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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Incidence and risk factors for the development of cytomegalovirus viremia in a steroid sparing liver transplant center

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Abstract

Background: Cytomegalovirus (CMV) is a common opportunistic infection in patients after liver transplant (LT). Guidelines recommend 900 mg daily of valganciclovir; however, valganciclovir commonly causes dose-dependent hematologic toxicities. Use of a low-dose valganciclovir (450 mg) has been used to prevent these adverse effects, but the data regarding this dosing strategy are not as robust in a steroid sparing LT center.

Methods: Retrospective chart review of adult LT recipients between January 1, 2008 and June 30, 2019. All patients received low-dose valganciclovir 450 mg PO daily for CMV prophylaxis. Primary outcome was the incidence of CMV viremia in LT recipients at 12 months post-LT. Secondary outcomes include time to CMV viremia, risk factors for the development of CMV viremia, and incidence of breakthrough CMV viremia while on valganciclovir prophylaxis.

Results: A total of 266 patients were included. Overall, the majority were male (63.2%) and Caucasian (45.5%). The most common indication for transplant was decompensated cirrhosis (82%). The incidence of CMV at 1 year posttransplant was 7.9%. Independent risk factors included high risk status (OR 5.97, 95% CI 2.14–16.61, $p = .001$) as well as having an episode of rejection (OR 5.99, 95% CI 2.16–16.66, $p = .001$).

Conclusion: Low-dose valganciclovir can be effective in the prevention of CMV viremia in LT patients and may be a beneficial strategy for CMV prophylaxis in a steroid-sparing transplant center. Further studies may be needed to determine appropriate length of prophylaxis therapy for different risk groups.

KEYWORDS
CMV, cytomegalovirus, immunosuppression, LIVER transplant, viremia

1 | INTRODUCTION

Cytomegalovirus (CMV), a β-herpes virus, is a common virus that infects approximately 50% of adults by age 40.[1] CMV first occurs as a primary infection, which is asymptomatic in the immunocompetent, and it then lays latent in lymphatic tissue, where it can be reactivated down the line.[2] Immunosuppressed patients have higher morbidity and mortality associated with this virus, as it can progress to tissue-invasive, multiorgan involvement.[2] Without prophylaxis posttransplant, the incidence of CMV disease is approximately 18.9%.[3] Because of this risk, universal CMV prophylaxis is currently recommended to minimize this opportunistic infection complication.[4]

The 2019 guideline from The American Society of Transplantation Infectious Disease for CMV prophylaxis utilizes risk stratification to indicate the length of CMV prophylaxis for liver transplant (LT) patients.[4] Valganciclovir 900 mg daily is recommended for all patients with either a donor (D) positive or recipient (R) positive serology. The length of therapy varies depending on their risk stratification, with those high risk patients (D+/R−) requiring up to 6 months of prophylaxis. This higher dose of valganciclovir is recommended to ensure adequate serum concentrations to prevent viral infection as well to minimize development of drug resistance.[5] Low-dose or "mini dosing" is not currently recommended, particularly in D+/R−, due to concern for drug resistance.

However, many recipients are impacted by the bone marrow toxicities of valganciclovir, resulting in pauses in therapy. These interruptions in valganciclovir due to adverse effects could predispose patients to CMV infection and downstream complications. There is a high interest into strategies of how to minimize exposure to valganciclovir utilizing various dosing strategies or even early discontinuation of valganciclovir.[6] A lower dose of valganciclovir could prove to be effective in CMV prophylaxis for LT recipients while reducing the incidence of side effects and the potential for interruptions in therapy. Neutropenia occurs in up to 10% of patients on traditional valganciclovir prophylaxis dosing, but low-dose valganciclovir prophylaxis regimens have been used to offset these tolerability issues and to reduce adverse effects.[7–10] However, there is sparse data to say that this dosing strategy is effective and safe in LT recipients. The concern for the development of breakthrough CMV viremia and resistance is concerning and keeps many institutions from pursuing this option given the paucity of allograft-specific data.

Therefore, the purpose of this retrospective study is to assess the incidence of CMV viremia in a steroid-sparing LT institution using a low-dose valganciclovir protocol.

2 | METHODS

This was a retrospective, single-center study of LT recipients at the University of Illinois at Chicago Hospital and Health Sciences System (UIH). Adult (>18 years) isolated LT recipients from January 1, 2008 to June 30, 2019 were assessed. Data elements were obtained from UIH's electronic medical record. Patients were excluded if they received multiorgan transplants, were lost to follow-up within 1 year post-LT, or died <30 days post-LT.

Patient information was collected from postoperative day (POD) of transplant (POD0) until 1 year post-LT. Recipient demographic information, including model for end-stage liver disease (MELD) and MELD sodium (MELD-Na) scorings, were collected in addition to donor demographic information and virological statuses.[11,12] The patients MELD score was collected as the last MELD score documented pretransplant. The MELD-Na score was calculated with the MELD score, and the last sodium level collected pretransplant. The recipient's serum creatinine (SCr), estimated glomerular filtration rate (calculated by the modification of diet in renal disease study equation), calcineurin inhibitor levels, and other concomitant immunosuppression were collected at the time of transplant, at initial hospital discharge, and then on POD7, 14, 28, 90, 180, and 365.[13]

Patients were evaluated for CMV viremia up to POD365, defined as any quantifiable CMV polymerase chain reaction (PCR) result (lab threshold of > 450 copies/ml), as well as the therapy to treat CMV. Data were collected on the date of completion of valganciclovir prophylaxis and interruptions in therapy, defined as a patient not taking valganciclovir for 1 week or longer during the time of scheduled protocolized prophylaxis. Organ involvement was identified with pathology confirmation. Gastrointestinal CMV and CMV hepatitis were confirmed via pathology from biopsy. CMV pneumonia was confirmed with a bronchoalveolar lavage. CMV retinitis was confirmed by an ophthalmologist, and CMV encephalitis was confirmed with a lumbar puncture.[4]

Episodes of acute rejection were also evaluated and confirmed with a biopsy. Banff criteria was used to classify acute allograft rejection.[14] Treatment of mild course of rejection involved escalation of maintenance immunosuppression. Moderate to severe biopsy-proven acute rejection was treated with a 3-day course of high-dose steroids (methylprednisolone 500 mg x three doses), and select patients were also given a steroid taper after an episode of treated acute rejection at the discretion of the transplant team. The steroid taper was at the discretion of the treating transplant hepatologist. Steroid refractory rejection episodes were treated with antithymocyte globulin per transplant hepatologist discretion.

2.1 | Outcomes

The primary outcome of this study was the incidence of CMV viremia (defined as PCR > 450 copies/ml) in LT patients within 1 year of transplant. Secondary outcomes were the time in days to CMV viremia, risk factors for developing CMV viremia, treatment of CMV viremia, organ involvement of CMV viremia, incidence of breakthrough CMV viremia while on valganciclovir prophylaxis, incidence of CMV viremia after completion of 6 months of prophylaxis, and the incidence of valganciclovir resistance.

2.2 | Immunosuppression protocol

At the time of LT, recipients received IL-2 receptor antagonist (IL2RA) induction (basiliximab or daculizumab based on era). Other induction selections were deviations from the protocol by transplant surgeon discretion. Methylprednisolone 500 mg IV was also given on POD0 followed by a rapid steroid taper to discontinuation by POD6. Patients were maintained on steroids if they were on them chronically pre-LT or at the discretion of the transplant hepatologist for specific disease states (i.e., autoimmune hepatitis). Mycophenolic acid (MPA) 720 mg twice daily was started on POD1, and tacrolimus was initiated by POD2.

Maintenance immunosuppression was either tacrolimus monotherapy or low-dose tacrolimus with mycophenolate, which was stratified based on renal function. Those patients with tacrolimus monotherapy underwent MPA discontinuation at 3 months post-LT. In this protocol arm, tacrolimus goals were 8–10 ng/ml (months 0–1), 5–8 ng/ml (months 1–6), and 3–5 ng/ml (>6 months). For those LT recipients under the renal-sparing protocol, MPA was continued indefinitely at 360 mg by mouth twice daily, and tacrolimus goals were 8–10 ng/ml (months 0 –1), 5–8 ng/ml (months 1–3), 4–6 ng/ml (months 3–6), and 3–5 ng/ml (>6 months).

2.3 | Valganciclovir protocol

The patients were risk stratified into high-risk (D+/R−), moderate risk (D+ or D−/R+), and low risk (D−/R−) for CMV IgG status pretransplant. Preoperative valganciclovir 900 mg was given on POD0 for D+/R− LT recipients. For all other patients, no preoperative valganciclovir was given. For high-risk recipients (D+/R−), valganciclovir 450 mg daily was started on POD1. For D+/R+ and D−/R+, valganciclovir 450 mg daily was started upon transplant hospitalization discharge or on POD7, whichever occurred first. If patients were maintained on valganciclovir, then prophylaxis was maintained for a total of 6 months. Patients who were CMV D−/R− received acyclovir prophylaxis for herpes simplex virus prophylaxis for 1 month post-LT.

2.4 | Statistical analysis

The Shapiro-Wilk was used to test normality for continuous data. Parametric continuous data were compared with the Student's *t*-test and mean (standard deviation) were reported. Nonparametric continuous and ordinal data were compared with the Wilcoxon rank-sum test, and median (interquartile range [IQR]) was reported. Categorical data were analyzed by a chi-square or Fischer's exact test, as appropriate. To assess variable associations to CMV viremia, univariate logistical regression was performed for all variables, and those with a *p*-value of $< .05$ were included in multivariate analysis. Multivariate logistic regression model optimization was performed with a backward elimination using the Akaike information criterion. Model fit was then verified with the Hosmer and Lemeshow goodness-of-fit test. A receiver operating characteristic (ROC) curve was also assessed, and the area under the curve was reported for the final model. A *p*-value of $< .05$ was considered statistically significant. Data analysis was completed using STATA version 13.0 (StataCorp LLC).

3 | RESULTS

A total of 266 LT recipients from January 1, 2008 to June 30, 2019 met inclusion criteria and were analyzed. The majority were male (63.2%) and Caucasian (45.5%). The most common indication for LT was decompensated cirrhosis (82%), and the most common liver disease etiologies were alcohol-related liver disease (39.9%), hepatitis C (34.6%), and nonalcoholic fatty liver disease non-alcoholic steatohepatitis (NASH) (16.5%). The majority of the patients were considered to be moderate risk (71.1%), and 17% of patients were high risk. Further baseline demographic information is summarized in Table 1.

A majority of patients (91.7%) received IL2-RA induction. Upon index hospitalization discharge, 80.6% of patients were on tacrolimus, 92.9% were on MPA, and 16.9% were on prednisone. By POD90, 86.8% were on tacrolimus, 82% were on MPA, and 19.9% were on prednisone. Table 2 detailed patient induction and maintenance immunosuppression. The use of prednisone was further evaluated at POD7, 14, 21, 28, 90, 180, and 365 illustrating no difference in rejection in patients who were maintained on prednisone ($p > .05$).

A total of 21 patients (7.9%) tested positive for CMV viremia within the first year of LT. Twenty percent of high risk patients developed CMV viremia. The median time in days to CMV viremia was 204 days (IQR 122 days) (Table 3). At the time of CMV viremia, 47.6% of the patients had completed their 6 months of prophylaxis, and 42.9% had their prophylaxis held. Breakthrough CMV viremia occurred in 9.5% of LT recipients. Most of the patients had no CMV organ involvement (76.2%). Of those with tissue-invasive CMV disease, 14.3% had gastrointestinal involvement, and 9.5% demonstrated CMV hepatitis. There was no statistically significant difference in organ involvement between low risk, moderate risk, or high risk subgroups ($p = .192$). The majority (85.7%) were treated with valganciclovir with appropriate response. One patient spontaneously cleared the virus on their own and did not require treatment. No patients developed resistant CMV within the context of the analysis. Of the patients who tested positive for CMV viremia or disease, 61.9% were also treated with steroids for rejection compared to 32.2% of patients who did not test positive for CMV ($p = .008$). Approximately half of these patients were treated for rejection prior to CMV viremia, and half were treated for rejection after CMV viremia.

In univariate analysis, CMV D+/R− serostatus (OR 5.45, $p < .001$), acute rejection within 12 months of LT (OR 4.80, $p = .001$), increasing MELD-NA (OR 1.05, $p = .019$), and rejection treatment (OR 3.41, $p = .009$) were associated with the development of CMV viremia. Induction or maintenance immunosuppression was not identified risk factors within the scope of this analysis. Table 4 details the variables assessed in univariate modeling.

TABLE 1 Liver transplant recipient demographic information

	Total (*N* = 266)	No CMV (*N* = 245)	CMV (*N* = 21)	*p*-Value
Age, median (IQR)	56 (13.0)	56 (13.0)	57 (7.0)	.373
Gender (female), *n* (%)	98 (36.8)	89 (36.3)	9 (42.9)	.552
Race/Ethnicity, *n* (%)				.301
White	121 (45.5)	108 (44.1)	13 (61.9)	
Hispanic	62 (23.3)	60 (24.5)	2 (9.5)	
Black	51 (19.2)	46 (18.8)	5 (23.8)	
Asian	15 (5.6)	14 (5.7)	1 (4.8)	
Other	17 (6.4)	17 (6.9)	0 (0.0)	
Body mass index, median (IQR)	28.7 (8.8)	28.7 (8.7)	28.0 (7.4)	.544
Indication for liver transplant, *n* (%)				
Decompensated cirrhosis	218 (82.0)	202 (82.5)	16 (76.2)	.474
Acute liver failure	13 (4.9)	12 (4.9)	1 (4.8)	1.000
Hepatocellular carcinoma	81 (30.5)	80 (32.7)	1 (4.8)	.006
Systemic complications of chronic liver disease	89 (33.5)	82 (33.5)	7 (7.9)	.990
Other	22 (8.3)	20 (8.2)	2 (9.5)	.688
History of autoimmune disease, *n* (%)	14 (5.3)	12 (5.0)	2 (9.5)	.309
Liver disease etiology, *n* (%)				
NAFLD	44 (16.5)	39 (15.9)	5 (23.8)	.350
ALD	106 (39.9)	99 (40.4)	7 (33.3)	.525
HCV	92 (34.6)	88 (35.9)	4 (19.1)	.153
HBV	16 (6.0)	14 (5.7)	2 (9.5)	.366
AIH	11 (4.1)	11 (4.5)	0 (0.0)	1.000
PBC	8 (3.0)	7 (2.9)	1 (4.8)	.487
PSC	11 (4.3)	11 (4.5)	0 (0.0)	1.000
Hemochromatosis	4 (1.5)	4 (1.6)	0 (0.0)	1.000
Alpha-1 antitrypsin	4 (1.5)	3 (1.2)	1 (4.8)	.282
Cryptogenic cirrhosis	20 (7.5)	19 (7.8)	1 (4.8)	1.000
Other	24 (9.0)	20 (8.2)	4 (19.1)	.107
Pretransplant metabolic syndrome, *n* (%)				
CAD	20 (7.5)	19 (7.8)	1 (4.8)	1.000
DM	76 (28.6)	68 (27.8)	8 (38.1)	.314
HTN	105 (39.5)	95 (38.8)	10 (47.6)	.426
History of other organs transplanted, *n* (%)				
Kidney	2 (0.75)	2 (0.82)	0 (0.0)	1.000
Number of transplant, *n* (%)				1.000
First transplant	258 (97.0)	237 (96.7)	21 (100.0)	
Second transplant	8 (3.0)	8 (3.3)	0 (0.0)	
Liver transplant type, *n* (%)				.449
OLT	243 (91.4)	224 (91.4)	19 (90.5)	
LDLT	18 (6.8)	17 (6.9)	1 (4.8)	
Split liver	5 (1.9)	4 (1.6)	1 (4.8)	
MELD, median (IQR)	26 (19)	26 (20)	32 (9)	.010
MELD-NA, median (IQR)	28 (19)	27 (20)	33 (6)	.010

(Continues)

TABLE 1 (Continued)

	Total (*N* = 266)	No CMV (*N* = 245)	CMV (*N* = 21)	*p*-Value
CMV status, *n* (%)				<.001
High risk (D+/R−)	45 (17.0)	35 (14.3)	10 (47.6)	
Moderate risk (D+ or D−/R+)	191 (71.1)	181 (73.9)	11 (52.4)	
Low risk (D−/R−)	29 (10.9)	29 (11.8)	0 (0.0)	
ABO incompatible	3 (1.1)	2 (0.8)	1 (4.8)	.219
eGFR baseline	65.4 (57)	68.3 (59)	48.8 (37)	.070

Abbreviations: AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; CAD, coronary artery disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBV, hepatitis B; HCV, hepatitis C; HTN, hypertension; IQR, interquartile range; LDLT, living donor liver transplant; NAFLD, nonalcoholic fatty liver disease; OLT, orthotopic liver transplant; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

TABLE 2 Liver transplant recipient immunosuppression regimens

	Total (*N* = 266)	No CMV (*N* = 245)	CMV (*N* = 21)	*p*-Value
Induction Immunosuppression, *n* (%)				
Thymoglobulin	4 (1.5)	3 (1.2)	1 (4.8)	.282
IL-2RA (Daclizumab or basiliximab)	244 (91.7)	224 (91.4)	20 (95.2)	1.000
No monoclonal antibody	18 (6.8)	18 (7.4)	0 (0.0)	.376
Methylprednisolone	266 (100.0)	245 (100.0)	21 (100.0)	—
Immunosuppression at transplant discharge, *n* (%)				
Tacrolimus	241 (80.6)	224 (91.4)	17 (81.0)	.120
Cyclosporine	21 (7.9)	18 (7.4)	3 (14.3)	.223
Mycophenolate or mycophenolic acid	247 (92.9)	228 (93.1)	19 (90.5)	.652
Azathioprine	1 (0.38)	1 (0.4)	0 (0.0)	1.000
mTORi	9 (3.4)	8 (3.3)	1 (4.8)	.529
Prednisone	45 (16.9)	40 (16.3)	5 (23.8)	.380
No CNI as backbone	3 (1.2)	2 (0.8)	1 (4.8)	.225
Immunosuppression at POD90, *n* (%)				
Tacrolimus	231 (86.8)	213 (86.9)	18 (85.7)	.746
Cyclosporine	28 (10.5)	26 (10.6)	2 (9.5)	1.000
Mycophenolate or mycophenolic acid	218 (82.0)	201 (82.0)	17 (81.0)	1.000
Azathioprine	0 (0.0)	0 (0.0)	0 (0.0)	—
mTORi	21 (7.9)	19 (7.8)	2 (9.5)	.676
Prednisone	53 (19.9)	49 (20.0)	4 (19.1)	1.000
No CNI as backbone	7 (2.7)	6 (2.5)	1 (4.8)	.447
Steroid treatment for rejection, *n* (%)	92 (34.6)	79 (32.2)	13 (61.9)	.008

Abbreviations: CMV, cytomegalovirus; CNI, calcineurin inhibitor; POD, postoperative day.

The final multivariate logistic regression model revealed that high-risk CMV serostatus (OR 5.79, $p = .001$) and development of acute rejection within 12 months post-LT (OR 5.93, $p = .001$) were independent risk factors for the development of CMV viremia. Those with HCC were less likely to develop CMV viremia (OR 0.08, $p = .019$). The ROC area under the curve (AUC) for this final model was 80.84%. Table 4 details the multivariate logistic regression.

4 | DISCUSSION

Valganciclovir is the guideline recommended agent of choice for prophylaxis of CMV in solid organ transplant recipients.[4] Although institutional practice may vary across centers, universal prophylaxis is a core component of opportunistic infection prevention in those patients with LTs. This study demonstrates the efficacy of using

TABLE 3 Time to cytomegalovirus (CMV) viremia, organ involvement (CMV disease), treatment, prophylaxis status, and resistance to valganciclovir

CMV disease (organ involvement), *n* (%)	
Gastrointestinal	3 (14.3)
Hepatitis	2 (9.5)
None	16 (76.2)
Treatment, *n* (%)	
Valganciclovir	18 (85.7)
Ganciclovir	2 (9.5)
None	1 (4.8)
Prophylaxis status, *n* (%)	
Prophylaxis complete	10 (47.6)
Held <6 months posttransplant	9 (42.9)
On prophylaxis	2 (9.5)
Resistance, *n* (%)	0 (0)
Time to CMV viremia (days), median (IQR)	204 (122)

Abbreviation: IQR, interquartile range.

low-dose valganciclovir in LT recipients to prevent CMV viremia and disease without increased risk of resistance.

One study, published in 2018, assessed low-dose valganciclovir for intermediate-risk LT patients (D+ or D−/R+). Within this evaluation, two hundred patients were evaluated, and only nine (5%) of patients developed CMV disease (defined as clinical signs as well as detection of virus in any body fluid or tissue).[15] Our study looked to build on this data and demonstrated that low-dose valganciclovir was an effective prophylaxis strategy across not only intermediate patient serostatuses but also those high-risk patients as well. Another study looked at 3 months of low-dose valganciclovir prophylaxis and found an incidence of CMV viremia and CMV disease was 13% at 1 year.[16] The majority of the patients with CMV viremia and disease in the course of this evaluation were those with high-risk (D+/R−) serostatus (44%).[16] While this study was similar to our evaluation, the critical difference was in that steroids were continued chronically within the scope of this cohort. In this way, assessing the impact of this immunosuppression strategy on our CMV prophylaxis strategy was not possible. An additional study evaluated valganciclovir 450 mg daily versus 900 mg daily in high-risk LT patients who received triple immunosuppression.[17] The primary outcome, CMV disease, was not found to be statistically significant between the two groups, but 75% of CMV infections in the low-dose

TABLE 4 Univariate and multivariate analyses for development of CMV viremia

	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age	1.02	0.98–1.06	.383			
Gender (female)	1.31	0.53–3.24	.553			
Race, (black)	1.35	0.47–3.88	.575			
BMI	0.98	0.93–1.04	.607			
Serologic risk status (high risk)	5.45	2.16–13.80	<.001	5.79	2.11–15.96	.001
Thymoglobulin	4.03	0.40–40.78	.236			
IL-2RA	1.87	0.24–14.68	.549			
Acute rejection	4.80	1.91–12.08	.001	5.93	2.14–16.40	.001
MELD-Na score	1.05	1.01–1.10	.019			
ABO incompatible	6.08	0.53–69.93	.148			
HCC	0.10	0.01–0.78	.028	0.08	0.01–0.66	.019
HCV	0.42	0.14–1.29	.129			
Transplant type (OLT)	0.89	0.19–4.09	.882			
Tacrolimus	0.90	0.25–3.23	.873			
Cyclosporine	0.88	0.20–4.02	.668			
Mycophenolate	0.88	0.28–2.82	.832			
mTORi	1.25	0.27–5.78	.773			
Rejection treatment	3.41	1.36–8.57	.009			
Time period	1.08	0.40–2.91	.872			
Baseline eGFR	0.99	0.97–1.00	.065			

Note: Area under ROC curve = 0.8437.

Abbreviations: CMV, Cytomegalovirus; eGFR, estimated glomerular filtration rate; HCV, hepatitis C; MELD, model for end-stage liver disease; OLT, orthotopic liver transplant; OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index; ABO, ABO Blood Group; HCC, Hepatocellular Carcinoma; mTORi, mammalian target of rapamycin inhibitors.

group had end-organ disease involvement. The study also found the standard-dose group had significantly more neutropenia than the low-dose group (10% vs. 60%, $p < .001$). A limitation of this study is the generalizability in a steroid sparing center. However, our study found similar findings with low incidence of CMV viremia with the use of low-dose valganciclovir in LT patients. We found no incidence of CMV resistance to ganciclovir utilizing a low-dose regimen in our study.

With regard to pharmacokinetics, valganciclovir is rapidly converted to ganciclovir, and valganciclovir has a much higher bioavailability than its parent drug.[18] Understandably, valganciclovir 450 mg has lower systemic exposure than valganciclovir 900 mg. However, low-dose valganciclovir shows similar exposure to oral ganciclovir 1 g three times a day, a previously common dosing strategy for CMV prevention. In this way, the low-dose valganciclovir provides ample drug concentration to serve as CMV prophylaxis. However, obese patients and those with other pharmacokinetic considerations seen after transplant (i.e., diarrhea and gastroparesis) were excluded from this evaluation—thus limiting its real world applicability.

In reviewing clinical studies that evaluated high-dose valganciclovir 900 mg daily, a study published in 2016 found an incidence of 2.1% in patients receiving prophylaxis but noted that leukopenia was higher in this group as well.[19] This study only looked at 47 high-risk patients and compared prophylaxis to a preemptive strategy. Our study aimed to include all patients, regardless of risk stratification, to assess the use of this low-dose strategy across both intermediate- and high-risk serostatus groups. Studies compared high-dose valganciclovir to ganciclovir prophylaxis and found the incidence of CMV viremia to be noninferior to ganciclovir.[20,21] However, a different analysis under steroid-sparing immunosuppression in LT recipients demonstrated an even higher incidence of CMV viremia (14.3% at 6 months) when utilizing valganciclovir 900 mg daily for prophylaxis.[22] Of note, the majority of the patients from this evaluation had completed prophylaxis at the time of detected CMV viremia, and only 3.9% patients developed CMV viremia while on valganciclovir prophylaxis. Although these studies differ from our institutional practices, most institutions within the United States still continue steroids chronically after LT; in addition, many employ IL2-RA induction and continue mycophenolate (MMF) long term.[23]

In terms of the risk factors for CMV viremia, high-risk serologic status and having an episode of acute rejection in the first year post-transplant were independently associated with increased risk for CMV viremia. High risk serologic status has been proven to be a risk factor in previous studies and aligns with our data.[24] High risk patients do not have immunity to CMV prior to transplant, which poses a higher risk for developing primary CMV infection post-LT compared to other serostatus groups where patients have demonstrated CMV-specific IgG antibodies. The relationship between CMV viremia and episodes of acute rejection could be a result of different factors. Having an episode of rejection could be indicative of poor compliance by the recipient.[25] Compliance was not evaluated in our study due to the nature of a retrospective chart review. However, this could have been a causative factor if compliance was an issue for both the anti-rejection and prophylaxis medications. Further, a biopsy-proven episode of rejection at UIH Health generally results in a high dose or multiple high doses of steroids. These high doses of steroids assist in treating rejection but ultimately place the patient at a higher risk of immunosuppression, which could increase the patient's risk for reactivating CMV. This study illustrates the importance of vigilance to monitoring for CMV PCR after an episode of acute rejection.

There were limitations in this study, most notably this study being a single center and retrospective study. Because of this, there was no steroid comparator group available to further support these conclusions. The study also encompassed a span of 11 years where protocols, clinical practice, and medication use have likely changed over time. We attempted to control for the different time periods of different protocols and did not see any statistical significance, but likely nuanced differences still remain. As noted previously, adherence to medications could not be evaluated within the context of data collection. Although compliance was not noted to be a large issue based on documentation, we cannot rule this out as a potential weakness. Lastly, one of the difficulties of this study was the inability to reliably obtain all laboratory values to assess for toxicities associated with valganciclovir. There were instances where the documentation would state the patient may have developed leukopenia, but the value was not clearly documented in the electronic medical record (EMR). As a result, this is a limitation of this study as we were not able to reliably assess the incidence of bone marrow suppression in the LT patients. Future studies are in the process of evaluating this phenomenon within the scope of this patient population.

5 | CONCLUSION

This study illustrates that a low-dose valganciclovir regimen may be effective in a steroid sparing LT center. The incidence of CMV viremia at 1 year was 7.9%, and the majority were not currently on prophylaxis at the time of diagnosis. There were no cases of resistance to valganciclovir, and patients with CMV viremia all had resolution of their infection. The major risk factors for development of CMV viremia appeared to be in high-risk patients as well as patients that had an episode of rejection.

AUTHOR CONTRIBUTIONS

Emily Viehl, Alicia Lichvar, Christine Chan, and David Choi contributed to the design of the manuscript, wrote and revised the manuscript, and gave final approval and are accountable for the information presented.

CONFLICT OF INTEREST

David Choi has served on the speakers bureau for Janssen Pharmaceuticals. Other authors have no conflict of interest to disclose.

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