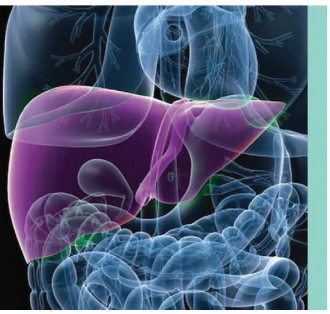

Spotlight on Impactful Research: Low-Dose Valganciclovir for Cytomegalovirus Prophylaxis in Intermediate-Risk Liver Transplantation Recipients

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Cytomegalovirus (CMV) is common after liver transplantation and can cause direct and indirect adverse effects in liver transplant recipients (LTRs).[1,2] CMV induces allostimulation and increases the risk for allograph rejection. Conversely, cytokine release after rejection and antirejection therapy increase the risk for CMV infection.

The occurrence of disease from CMV after transplantation varies according to the serological match between donor and recipient. In solid organ transplant (SOT), the greatest risk factor is the mismatch between donor and recipient when the donor is CMV positive (D+) and the recipient is CMV negative (R–); the patient is considered high risk for CMV disease. Patients with D+ and recipient CMV positive (R+) or CMV donor negative (D–) and R+ are considered at intermediate risk for CMV disease (Table 1). Prevention of CMV after SOT can be achieved with antiviral prophylaxis. Prophylaxis is the administration of antiviral drugs to all patients or higher risk patients for predetermined time periods after transplantation. Common antiviral regimens include oral valganciclovir (VGCV) or intravenous ganciclovir. Prior to the VGCV era, oral ganciclovir was used and has since been found to be less effective.

Mortality remains high even in the VGCV era, as high as 36% according to a study of SOT, including both high- and intermediate-risk patients. The recurrence rate of CMV is known to be as high as 30%.[3] Ganciclovir-resistance CMV

Abbreviations: AIH, autoimmune hepatitis; CMV, cytomegalovirus; D, donor; D+, donor is CMV positive; D–, donor is CMV negative; DDLT, deceased donor liver transplantation; FHF, fulminant hepatic failure; GCV, Gancyclovir; G-CSF, granulocyte colony-stimulating factor; GR-CMV, ganciclovir-resistance CMV; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; LDLT, living donor liver transplantation; LTR, liver transplant recipient; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; R, recipient; R+, recipient is CMV positive; R–, recipient is CMV negative; SOT, solid organ transplant; VGCV, valganciclovir; WBC, white blood cell.

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(GR-CMV) is emerging as a significant infection, which is difficult to manage with limited treatment options.[4-6] The reported rates are low while receiving prophylactic VGCV (0%-5%).

In LTRs who receive prophylaxis with VGCV, the incidence rates range from 12% to 30% in high-risk groups, D+/R–, to <10% in CMV R+ groups. Current guidelines recommend 3 to 6 months of prophylaxis in R+ groups who receive anti-lymphocyte antibody induction, with the AST guidelines in 2019 specifically recommending 900 mg/day renally dosed.[2,7,8] Unfortunately, many patients struggle with leukopenia and diarrhea secondary to use of VGCV requiring filgrastim (Neupogen).[9] The dose and duration of VGCV prophylaxis that are appropriate for intermediate-risk CMV LTRs remain unclear. Khan et al.[10] address this important issue in one of the highest downloaded articles from the journal *Liver Transplantation* in 2018, "Low-Dose Valganciclovir for Cytomegalovirus Prophylaxis in Intermediate-Risk Liver Transplantation Recipients."

Khan et al.[10] investigate the use of low-dose VGCV 450 mg/day adjusted for renal function for CMV prophylaxis in intermediate-risk LTRs. This retrospective, single-center study reviewed 200 LTRs meeting inclusion criteria from 2011 to 2014. The aim of the study was to demonstrate whether low-dose VGCV would be effective in preventing CMV disease and potentially safer in regard to leukopenia. Patient characteristics are noted in Table 2. R+ LRTs received VGCV 450 mg/day adjusted for renal function for 3 months or extended to 6 months if patient had rejection per hospital protocol. Immunosuppression included tacrolimus, mycophenolate, and prednisone, per hospital protocol. R+ LRTs receiving high-dose VGCV were identified via PubMed search. CMV disease occurring up to 1 year after liver transplant, leukopenia defined as <4000/mL white blood cell (WBC) count, and biopsy-proved rejection were the study endpoints. These patients were compared with historic control patients because this center has always used low-dose VGCV for prophylaxis in this group. Studies used for historic control patients are noted in Table 3.

In the study population, CMV DNAemia occurred in 8% of patients. CMV disease occurred in 5% of patients. Two-thirds of the patients who had CMV disease experienced this after the VGCV prophylaxis period had ended, with a median of 77 days (interquartile range [IQR] 38-94 days). None of the patients with CMV DNAemia had CMV disease in the follow-up period. The rate of CMV disease was similar to historic control patients receiving high-dose VGCV.

Leukopenia developed in more than three-fourths of patients in the low-dose VGCV cohort. The rate is similar to 69% in the historic control patients, although the control group used a lower cutoff WBC count of <3000/mL

TABLE 1. CMV RISK FOR SOT RECIPIENTS

Risk Category	D and R Seropositivity (+/–)
High risk	D+/R–
Intermediate risk	D+/R+, D–/R+
Low risk	D–/R–

TABLE 2. BASELINE PATIENT CHARACTERISTICS OF 200 R+ LT AT THE MOUNT SINAI HOSPITAL IN NEW YORK CITY 2011-2014

Characteristic	Value (n = 200)
Age, years	60 (54-66)
Male sex	129 (65)
MELD score	22 (14-31)
CMV serostatus	
D+R+	122 (61)
D–R+	78 (39)
Transplant type	
LDLT	22 (11)
DDLT	178 (89)
VGCV duration, months	3.4 (3.1-4.3)
Indications for transplant	
HCC	108 (54)
HCV	95 (48)
HBV	32 (18)
Alcoholic liver disease	21 (11)
NASH	15 (8)
Other*	32 (16)

Note: Data are given as n (%) or median (IQR).
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*Other includes cryptogenic cirrhosis, 9 (4.5%); PBC, 9 (4.5%); FHF, 8 (4%); AIH, 4 (2%); and PSC, 2 (1%).

TABLE 3. UNIVARIATE ANALYSES OF LEUKOPENIA COMPARING LTR ON LOW-DOSE VERSUS HIGH-DOSE VGCV

	VGCV 450 mg/day (n = 200)	VGCV 900 mg/day (n = 25)	*P* Value
Leukopenia	151 (76)	20 (80)	0.66
VGCV stopped early	12 (6)	0	0.37
G-CSF use	12 (6)	2 (8)	0.65
WBC nadir	2.5 (1.7-3.2)	2.3 (1.7-3.0)	0.35

Note: Data are given as n (%) or median (IQR).
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TABLE 4. HISTORICAL CONTROLS OF R+ LTR RECEIVING HIGH-DOSE VGCV PROPHYLAXIS

Study	Sample	Maintenance Immunosuppression	Prophylactic Regimen	CMV Disease Incidence, n (%)	CMV Disease Type	*P* Value*
Lindner et al.[12] (2016)	21 D+R+	Glucocorticoids, tacrolimus, MMF	VGCV 900 mg/day for 100 days	1 (5)	Tissue-invasive	1.00
Fayek et al.[13] (2010)	109 non-D+R–	Prednisone, tacrolimus or cyclosporine, MMF	VGCV 900 mg/day (n = 61) or oral GCV 1 g tid (n = 48) for 90 days	5 (5)‡	CMV syndrome (n = 4); tissue-invasive (n = 1)	0.97
Limaye et al.[14] (2006)	294 R+	Prednisone, tacrolimus or cyclosporine A, azathioprine or MMF	VGCV 900 mg/day or oral GCV 1 g tid for 90 days	14 (5)‡	CMV syndrome (n = 9); tissue-invasive (n = 5)	0.89
Jain et al.[15] (2005)	114 R+	Steroids, tacrolimus, MMF	VGCV 900 mg/day or 450 mg every other day depending on renal function for 90-180 days	15 (13)	"Symptomatic" nontissue invasive (n = 13); tissue-invasive (n = 2)	0.005

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*Probability of CMV disease compared with our cohort using Fisher's exact test or Pearson chi-square test as appropriate.
‡Not specified which patients received VGCV versus GCV; no significant difference in CMV disease incidence between VGCV and GCV groups.

to be considered as leukopenia. Rates of rejection were similar in both groups (Table 4).

One limitation to the study is the design of comparing different transplant centers in the low-dose and standard-dose groups. CMV prevalence and resistance profiles may vary from center to center and could be dependent on the immunosuppression regimen and patient population. The studies used vary in year from 2006 to 2016, as opposed to 2011 to 2014, which may have importance in the prevalence of CMV. Finally, the study group and historic control patients used a different cutoff for leukopenia.

Another significant limitation to the study is that it was completed reviewing LTRs from 2011 to 2014 in a setting without known GR-CMV. The prevalence of GR-CMV has significantly increased since that time. Rolling et al.[11] describe the first case at their institution in 2014 and up to 50% by 2015. All patients who acquired GR-CMV had been receiving dose-reduced VGCV. A total of 60% had rejection, and 100% had major complications. Notably, in this study, only 13% of patients were R+ LRTs.

Although the study by Khan et al.[10] confirms that low-dose VGCV has equal incidence of CMV, it cannot accurately discuss the risk for resistant strain CMV in those who become viremic.[11] In addition, this study did not show lower rates of leukopenia, which one would argue is a main incentive for lowering the dose of VGCV. Prior to universally accepting a low-dose VGCV regimen in this patient population, more studies will be needed in a patient population where GR-CMV is present.

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