Volume 07, Issue 04 (July-August 2024), PP 90-95 **www.ijmsdr.org**
ISSN: 2581-902X

International Journal of Medical Science and Dental Research

Effectiveness of Low Dose Valganciclovir for Cytomegalovirus Prophylaxis in Liver Transplant Recipients

Naomi Pierre, PharmD, BCTXP[1], Nina Joiner, PharmD, BCPS, BCTXP[1]; Jillian Dietz, PharmD, BCTXP[1]
[1](*Department of Pharmacy, Cleveland Clinic, Weston, Florida, United States)*

Abstract.
Background: There is a lack of strong evidence supporting the use of low-dose valganciclovir (450 mg) for cytomegalovirus prophylaxis. The objective of this study was to compare the rates of cytomegalovirus viremia in liver transplant patients who received standard-dose valganciclovir (900 mg daily, adjusted for renal function) to those who received low-dose valganciclovir (450 mg, adjusted for renal function).

Methods: A retrospective chart review was conducted on liver transplant recipients to evaluate the safety and efficacy of low-dose valganciclovir compared to standard-dose. The primary outcome assessed was the incidence of cytomegalovirus viremia within 12 months. Safety endpoints included the incidence of leukopenia, thrombocytopenia, allograft loss, rejection, all-cause mortality, and death-censored allograft rejection between both groups.

Results: A total of 177 patients were included; 133 received standard-dose valganciclovir, and 44 received low-dose valganciclovir. The incidence of cytomegalovirus viremia was higher in the low-dose group as compared to the standard-dose group (16.2% vs. 6.0%; $p = 0.02$). All safety outcome measures were similar between both groups ($p > 0.05$).

Conclusion: The use of low-dose valganciclovir for prophylaxis in liver transplant patients was associated with an increased incidence of cytomegalovirus viremia as compared to the standard-dose group, but without any apparent safety benefits.

Keywords – *Cytomegalovirus, Opportunistic Infection, Valganciclovir, Liver transplantation, Neutropenia*

I. INTRODUCTION

Solid-organ transplant (SOT) recipients are at an increased risk for opportunistic infections due to the use of potent immune suppression medications aimed at preventing rejection. Cytomegalovirus (CMV) is one of the most common opportunistic infections associated with complications in SOT recipients.[1] Current guidelines recommend a target dose of valganciclovir (VGCV) 900 mg daily for CMV prophylaxis in intermediate and high-risk patients for a duration of 3-6 months respectively.[1-2] Some centers, however, use a reduced dose of 450

mg daily in liver transplant recipients. This lower dosage strategy is based on the notion that these patients generally carry a lower infection risk due to reduced use of induction therapy and lower immunosuppression targets. Additionally, this practice is also thought to reduce the risk of adverse effects, such as leukopenia and thrombocytopenia commonly associated with valganciclovir. Current guidelines do not recommend the use of low-dose VGCV given limited efficacy and safety data.[1-3] Furthermore, suboptimal dosing of VGCV has been associated with an increased risk of drug resistance.[2,4] The data used in formulating the guideline recommendations were however extrapolated from studies conducted in renal transplant recipients who generally require more immunosuppression as compared to liver transplant recipients. There is however some evidence in liver transplant recipients to suggest that the use of low-dose VGCV is safe and effective. Khan et al. conducted a retrospective review comparing standard-dose and low-dose valganciclovir for approximately 3 months in CMV intermediate-risk liver transplant recipients (CMV seropositive at baseline). Their findings revealed no difference in the rate of CMV disease, rejection, or leukopenia.[5] The purpose of this study was to determine the safety and efficacy of a reduced dose valganciclovir regimen in liver transplant recipients.

II. METHODS

2.1 Study Design and Protocol

This study was a single-center observational, retrospective historical comparison analysis conducted through chart review. All adult patients who underwent liver transplantation at the study center from January 2013 to January 2019 were assessed for eligibility. All liver transplant patients received a VGCV target dose of 900 mg daily for CMV prophylaxis from 2013 until 2018. Afterward, a lower target dose of 450 mg daily was implemented. Patients were included if they underwent liver transplant within the pre-specified time frame and received VGCV for CMV prophylaxis. Patients who underwent multi-organ transplant, retransplant, or who received other antivirals for CMV prophylaxis were excluded. Patients were stratified into the comparison arms respective to the dose of VGCV received. Standard-dose VGCV was defined as 900 mg daily adjusted for creatinine clearance (CrCl) per manufacturer's recommendation. Low-dose was defined as 450 mg daily, adjusted for CrCl in accordance to institutional protocol: a target dose 450 mg daily for CrCl 40 mL/min or above, 450 mg every other day for CrCl 25-39 mL/min, and 450 mg twice per week for CrCl less than 25 mL/min. The study protocol was approved by the hospital's institutional review board.

2.2 Outcomes

The primary efficacy outcome was CMV viremia within 12 months of transplantation, defined as a polymerase chain reaction (PCR) result greater than 137 copies/mL. Secondary outcomes included time to CMV viremia, incidence of leukopenia within 6 months defined as at least one incidence of white blood cell (WBC) count less than 4.0 K/µL, incidence of mild and severe thrombocytopenia within 6 months, defined as platelet (PLT) count less than 150,000/µL and PLT count less than 50,000/µL respectively, biopsy proven acute rejection within 12 months, time to rejection, allograft loss within 12 months leading to death or re-transplantation, incidence of other opportunistic infections, including Pneumocystis Jirovecii, Epstein-Barr virus, candida, aspergillosis, and cryptosporidium, mortality at 6 and 12 months, and death-censored allograft survival.

2.3 Statistical Analysis

Chi squared tests were used to analyze nominal dichotomous variables, student's t-test was utilized for continuous normally distributed variables, and Wilcoxon rank sum test was used for discrete and non-normal data. Statistical significance was defined as a p value of less than 0.05. All analyses were conducted using JMP SAS version 14.2.0 (SAS Institute Inc.).

III. RESULTS

3.1 Population Characteristics

A total of 242 patients were initially assessed for eligibility and 65 were excluded. Among the remaining 177 patients, 44 received low-dose valganciclovir (VGCV), while 133 patients received standard-

dose VGCV (Figure 1). At baseline, the average age was 59 years, with a majority of patients being males (61%). There were no significant differences observed between the low-dose and standard-dose groups in terms of gender distribution. The primary indication for transplantation was cirrhosis secondary to hepatitis C (33.3%, 59 patients). Most patients were classified as intermediate risk for CMV (62.1%, 110 patients).

Patients in the low-dose group had a higher baseline median serum creatinine (SCr) (1.3 [0.9 – 2.0] vs. 0.87 [0.7 – 1.3]; $p < 0.01$) and received induction therapy more often than patients in the standard-group (15.9% vs. 6%; $p = 0.04$). These findings aligned with the indication for the use of induction immunosuppression per institutional protocol for liver transplant. Patients in the standard-dose group received CMV prophylaxis for an average of one month longer than patients in the low-dose group (6.2 ± 1.9 vs. 7.1 ± 2.6; $p = 0.01$) (Table 1).

3.2 Outcomes

The incidence of CMV viremia within 12 months was significantly higher in the low-dose group compared to the standard-dose group (18.2% vs. 6.0%; $p = 0.02$). CMV viremia did not occur in low-risk patients (D-/R-). There were 6 cases amongst intermediate-risk patients (D±/R+), with 3 cases in the standard group (2.3%) and 3 cases in the low-dose group (6.8%). Patients who were high-risk (D+/R-) had the highest incidence at 10 cases, with 5 cases in the standard group (3.8%) and 5 cases in the low-dose group (11.4%). The average time to CMV viremia was 164 days in both groups ($p = 0.89$) (Table 2).

There was no difference in the incidence of leukopenia between 1 and 6 months when comparing the low-dose group and the standard group (86.4% vs. 74.4%; $p = 0.10$). The incidence of mild and severe thrombocytopenia was also similar (73.7% vs. 75.0%; $p = 0.86$; 17.3% vs. 13.6%; $p = 0.57$ respectively). There was no difference in the incidence of acute rejection within 12 months (22.7% vs. 15.8%; $p = 0.29$), or in allograft loss within 12 months (9.1% vs. 6.0%; $p = 0.48$). Death at 6 and 12 months occurred at similar rates (0.0% vs. 4.6%; $p = 0.13$; 0.0% vs. 0.8 %; $p = 0.56$ respectively), and death censored allograft survival was also similar (2.3% vs. 0.8%; $p = 0.71$). Patients in the low-dose group had a higher incidence of other opportunistic infections (22.7% vs. 9.8%; $p = 0.03$) (Table 2).

IV. DISCUSSION

In this single-center, retrospective, chart review, the use of low-dose VGCV compared with standard-dose VGCV significantly increased the incidence of CMV viremia without any appreciable reduction in the risk of adverse events.

Length of therapy is a key factor in adequate prophylaxis against CMV in immunocompromised transplant recipients. The standard duration per institutional protocol for CMV prophylaxis is 6 months for all risk stratifications. In this study, although patients in the low-dose group received prophylaxis for an average of 1 month shorter as compared to the standard-dose group, both groups received therapy for a sufficient length of time per guideline recommendations, which recommends 3 to 6 months for intermediate risk patients, and 6 months for high-risk patients.[1]

According to current guidelines, low-risk patients do not require CMV prophylaxis therapy; however, therapy with acyclovir, famciclovir, or valacyclovir should be considered against other herpes infections in corresponding seropositive patients.[1] Although the results of this study show no incidence of CMV viremia within low-risk patients in both groups, caution should be taken with interpretation as both groups received prophylaxis.

Khan et al. found no significant difference in CMV occurrence for intermediate-risk patients who received low-dose vs. standard-dose valganciclovir. In this study there was a difference between the two groups without account of risk stratification. The subset analysis revealed that most cases occurred in high-risk patients, followed by intermediate-risk patients. This is congruent with the expected risks associated with these respective serology donor-recipient matches. This suggests that utilizing low-dose valganciclovir for CMV prophylaxis in

low-risk liver transplant recipients rather than higher-risk patients, may be effective. Further analysis may be required to explore additional risk factors in addition to baseline CMV risk.

The study showed no significant difference in the incidence for leukopenia and thrombocytopenia. Additionally, the dose of VGCV did not have an effect on the incidence of acute rejection, allograft-loss, all cause-mortality, and death-censored allograft loss. In addition, a significant correlation was noted with increased incidence of other opportunistic infections in patients in the low-risk group. These results reinforce that there may be no safety benefit to using low-dose VGCV as compared to standard-dose VGCV.

This study has several inherent limitations due to its retrospective nature. CMV viremia was used as a surrogate outcome for CMV disease, due to inconsistent reporting in the medical record. Although there is data to suggest that viremia is predictive for disease, some studies have found that the quantitative CMV nucleic acid amplification test may not be suitable to detect compartmentalized cases, such as with CMV gastritis without dissemination.[6-9] Additionally, it was observed that patients in the low-dose group received more induction therapy with both a T-cell depleting and a non-T-cell depleting agent; however, this was not associated with an increased risk for CMV viremia, as none of these patients developed the outcome. Consideration should be given to data interpretation as patients with a CrCl 25-39 mL/min and CrCl less than 25 mL/min were dose-adjusted in a similar manner in both groups per protocol. Lastly, this study design was unable to assess for the emergence of drug-resistant CMV, which has been associated with the use of low-dose VGCV.[4]

V. Conclusion

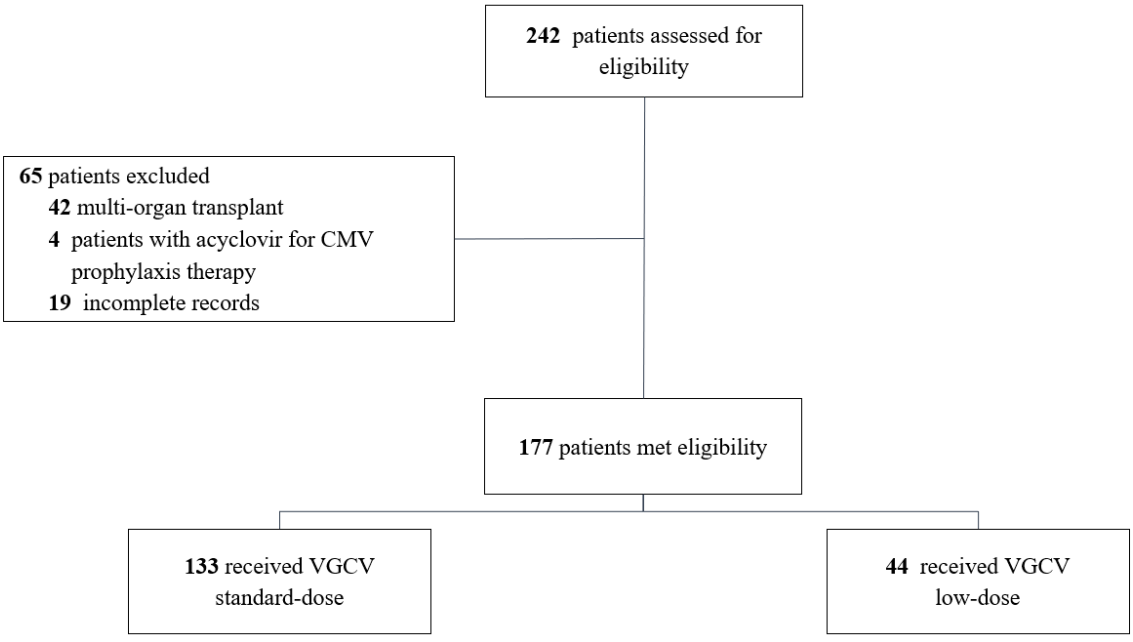
This study demonstrated that the use of low-dose VGCV was associated with a higher risk of CMV viremia in liver transplant patients compared to standard-dose VGCV with no safety benefit. Additional studies may help to validate these results and provide further recommendations for the prophylaxis of CMV in liver transplant recipients.

VI. Disclosure

The authors of this manuscript have no industry relations or financial conflicts of interest to disclose.

VII. Figures and Tables

Figure 1: Flow of Patients



VGCV, valganciclovir
Standard dose: 900 mg; adjusted for renal clearance; low-dose: 450 mg; adjusted for renal clearance

Table 1: Baseline Participant Characteristics

Variable	Standard-Dose VGCV (n = 133)	Low-Dose VGCV (n = 44)	*P* Value
Male, n (%)	87 (65.4)	25 (56.8)	0.31
Age at transplantation, Avg. ± SD	58.6 ± 10.1	60.5 ± 9.8	0.23
Liver transplant indication, n (%)			
Cirrhosis	125 (94.0)	39 (88.6)	0.24
Hepatocellular carcinoma	26 (19.5)	8 (18.2)	0.84
Hepatitis C	49 (36.8)	10 (22.7)	0.09
Hepatitis B	9 (6.7)	1 (2.3)	0.26
Alcoholic liver disease	23 (17.3)	10 (22.7)	0.42
Non-alcoholic fatty liver disease	23 (17.3)	7 (15.9	0.57
Other *	12 (9.0)	7 (15.9)	0.20
Past Medical History, n (%)			
Malignancy	25 (18.8)	12 (27.3)	0.23
Human Immunodeficiency Virus	2 (1.5)	0 (0.0)	0.41
Asplenia	0 (0.0)	0 (0.0)	-
Autoimmune disease	4 (3.0)	2 (4.6)	0.63
Diabetes	47 (35.3)	15 (34.1)	0.88
Donor (D)/Recipient (R) Serostatus at Transplantation, n (%)			
D-/R-	21 (15.8)	8 (18.2)	0.71
D± / R+	84 (63.2)	26 (59.1)	0.62
D+/R-	28 (21.1)	10 (22.7)	0.81
Baseline Labs, median [IQR]			
Baseline serum creatinine (mg/dL)	0.87 [0.7 -1.3]	1.3 [0.9 – 2.0]	< 0.01
Baseline white blood cell count (k/uL)	5.7 [4.1 -8.8]	5.49 [4.0 -7.9]	0.81
Baseline platelets (K/uL)	67 [44.3-103.5]	75 [61.3 -117.5]	0.09
Length of Prophylaxis Therapy in months, Avg. ± SD	7.1 ± 2.6	6.2 ± 1.9	0.01
Induction Therapy, n (%)			
Use of induction, n (%)	8 (6.0)	7 (15.9)	0.04
Anti-thymocyte globulin (rabbit)	4 (3.0)	3 (6.8)	0.26
Basiliximab	4 (3.0)	4 (9.1)	0.09
Dose Adjusted For creatinine clearance during course of therapy, n (%)	79 (59.4)	29 (65.9)	0.44

* *Other indications: Autoimmune Hepatitis; Wilson 's disease; Laennec's Disease; Hepatitis A; Primary Sclerosing Cholangitis; Cryptogenic Cirrhosis; Polycystic Liver Disease*
AVG, Average; IQR, interquartile range; SD, standard deviation; VGCV, valganciclovir

Table 2: Primary and Secondary Outcomes

Variable	Standard-Dose VGCV (n = 133)	Low-Dose VGCV (n = 44)	*P* Value
Primary Efficacy Outcome, n (%)			
CMV viremia within 12 months	8 (6.0)	8 (18.2)	0.02
D-/R-	0 (0.0)	0 (0.0)	-

D± / R+	3 (2.3)	3 (6.8)	-
D+/R-:	5 (3.8)	5 (11.4)	-
Primary Safety Outcome, n (%)			
At least one incidence of leukopenia between 1 to 6 months	99 (74.4)	38 (86.4)	0.10
Secondary Safety Outcomes, n (%)			
At least one incidence of mild thrombocytopenia between 1 and 6 months	98 (73.7)	33 (75.0)	0.86
At least one incidence of severe thrombocytopenia (PLT < 50,000/μL) between 1 and 6 months	23 (17.3)	6 (13.6)	0.57
Acute rejection within 12 months	21 (15.8)	10 (22.7)	0.29
Incidence of other opportunistic infections	13 (9.8)	10 (22.7)	0.03
Allograft loss within 12 months	8 (6.0)	4 (9.1)	0.48
Mortality within 6 months	0 (0.0)	2 (4.6)	0.13
Mortality within 12 months	1 (0.8)	0 (0.0)	0.56
Death censored allograft survival	1 (50.0)	1 (33.3)	0.71
Other Outcomes			
Time to CMV diagnosis (days post SOT), Avg. (SD)	164.6 (87.4)	164.0 (74.9)	0.89
Time to rejection (days post SOT), Avg. (SD)	138.7 (123.6)	96.8 (57.8)	0.21
Time to retransplantation (days post SOT), median [IQR]	19 (6 -145.5)	222 (18-222)	0.55

AVG, Average; IQR, interquartile range; SD, standard deviation; PLT, platelet; SOT, solid organ transplant VGCV, valganciclovir

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