypsin deficiency	5 (8%)	2 (6%)
Cryptogenic	3 (5%)	3 (8%)
Other	3 (5%)	4 (11%)
MELD, Mean ± SD	18.1 ± 5.2	18.9 ± 6.6
Immunosuppression at baseline†		
Basiliximab	36 (59%)	19 (54%)
Tacrolimus	59 (97%)	34 (97%)
Mycophenolate	59 (97%)	34 (97%)
Prednisone	61 (100%)	35 (100%)

Abbreviations: AIH, autoimmune hepatitis; HCV, hepatitis C virus; MELD, model for end-state liver disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SD, standard deviation.

$p > 0.05$ for all baseline characteristics.

†Immunosuppression at discharge from hospital after transplant.

3.2 | Primary and secondary outcomes

3.2.1 | CMV disease

The composite incidence of CMV disease (syndrome or end-organ involvement) was 26% in the low-dose group versus 23% in the standard-dose group ($p = 0.71$). Although not statistically significant, there was a higher percentage of patients in low-dose group with CMV end-organ disease (75% vs. 38% of CMV cases, $p = 0.07$) and a higher percentage of the standard-dose group with CMV syndrome (25% vs. 63%, $p = 0.71$) (Table 3). Biopsy-proven CMV was only identified in low-dose group. Two patients developed ganciclovir-resistant CMV in the low-dose group. The first patient developed CMV colitis on postoperative day 211. A UL54 mutation resulting in ganciclovir and cidofovir resistance detected on postoperative day 242, and the patient was treated with foscarnet. The second patient developed CMV infection on postoperative day 63 and was initiated on VGCV induction. Due to worsening colitis symptoms, on postoperative day 110, the patient

TABLE 3 Outcomes

Outcome	VGCV 450 mg/day for 90 days ($n = 61$)	VGCV 900 mg/day for 180 days ($n = 35$)	p-Value
CMV disease (composite)	16 (26%)	8 (23%)	0.71
CMV syndrome[†]	4 (25%)	5 (63%)	0.07
CMV end-organ disease[†]	12 (75%)	3 (38%)	0.60
Hepatitis	3 (19%)	2 (25%)	
Colitis	8 (50%)	1 (13%)	
Pneumonitis	1 (6%)	0 (0%)	
Biopsy-proven CMV[†]	4 (25%)	0 (0%)	0.12
Ganciclovir-resistant CMV[†]	2 (13%)	0 (0%)	0.54
Break-through CMV[†]	2 (13%)	1 (13%)	0.99
Time to CMV (days), mean ± SD[†]	149 ± 44	148 ± 73	0.96
CMV < 90 days	2 (13%)	2 (25%)	
CMV 90–180 days	10 (63%)	3 (38%)	
CMV > 180 days	4 (25%)	3 (38%)	
Interruption of VGCV in patients with CMV Disease[†]	1 (6%)	4 (50%)	0.03

[†]Out of CMV composite cases.

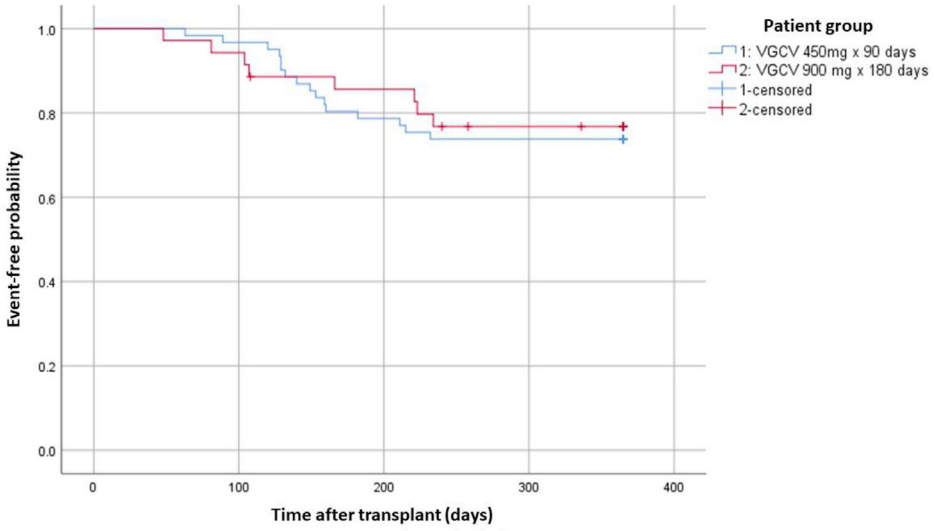

FIGURE 1 Kaplan–Meier plot of time to CMV disease at 1 year; VGCV dosing for Group 1: 450 mg/day for 90 days and Group 2: 900 mg/day for 180 days, there was no statistical difference in CMV disease ($p = 0.76$)

was admitted for IV ganciclovir, and a colon biopsy and CMV resistance were obtained. The biopsy confirmed CMV colitis, and a UL97 mutation resistant to ganciclovir was detected. Patient was started on IV foscarnet and then enrolled in a maribavir study.

Breakthrough CMV and mean time to CMV disease was similar between groups. There was no difference in time to CMV between groups (Figure 1, $p = 0.76$).

3.2.2 | Hematologic outcomes

Significantly more patients in the standard-dose group developed neutropenia during prophylaxis with VGCV (Table 4), odds ratio 12.2 (95% confidence interval [CI] 4.17–35.9). Additionally, patients in the standard-dose group experienced a higher degree of neutropenia as demonstrated by a lower ANC nadir. Based on renal function at 3 and 6 months, none of the patients in the standard-dose group who developed neutropenia received a higher dose than recommended per protocol.

Due to neutropenia, 29% of the standard-dose group required early discontinuation of VGCV (Table 4). There was no difference in CMV disease among those that discontinued VGCV prophylaxis early due to neutropenia and those who remained on treatment (33% vs. 31%; $p = 0.99$). In the standard-dose group, four of the eight patients that developed CMV disease had early VGCV discontinuation preceding

TABLE 4 Hematologic outcomes during VGCV prophylaxis

Outcome	VGCV 450 mg/day for 90 days ($n = 61$)	VGCV 900 mg/day for 180 days ($n = 35$)	*p*-Value
Interruption of VGCV, *n* (%)	3 (5%)	10 (29%)	<0.001
Days to early interruption of VGCV, mean ± SD	68 ± 16	94 ± 53	0.43
Neutropenia (ANC < 1,000/mm^3), *n* (%)	6 (10%)	21 (60%)	<0.001
ANC Nadir, mean ± SD	2.4 ± 1.3	0.99 ± 0.9	<0.001
Leukopenia (WBC < 3500 cells/mm^3), *n* (%)	28 (46%)	33 (94%)	<0.001
WBC Nadir, mean ± SD	3.9 ± 1.9	1.9 ± 1.2	<0.001
Patients requiring G-CSF, *n* (%)	3 (5%)	7 (20%)	0.02

TABLE 5 VGCV dosing based on compliance with renal dosing protocol

	VGCV 450 mg/day ($n = 61$)	VGCV 900 mg/day* ($n = 35$)	
n (%)	90 days†	90 days	180 days‡
Higher dose	12 (19.7)	3 (8.6)	3 (8.6)
Appropriate dose	43 (70.4)	28 (80)	19 (54.3)
Lower dose	1 (1.6)	1 (2.9)	0 (0)
VGCV held	3 (4.9)	3 (8.6)	10 (28.6)

*Patients in the VGCV 900 mg/day for 180 day group were assessed at both 90 days and 180 days.
†Two patient excluded from analysis ($n = 1$ patient on VGCV for treatment of CMV disease and $n = 1$ patient deceased).
‡One patient excluded for lost to follow-up.

infection. Mycophenolate was stopped in 61.5% of patients prior to discontinuation of VGCV (33% vs. 70%, $p = 0.14$). There was no difference in CMV disease between patients that completed therapy and those that discontinued prematurely in either the low-dose ($p = 0.72$) or standard-dose ($p = 0.27$) groups (Figure 2). Of the patients that experienced neutropenia, 17% patients in the low-dose group versus 30% of the standard-dose group were readmitted to the hospital for infection related causes.

3.2.3 | Renal function

Renal function and dose appropriateness was assessed at 3 months posttransplant. In the low-dose group, none of the 16 patients that developed CMV disease were underdosed, and four of them received higher doses than recommended based on renal function. In the standard-dose group, no patients with CMV disease were inappropriately dosed at 3 months. Clinician compliance with our VGCV renal dosing protocol was reviewed (Table 5). Of the 13 patients, overall that stopped VGCV prophylaxis early due to cytopenias, none were considered overdosed based on renal function at 3 months.

3.2.4 | Graft outcomes

Both cohorts had similar rates of BPAR (16% vs. 14%, $p = 0.99$), graft loss (5% vs. 3%, $p = 0.99$), and death (3% vs. 3%, $p = 0.99$) at 1 year. The mean time to rejection was 113 ± 109 versus 190 ± 122 days ($p = 0.24$). No patients in the standard-dose cohort experienced both rejection and CMV disease during the follow-up period. However, in the low-dose cohort, four of 10 patients with BPAR experienced subsequent CMV disease. One patient was treated with G-CSF for neutropenia before developing BPAR.

4 | DISCUSSION

Across the entire cohort, the incidence of CMV disease was 25% in high-risk LT recipients, with no difference between dosing regimens. We found higher rates of CMV disease in the low-dose group than seen in previous literature (CMV disease range 7% to 22% in previous studies vs. 26% in our study).[8,11,12] However, our rates of CMV disease in the standard-dose group are similar to what has been observed with 900 mg/day for 90 days (range 10%–28%).[6,13–18] Despite no statistical difference in ganciclovir-resistance between groups, morbidity and mortality among patients with CMV resistance are historically poor, making the two cases in the low-dose group important to note.[19] Time to CMV disease was likely similar between groups (around 150 days), due to the large number of patients (29%) in the standard-dose group unable to tolerate the full 180 day course of therapy due to hematologic events. Additionally, these patients finished their 180 days with CMV surveillance PCRs, which may be why we observed a higher percentage of CMV syndrome (leukopenia + CMV viremia) in this group over CMV end-organ disease.

In this study, 63% of patients developed leukopenia during VGCV prophylaxis (low-dose 46% vs. standard-dose 94%, $p < 0.001$), which was significantly higher than previous reports (range 14%–38%).[6,13,20,21] Leukopenia was more common in the standard-dose group despite no differences in mycophenolate use or dosing.[6,13,22] In the IMPACT study, VGCV prophylaxis (900 mg/day) for 100 versus 200 days was associated with leukopenia in 26% versus 38% and neutropenia in 15% versus 15% of kidney transplant recipients, respectively.[20–21] Compared to kidney transplant recipients, LT recipients are at a higher risk of developing neutropenia, and thus a higher incidence of leukopenia and neutropenia was expected.[23] Neutropenia led to more patients in the standard-dose group to discontinue prophylaxis early. Although the absence of a comparator group limits interpretation, infections occurred frequently in patients with neutropenia (27%). The hematologic outcomes, occurring around 3 months posttransplant in the standard-dose group, bring into question whether 180 days of full dose VGCV prophylaxis is the most tolerable regimen for high-risk LT recipients.

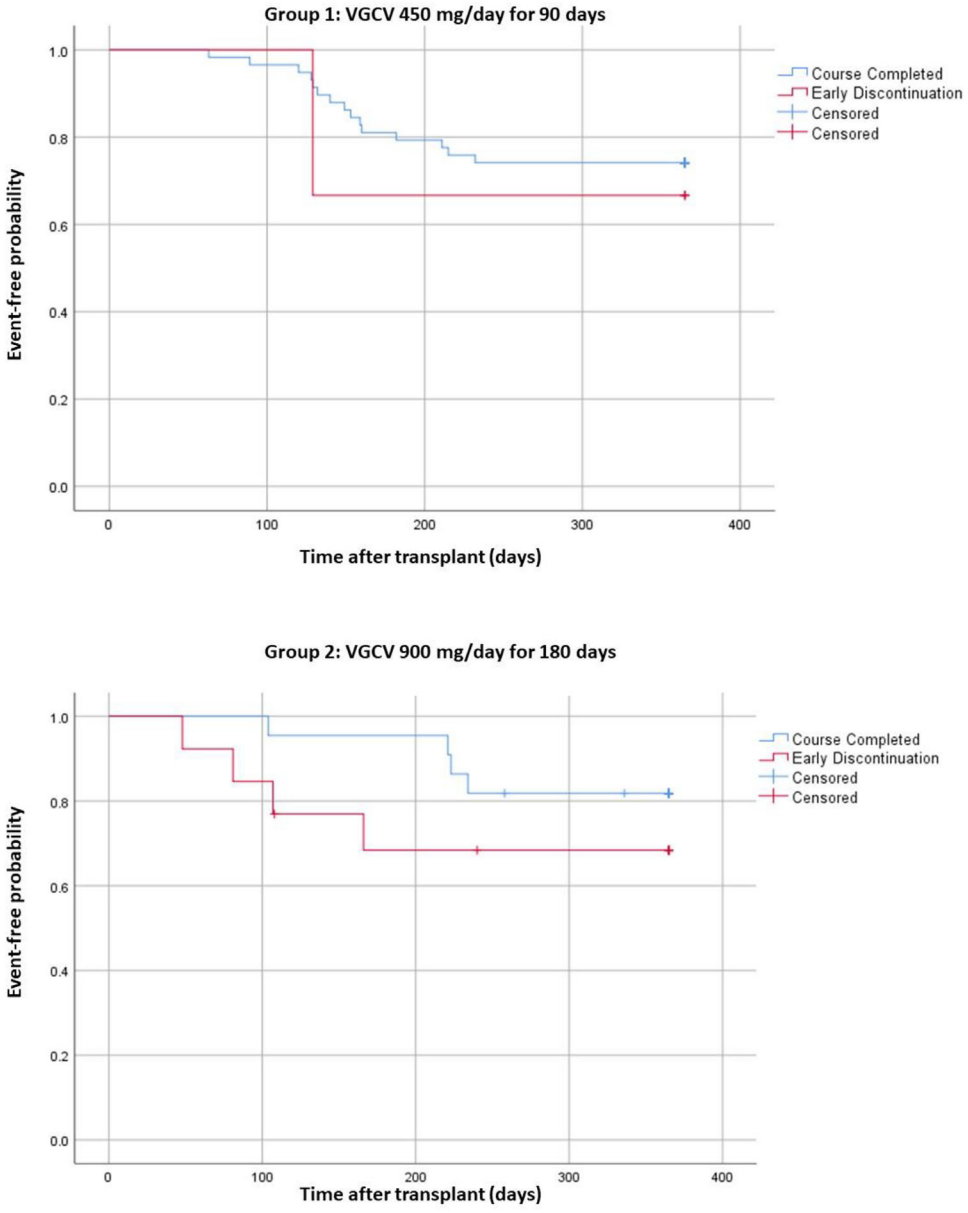

FIGURE 2 Kaplan–Meier plot of time to CMV disease at 1 year; VGCV dosing for (A) Group 1: 450 mg/day for 90 days and (B) Group 2: 900 mg/day for 180 days separately, there was no statistical difference in CMV disease between those that completed therapy versus those that discontinued early, $p = 0.72$ and 0.27, respectively

Due to the conflicting data regarding optimal VGCV prophylaxis in LT recipients, Kalil et al published a meta-analysis examining VGCV prophylaxis in high-risk LT recipients.[13] The meta-analysis of five controlled studies found that CMV disease was higher with VGCV than oral GCV with a risk of 1.96 (95% CI 1.05–3.67, $p = 0.035$) and remained significant in patients treated with VGCV 900 mg daily but not 450 mg daily ($p = 0.04$ and $p = 0.76$, respectively). Because only three studies utilized the VGCV 450 mg daily dosing, the risk of leukopenia could not be assessed by VGCV dose. Therefore, it was possible that the higher risk of CMV disease in the VGCV 900 mg arm could be associated with discontinuation of VGCV due to leukopenia. Although this meta-analysis suggested a two-fold increase in the risk of CMV disease with the use of VGCV 900 mg daily, use of lower doses has not been supported by the FDA or consensus guidelines. In fact, the 2018 International Consensus Guidelines acknowledge the absence of comparative dose-finding studies in non-kidney transplant recipients and the lack of standardized renal dosing protocols or immunosuppression regimens across studies. Based on limited evidence and concern for the development of resistance, the CMV practice guidelines recommend against routine use of low-dose VGCV.[1,2]

Current evidence also does not address the optimal duration of VGCV prophylaxis. Patients with D+/R- serostatus and shorter courses of prophylaxis are at highest risk of late-onset CMV disease.[2] However, longer courses of VGCV prophylaxis may lead to higher rates of leukopenia and greater drug costs. Consensus guidelines recommend a 3–6 month duration of CMV prophylaxis in high-risk LT recipients.[2]

In the IMPACT study in D+/R− kidney recipients, a decreased risk of CMV disease was observed in patients given 200 days of prophylaxis (21.3%) compared with those given 100 days of prophylaxis (36.8%).[20,21] Although only studied in kidney transplant recipients, these results are often extrapolated to other organ types.

Recently, a randomized controlled trial of 205 CMV D+/R− LT recipients compared preemptive CMV monitoring to antiviral prophylaxis with VGCV 900 mg for 100 days.[24] This study found a lower incidence of CMV disease with the preemptive therapy group compared to the antiviral prophylaxis group (9% vs. 19%, $p = 0.04$) with no difference in neutropenia (ANC < 500/mm^3). Additionally, T-cell responses and neutralizing antibodies were increased in the preemptive group. These results suggest that preemptive monitoring appears to be a promising strategy for the prevention of CMV disease in CMV D+/R− LT.

In addition to not comparing these dosing strategies to the preemptive monitoring approach, our study has several other important limitations. First, it was a single-center study which may limit the generalizability between transplant centers with various immunosuppression and CMV prophylaxis practices. Given that a historical comparator arm was used in this study, there could be practice changes between the two groups that were not captured. Additionally, this study focused only on CMV D+/R− LT recipients, and the results cannot be extrapolated to other transplant organ recipients or CMV low and intermediate risk LT recipients. Given the high incidence of leukopenia, differentiating between CMV syndrome and viremia by chart review was challenging. Thus, patients with untreated, asymptomatic CMV viremia were not captured in this study. Additionally, our study did not analyze how preemptive monitoring compares to either VGCV dosing regimen. The simultaneous institutional protocol changes for both the VGCV dose and duration are an additional confounder given that the risk for CMV is typically higher in the period after prophylaxis is completed. Given the similar incidence of CMV disease at 1 year between the two groups and the high rates of leukopenia leading to early discontinuation, a shorter duration of VGCV prophylaxis may be considered. A hybrid approach of VGCV 900 mg daily for 90 days followed by weekly CMV PCR for post prophylaxis surveillance may be a reasonable approach in high-risk LT recipients unable to tolerate more than 90 days of VGCV. Further examination is warranted regarding the utility of the CMV cell mediated immunity in assessing CMV risk to guide duration of VGCV prophylaxis.

Our study is the first comparative study examining the safety and efficacy of standard-dose VGCV and low-dose VGCV for CMV prophylaxis in high-risk LT recipients. Additionally, it is one of the largest analyses of VGCV 450 mg in high-risk LT recipients. The analysis of renal dose adjustments to ensure patients were not being overdosed (leading to leukopenia) or underdosed (leading to increased rates of CMV) is an additional strength.

5 | CONCLUSIONS

Although the incidence of CMV disease was similar between groups, patients in the low-dose group experienced more severe cases and ganciclovir-resistance, raising concern for using 450 mg/day. The risk for severe CMV disease with low-dose VGCV must be weighed against the risk of cytopenias with standard-dose VGCV. This study demonstrated high rates of VGCV discontinuation due to neutropenia, particularly in the 900 mg/day for 180 days group. Strategies for neutropenia risk reduction should be considered in high-risk LT recipients.

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CONFLICT OF INTEREST

Daniel Kaul receives research support from Nobelpharma. All other authors have no relevant conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Sarah Tischer designed this study. Alexandra L. Bixby and Sarah Tischer collected the data. Alexandra L. Bixby and Sarah Tischer analyzed the data. All authors interpreted the data. Alexandra L. Bixby wrote the manuscript, and all authors were involved in editing, reviewing, and final approval.

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