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ORIGINAL ARTICLE

Multicenter evaluation of efficacy and safety of low-dose versus high-dose valganciclovir for prevention of CMV disease in donor and recipient positive (D+/R+) renal transplant recipients

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Abbreviations:

BPAR, biopsy-proven acute rejection; CI, confidence interval; CMV, cytomegalovirus; CrCl, creatinine clearance; D+, seropositive donor; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; GCV, ganciclovir; HR, hazard ratio; MPA, mycophenolic acid mTOR, mammalian target of rapamycin; NODAT, new-onset diabetes after transplantation; OI, opportunistic infection; OR, odds ratio; PK, pharmacokinetic; R–, seronegative recipient; R+, seropositive recipient; rATG, rabbit anti-thymocyte globulin; RTR, renal transplant recipient; VGCV, valganciclovir.

Abstract

Background: The cytomegalovirus (CMV) donor-positive/recipient-positive (D+/R+) population is the largest proportion of renal transplant recipients (RTR). Guidelines for prevention of CMV in the intermediate-risk D+/R+ population include prophylaxis with valganciclovir (VGCV) 900 mg/day for 3 months. This study is the first head-to-head analysis comparing the efficacy and safety CMV prophylaxis of VGCV 450 vs. 900 mg/day for 3-months in D+/R+ RTR.

Methods: A multicenter, retrospective analysis evaluated 478 adult RTR between 01/2008 and 10/2011. Study participants received VGCV 450 mg/day (Group 1; n = 398) or 900 mg/day (Group 2; n = 89) x 3 months for CMV prophylaxis. All VGCV was adjusted for renal function. All groups included in this study received study approved induction and maintenance immunosuppression regimens. The primary endpoint was incidence of CMV disease at 12 months.

Results: The rates of graft loss, patient survival, T-cell and/or antibody mediated rejection, hematological adverse events, opportunistic infections, and early VGCV discontinuation were evaluated. Patient demographics were comparable, but had significant differences in ethnicity and donor type between the groups.

Conclusion: The occurrence of CMV disease at 12 months was similar between the groups (3.5% vs. 3.4%; *P* = 1.000). Log-rank test found no statistically significant difference in the time to development of CMV between the 2 groups (*P* = 0.939).

KEYWORDS

Antivirals, cytomegalovirus, prophylaxis, valganciclovir

1 INTRODUCTION

Cytomegalovirus (CMV) continues to pose a significant challenge following renal transplantation due to its high degree of associated morbidity.[1,2] The direct effects of CMV disease, such as viral syndrome, tissue invasion, myelosuppression, and graft dysfunction, represent significant illness, yet it is the indirect effects of CMV disease that often are associated with more insidious consequences. These indirect effects may include an amplified risk for both graft rejection and new-onset diabetes after transplantation (NODAT), as well as an enhanced predisposition to super-infection with other opportunistic infections (OI). The serostatus of both the donor and recipient constitutes the principal risk factor for the development of CMV disease post-transplant. The highest risk group for developing CMV disease is the combination of a CMV seropositive donor (D+) transplanted into a seronegative recipients (R–). The type and degree of immunosuppression used and a variety of host features, including age, comorbidity and neutropenia, comprise additional risk factors.[1,2]

CMV seroprevalence in adults in the United States, according to the Centers for Disease Control and Prevention, is 50–80%. This would mean that a D+/R– transplant would occur in approximately 16–25% of all renal transplants performed. The largest at-risk group would be seropositive recipients (R+) receiving kidneys from a D+, which would account for 25–64% of all renal transplants. The D+/R+ and D–/R+ populations are often considered to be at intermediate-risk for the development of CMV disease. However, the D+/R+ group not only are at risk for reactivation of the latent virus, but also for a superinfection with a new viral strain. The D+/R+ population is more likely to

develop CMV viremia during preemptive therapy compared to D–/R+ patients, as well as being the population where the worst outcomes of CMV disease generally occur, in terms of graft and patient survival.[3–5] Given these outcomes and the overall number of D+/R+ transplant recipients, it is imperative that this population be studied for adequate CMV prophylaxis post-transplant and why we chose to evaluate this under-studied subgroup.

CMV prophylaxis is widely used among renal transplant recipients (RTR) and has been associated with reductions in CMV disease, mortality and graft rejection in at-risk individuals.[7–9] International consensus guidelines recommend the use of valganciclovir (VGCV), oral or intravenous ganciclovir (GCV), or valacyclovir as prophylaxis options for preventing CMV disease in D+/R+ RTR.[6,7] GCV has proven efficacy in the D+/R+ population.[8–11] However, given its ease of administration and proven efficacy in high-risk individuals, VGCV has become the preferred agent for CMV prophylaxis, despite its lack of indication for prophylaxis in the intermediate-risk population.[12,13] Witzke et al.[14]were the first to evaluate the use of high-dose VGCV (900 mg/day) for prophylaxis in D+/R+ RTR. This analysis revealed that VGCV prophylaxis was effective at preventing CMV viremia and disease compared to pre-emptive therapy.

VGCV is a prodrug for GCV and exhibits superior bioavailability compared to oral GCV.[12] The FDA approved dose of VGCV for prevention of CMV in high-risk RTR is 900 mg/day. Despite its lack of specific FDA approval for use in intermediate-risk patients, most centers utilize this agent in these patient populations and do so using the approved, guideline recommended, high-dose regimen. However, some transplant centers utilize low-dose (450 mg/day) prophylaxis based on pharmacokinetic (PK) data and experience.[15,16] Several groups have reported acceptable efficacy and tolerability with low-dose VGCV in high-risk abdominal organ transplant recipients.[15–24] In an international survey on CMV management, 34% of respondents acknowledged using low-dose VGCV for CMV prophylaxis in their D+/R+ population.[13] Given the varying dosing strategies among centers and the limited data comparing these dosing paradigms, this study was undertaken to compare the efficacy and safety of low-dose

vs. high-dose VGCV for prevention of CMV disease in intermediate-risk RTR. There are currently no studies in the literature evaluating high-dose vs. low-dose VGCV in the D+/R+ population.

2 METHODS

2.1 Study design and patient population

This is a multicenter, retrospective analysis evaluating the impact of 2 different 3-month prophylactic strategies of VGCV, 450 mg/day vs. 900 mg/day, on the prevalence of CMV disease in D+/R+ population during the first 12 months following transplantation. Adult RTR who were transplanted between January 1, 2008 and October 31, 2011 were evaluated. All patients' CMV prophylactic regimens were determined and implemented by individual transplant centers and were based on clinical experience and center-specific protocols. Centers participating in this study employed standardized 3-month anti-CMV regimens for all intermediate-risk recipients during the evaluation period. Group I (n = 398) patients were from seven transplant centers and received 450 mg/day of VGCV and patients in Group II (n = 89) consisted of patients from 3 transplant centers that utilized 900 mg/day of VGCV. No contributing transplant center changed their CMV prophylaxis protocols in intermediate-risk patients during the evaluation period. All participating centers received approval from their institutional review boards as a retrospective analysis; therefore, informed consent was not required. Inpatient and outpatient physical and electronic medical records, including laboratory data, clinic visit notes and medication histories, were reviewed for demographics, laboratory values, CMV viral loads, immunosuppressive therapies, transplant characteristics, pathology reports and patient and allograft outcomes. Laboratory values were only evaluated at the end of post-transplant months 1, 2, 3, 4, 5, 6, 9 and 12, ± 10 days. If laboratory values were only available outside of this 20-day range for each time point, they were not included in the analysis.

Eligible patients included RTR between 18 and 75 years of age who were seropositive for CMV prior to transplant and who received an organ from a CMV

seropositive donor. Patients must have received induction therapy using either an interleukin-2 receptor antagonist or rabbit anti-thymocyte globulin (rATG) to ensure similar induction regimens for all centers. Initial maintenance therapy was similar for all centers with patients receiving regimens including tacrolimus and mycophenolic acid (MPA), with or without early steroid withdrawal. Patients requiring a post-transplant conversion to a mammalian target of rapamycin (mTOR) inhibitor during the evaluation period remained in the study, despite data demonstrating that mTOR inhibitor-based immunosuppression can reduce CMV-related complications.[25] Reasons for exclusion from this analysis included patients with pre-existing infection from HIV, hepatitis B, hepatitis C, recipients of multi-organ transplantation (e.g., kidney/pancreas, etc.), patients receiving no induction therapy or receiving induction therapy or initial maintenance immunosuppression using any agent not listed in the inclusion criteria (e.g., OKT3, alemtuzumab, sirolimus, everolimus, or azathioprine), recipients with donor-specific antibodies that underwent pre-transplant desensitization and any patient where routine CMV viral load screening was performed during the first 12 months post-transplant, which was not standard-of-care at any site.

Regardless of the dose used, each contributing center started VGCV as soon as clinically feasible (i.e., stable urine output, improving creatinine clearance [CrCl], on oral medications) following transplantation, no later than 10 days, as per their clinical practice and transplant protocols. The initial intended VGCV duration for patients in this analysis was 3 months. Some patients received a longer duration of prophylaxis based on the local treating physician's discretion. Patients with compromised renal function, based upon calculated CrCl (calculated using the Cockcroft–Gault formula), received appropriate dosage adjustments. All renal dose adjustments in each group were done at the discretion of the treating transplant center. See Table 1 for an approximation of the renal dosing strategies used in each group.

Patients with evidence of either tissue-invasive CMV or CMV viral syndrome were considered to have CMV disease.[26] Patients diagnosed with CMV disease were treated using institution-specific practice guidelines. CMV viral syndrome was defined

as CMV viremia identified by quantitative polymerase chain reaction or pp65 antigenemia (center-specific) and at least 1 of the following: fever≥38 °C; new onset symptoms of viral illness; or leukopenia on 2 consecutive measurements.[26,27] Tissue invasive CMV was diagnosed in the presence of localized CMV infection (i.e., CMV inclusion cells, in situ detection of CMV antigen, cell culture, or DNA by immunostain or hybridization) in a biopsy specimen along with symptoms of organ dysfunction.

2.2 Efficacy

The primary efficacy endpoint was the number of patients who developed CMV disease within 12 months of transplant. Secondary efficacy parameters included the prevalence of breakthrough CMV (CMV infection while on VGCV therapy), GCV-resistant CMV, allograft loss, patient death, OI, and NODAT. OI was defined as documented infections within 12 months post transplantation including BK polyomavirus (urine or kidney), oral or systemic *Candida*, non-CMV human herpes viruses, and "other" unspecified OI. NODAT was defined as a composite endpoint consisting any of the following within 12 months of transplantation: symptoms of diabetes with random plasma glucose level ≥ 200 mg/dL, 2 fasting plasma glucose levels ≥ 126 mg/dL, or a glucose tolerance test resulting in a 2 hour post plasma glucose ≥ 200 mg/dL.

2.3 Safety

Safety was evaluated by the presence of abnormal hematological laboratory values. For this analysis, leukopenia was defined as a reduction in the circulating white blood cell count to < 3000/µL, and thrombocytopenia was defined as a platelet count of less than 150,000/µL. Safety was also assessed by need for premature VGCV discontinuation or dose reductions secondary to adverse events. Given the manner in which we measured the safety parameters and in order to capture as many hematological adverse events as possible, we also evaluated the use of granulocyte colony-stimulating factor (G-CSF) for treatment of leukopenia while patients were receiving VGCV prophylaxis.

2.4 Statistical methods

Comparisons of continuous variables between the 2 groups were performed by a nonparametric Wilcoxon rank-sum test and of categorical variables by a Fisher's exact test. Kaplan–Meier (KM) method was used to estimate the survival functions of CMV disease stratified by group. Log-rank test was used to test the statistical significance between the survival curves. Multivariable logistic regression was used to compare incident rates of CMV disease between the 2 groups. We considered all patient baseline demographic and transplant characteristics as well as early VGCV discontinuation status as potential confounders. Only those potential confounders that were statistically significantly different between the 2 groups at P <0.20 (i.e., race [nonwhite vs. white], donor type [living donor vs. deceased donor], rATG induction, and early VGCV discontinuation [defined as discontinuation of VGCV treatment before 3 months]) were included in the regression model. Cox's proportional hazard models were used to compare the time to the first CMV disease within 12 months of transplant between the 2 groups, adjusted for the same set of potential confounders. Time to event was censored at death, lost to follow-up (e.g. transfer, relocation), or end of 1-year post treatment period, whichever occurred first. Proportional hazards assumption of the Cox model was tested by including a time interaction with the group indicator.

We tested for differences in CMV disease rate across centers using Fisher's exact test and log-rank tests were then used to compare KM survival curves across centers.

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA)

3 RESULTS

3.1 Patients

A total of 478 patients were evaluated from 10 different transplant centers in the United States. Baseline demographics and transplant characteristics were reported in Table 2. The low-dose group containing significantly more living donor transplants (38.2% vs. 18.0%; P <0.001) and more patients of self-reported non-white race (60.1%

vs. 49.4%; *P* = 0.028). In terms of immunosuppression, induction with rATG use was more common in the low-dose group (70.4% vs. 41.6%; *P* <0.001). The types of maintenance immunosuppressants used were similar between the 2 groups, including early sterid withdrawal and conversion to sirolimus. However, tacrolimus levels were higher in the high-dose group vs. the low-dose group at both months 2 and 12 (10.3 ± 3.8 vs. 9.1 ± 3.5 ng/mL; *P* = 0.002, and 8.6 ± 2.6 vs. 6.9 ± 3.0 ng/mL; *P* <0.001, respectively), but similar at all other time points. MPA daily doses also trended lower during months 1 and 2 in the low-dose group with the only significant difference in the mean daily dose occurring at month nine (1544.9 ± 516.3 mg/day vs. 1704.9 ± 503.1 mg/day, expressed in mycophenolate mofetil equivalents; *P* = 0.024).

3.2 Efficacy

3.2.1 CMV disease:

CMV disease occurrence was similar between the 2 groups (3.5% vs. 3.4%; *P* = 1.000; Table 3). There was 1 case of breakthrough CMV disease in the high-dose group and no GCV-resistant CMV disease diagnosed in either group (Table 4). The KM survival curve is shown in Figure 1. Log-rank test found no statistically significant difference in the time to development of CMV between the 2 groups (*P* = 0.939).

Even after adjusting for demographic (race) and clinical differences (donor type, rATG induction, and premature VGCV discontinuation), no statistically significant difference in the risk of developing CMV disease were found between the 2 groups (odds ratio [OR]: 1.56; 95% confidence interval [CI]: 0.41–5.89, *P* = 0.513) [Table 5]. Consistent with this finding, Cox regression model shown in Table 6 found no difference in the time to CMV disease (hazard ratio [HR]: 1.52; 95% CI: 0.42–5.50, *P* = 0.527) within 12 months post-transplant. Test of proportional hazards assumption of the Cox model found no violation of this assumption (*P* = 0.695). Early discontinuation of the VGCV treatment before 3 months was associated with significantly increased risk of CMV disease (OR: 5.29; 95% CI: 1.35–20.87; *P* = 0.017) and shorter time to CMV disease (HR: 5.43; 95% CI: 1.51–19.58; *P* = 0.010).

No statistically significant variability of CMV disease across transplant centers were found (P = 0.3905). Log-rank test comparing the KM survival curves across centers found no significant difference in overall time to the first CMV disease within 12 months post-transplant (P = 0.460).

3.2.2 Acute rejection and graft function:

Overall, there were similar rates of biopsy-proven acute rejection (BPAR) in the low-dose group vs. the high-dose group (10.3% vs. 11.2%; P = 0.848) [Table 2]. Only 1 patient in each group had both BPAR and CMV disease. For the patients in the low-dose group, CMV diagnosis preceded the rejection episode by 3 months. For the patients receiving high-dose VGCV, BPAR occurred before the CMV disease diagnosis. Very few patients experienced graft loss during the study and the rate was similar for both dosing regimens (P = 0.403). While receiving prophylaxis, renal function was similar between the 2 groups. However, renal function, evaluated by serum creatinine and eGFR, was significantly higher in the low-dose group at 12 months (52.9 ± 20.0 vs. 45.9 ± 19.8 mL/min, P = 0.011) (Table 4); nonetheless, estimated CrCl was similar between the groups at 12 months.

3.3 Safety

Safety outcome were reported in Table 4. Despite the intended duration of prophylaxis being 3 months, the high-dose group had a significantly longer mean prophylaxis duration compared to the low-dose group (3.2 ± 0.8 vs. 3.5 ± 1.3 months; P = 0.002). The most common reason for the extended duration of prophylaxis was treating physician discretion or lack of communication with patients at 3 months post-transplant instructing them to discontinue therapy. Leukopenia, defined as a single white blood cell count <3 K/µL, was similar between both groups while receiving VGCV prophylaxis; however the high-dose group did demonstrate more leukopenia at month nine compared to the low-dose group (12.2% vs. 3.0%; P = 0.016). Thrombocytopenia, defined as a single platelet count < 150 k/uL, was similar between both groups during

the evaluation period. Despite similar rates of leukopenia, early VGCV discontinuation occurred more frequently in the high-dose group (13.6% vs. 6.5%; *P* = 0.045). The primary reason for VGCV discontinuation was hematologic adverse events in both groups (low-dose = 2.3% vs., high-dose = 11.2%; *P* <0.001). The prevalence of VGCV dose-reductions secondary to leukopenia was more common in the high-dose group (2.5% vs. 10.1%; *P* = 0.003). Given that we did not collect data on neutropenia, combined with the fact that our laboratory data collection techniques may have underestimated the true incidence of myelosuppression, we also evaluated the use of G-CSF for treatment of leukopenia in the 2 groups. G-CSF use was more common in patients receiving high-dose VGCV (7.0% vs. 19.1%; *P* = 0.001).

3.4 Other outcomes

The proportion of patients with confirmed OI, other than CMV disease, at 12 months post-transplant was comparable between the groups (low-dose = 20.6% vs. high-dose = 28.1%; *P* = 0.156). (Table 3) A closer look at the individual pathogens revealed that the rates of BK virus and herpes infections seen within the groups were similar, but thrush (1.8% vs. 5.6%, *P* = 0.049), systemic fungal infections (0.5% vs. 3.4%, *P* = 0.045), and other OI (8.3% vs. 18.0%, *P* = 0.010) were higher in the high-dose group. (Table 3) The proportion of non-diabetic patients with confirmed NODAT was similar (low-dose = 7.3% vs. high-dose = 6.7%, *P* = 1.000) at the end of the evaluation period. (Table 3)

4 DISCUSSION

National and international consensus guidelines have recommended the use antiviral prophylaxis as a method of CMV disease prevention in D+/R+ RTR.[6,7] The suggested prophylaxis agents and doses for intermediate-risk RTR include VGCV 900 mg/day, oral GCV 1 g 3 times daily, intravenous GCV 5 mg/kg/day, and valacyclovir 2 g 4 times daily. The goal duration of prophylaxis is 3 months in this population, but an expanded duration of 6 months may be considered in patients receiving an antilymphocyte antibody or undergoing pre-transplant desensitization. [6,7] Neither set of guidelines

condone the use of low-dose VGCV; however, as stated earlier, nearly 35% of centers report using the low-dose regimen in the intermediate-risk population.[13]

The low incidence of CMV disease in our large sample from multiple transplant centers indicates that a 3-month VGCV prophylaxis at either 450 mg/day or 900 mg/day is effective in the CMV D+/R+ population. Despite the major concern for emergence of GCV-resistance with low-dose VGCV prophylaxis, we did not observe any case of GCV-resistant CMV disease in our cohort. This is similar to what has been seen with low-dose VGCV prophylaxis in CMV high-risk patients.[15-24] In our analysis, neither VGCV regimen conferred a benefit on graft outcomes, patient survival or rejection. This result is in contrast to the meta-analysis completed by Kalil et al.[25]which, using an adjusted indirect comparison, showed a higher risk of allograft rejection with high-dose VGCV.

As mentioned previously, there is supporting evidence in favor of low-dose VGCV. Several PK studies have demonstrated that low-dose VGCV achieves GCV exposure comparable to that of oral GCV 3 g/day. These analyses concluded that low-dose VGCV provides ample drug exposure for effective CMV prophylaxis.[27–30] Kalil et al. [25] demonstrated, in a meta-analysis, that the low- and high-dose VGCV regimens provide equivalent efficacy for CMV prophylaxis (97% statistical power). Our group has recently published on the efficacy and safety of low-dose vs. high-dose VGCV in high-risk RTR showing equivalent efficacy between the 2 different dosing regimens.[24] With growing clinical evidence supported by PK data for the use of low-dose VGCV, it is reasonable to evaluate this regimen in the D+/R+ population.

In terms of other outcomes, the rates of leukopenia and thrombocytopenia were similar between the groups while they were receiving antiviral prophylaxis. Despite this, early VGCV discontinuation was more common in the high-dose group. In the majority of these patients, the primary reason for premature discontinuation was leukopenia. This trend was also noted in the increased use of G-CSF to manage leukopenia in patients receiving high-dose VGCV. We did note a significant difference in terms of invasive fungal infections, and other OI, reported as mostly varicella zoster and *Candida*

esophagitis, between the groups. However, data collection evaluating these infections was not significant enough to draw any firm conclusions from this observation.

Although a formal pharmacoeconomic evaluation was not completed in this analysis, one obvious advantages of the low-dose VGCV regimen is cost avoidance. Despite its availability as a generic, a 450 mg tablet of VGCV has a median wholesale price of $64.40. Based purely on cost avoidance, low-dose VGCV could provide a drug cost savings of nearly $5800 per patient. If cost for the decreased need of G-CSF therapy is considered, at $286.80–$601.56 per dose depending on formulation and dose, low-dose VGCV therapy is associated with a significant drug cost-avoidance benefit. This savings is important, as drug cost is a known risk factor for medication nonadherence.[34–36]

We acknowledge our study's limitations. Data was collected retrospectively and the safety analysis was based on a singular time points with a small window for evaluation (i.e., laboratory values were evaluated at the end of post-transplant months 1, 2, 3, 4, 5, 6, 9, and 12 [±10 days]). This may have led to an under representation of hematologic adverse events and missed periods of over- or under-immunosuppression in each group. Renal dosing may not have been consistent within each center or from center-to-center, particularly in the low-dose group given the lack of renal dosing guidelines for this regimen. However, renal dosing of any medication in patients with a fluctuating renal function, especially RTR, is a "clinician-specific" task that requires the use of many other clinical factors beyond serum creatinine, eGFR and creatinine clearance. This clinical judgment is applied to all medications that require renal dosing and is not limited to VGCV, regardless of the regimen used in this study. We depended on local CMV diagnoses, and evaluation of GCV-resistance, laboratory data and transplant-related outcomes. A thorough evaluation of all concomitant non-immunosuppressive medications was not undertaken. Data was collected over a large time period, where changes in clinical practice that may have influenced CMV disease may have occurred. Finally, CMV events were rare in this medium risk transplant patient population, limiting our ability to conduct more extensive statistical adjustments for

differences across the 2 treatment groups. Although we have adjusted for all available baseline patient demographic and transplant characteristics that are statistically significantly different between the groups at $P<0.2$, residual confounding is still possible.

This analysis is the first head-to-head study evaluating low- vs. high-dose VGCV in the intermediate-risk population. Along with previously published PK and retrospective studies in high-risk patients, we conclude that low-dose VGCV may provide adequate prophylaxis against CMV in D+/R+ RTR. It was noted that low-dose VGCV was associated with less G-CSF use and less premature discontinuation of prophylaxis because of leukopenia. There also appears to be a coincidental lower rate of invasive fungal infections, varicella zoster infection, and *Candida* esophagitis in patients treated with low-dose VGCV. The performance of a prospective, blinded, randomized evaluation is needed to truly evaluate the exact differences between these 2 dosing regimens.

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Author contributions:

S.H.: study design, data gathering, manuscript generation, editing and review; C.L.: data analysis, manuscript generation, editing and review; R.P.C., K.A.D., T.B.D., K.F., M.K., E.N., J.M.P., J.S.-K., E.M.T., K.R.U., R.W., and J.W.: data gathering, manuscript generation, editing; S.G.: study design, data gathering, data analysis, manuscript generation, editing and review.

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Figure legend:

FIGURE 1 Kaplain–Meier plot of time to cytomegalovirus (CMV) within 12 months post transplant, with number of subjects at risk.

TABLE 1 Renal dosing strategies used in each group

CrCl (mL/min)	Group I	Group II
>60	450 mg/day	900 mg/day
40–59	450 mg every other day	450 mg/day
25–39	450 mg twice weekly	450 mg every other day
10–24	450 mg twice weekly	450 mg twice weekly

CrCl, creatinine clearance.

TABLE 2 Patient demographic and transplant characteristic data

Characteristic	Group I (n = 398) VGCV 450 mg/day	Group II (n = 89) VGCV 900 mg/day	P-value
Age (yrs)	49.9 ± 13.2	51.6 ± 13.5	0.302
Weight (kg)*	77.7 ±18.6	78.5 ± 17.1	0.456
Male gender	230 (57.8%)	46 (51.7%)	0.344
Ethnicity/race			0.028
Asian/Pacific islander	35 (8.8%)	8 (9.0%)	
Black	92 (23.1%)	22 (24.7%)	
Hispanic	102 (25.6%)	10 (11.2%)	
Other	10 (2.5%)	4 (4.5%)	
White	159 (39.9%)	45 (50.6%)	
Donor Type			<0.001
LD	152 (38.2%)	16 (18.0%)	
SCD	92 (48.2%)	61 (68.5%)	
Other	54 (13.6%)	12 (13.5%)	
DCD	25	2	
ECD	27	10	
ECD/DCD	2	0	
Initial transplant	352 (88.4%)	83 (93.3%)	0.253
rATG induction	280 (70.4%)	37 (41.6%)	<0.001
ESW	30 (7.5%)	9 (10.1%)	0.393
mTOR inhibitor conversion	8 (2.0%)	1 (1.1%)	1.000
BPAR	41 (10.3%)	10 (11.2%)	0.848
Antibody-mediated rejection	8 (2.0%)	1 (1.1%)	1.000
Mean TAC conc. (mg/dL)			
Month 1	9.3 ± 3.5 (n = 396)	10.2 ± 4.3 (n = 86)	0.192
Month 2	9.1 ± 3.5 (n = 396)	10.3 ± 3.8 (n = 71)	0.002

Month 3	8.5 ± 3.4 (n = 389)	8.6 ± 3.5 (n = 65)	0.629
Month 6	7.5 ± 3.1 (n = 354)	8.7 ± 4.1 (n = 37)	0.052
Month 9	7.1 ± 4.3 (n = 349)	7.2 ± 2.6 (n = 35)	0.673
Month 12	6.9 ± 3.0 (n = 348)	8.6 ± 2.6 (n = 34)	<0.001
Mean MPA dose (mg/day)**			
Month 1	1856.7 ±3 70.4 (n = 396)	1812.5 ± 350.0 (n = 88)	0.089
Month 2	1793.8 ± 418.4 (n = 394)	1726.2 ± 428.0 (n = 84)	0.089
Month 3	1725.9 ± 450.5 (n = 384)	1700.0 ± 465.0 (n = 75)	0.571
Month 6	1585.7 ± 518.7 (n = 356)	1634.3 ± 519.2 (n = 67)	0.378
Month 9	1544.9 ± 516.3 (n = 340)	1704.9 ± 503.1 (n = 61)	0.024
Month 12	1513.2 ± 520.3 (n = 342)	1553.9 ± 587.1 (n = 65)	0.485

*One patient had missing weight measure.

** MPA doses are expressed in mycophenolate mofetil equivalents, where 720 mg of enteric-coated MPA = 1000 mg of mycophenolate mofetil.

VGCV, valgancicovir; yrs, years; LD, living donor; ; SCD, standard criteria donor; DCD, donation after cardiac death; ECD, expanded criteria donor; rATG, rabbit anti-thymocyte globulin; ESW, early steroid withdrawal; mTOR, mammalian target of rapamycin; BPAR, biopsy-proven acute rejection; TAC conc., tacrolimus concentration; MPA, mycophenolic acid.

TABLE 3 Primary and secondary efficacy endpoints at 12 months

Characteristic	Group I (n = 398)	Group II (n = 89)	P-value
Primary endpoint			
CMV disease	14 (3.5%)	3 (3.4%)	1.000
Viral syndrome	13	1	
Tissue invasive	1	2	
Secondary endpoints			
CMV diagnosis (days)	143.4 ± 42.4 (n = 14)	157.3 ± 107.4 (n = 3)	0.499
Breakthrough CMV	0	1	
Resistant CMV	0	0	
Allograft loss	17 (5.0%)	6 (6.7%)	0.403
Patient death	7 (1.8%)	3 (3.4)	0.400
Opportunistic Infections	82 (20.6%)	25 (28.1%)	0.156
BKV infection	58 (14.6%)	12 (13.5%)	0.869
Thrush	7 (1.8%)	5 (5.6%)	0.049
Herpes infection	9 (2.3%)	2 (2.2%)	1.000
Systemic fungal infection	2 (0.5%)	3 (3.4%)	0.045
Other opportunistic infections	33 (8.3%)	16 (18.0%)	0.010
NODAT	29 (7.3%)	6 (6.7%)	1.000

CMV, cytomegalovirus; NODAT, new onset diabetes after transplant; BKV, BK polyomavirus.

TABLE 4 Safety endpoints at 12 months

Characteristic	Group I (n = 398)	Group II (n = 89)	P-value
VGCV duration (months)*	3.2 ± 0.8	3.5 ± 1.3	0.002
Leukopenia (white blood cell < 3 (K/μL)			
Month 1	6 (1.5%) (n = 398)	1 (1.1%) (n = 88)	1.000
Month 2	22 (5.5%) (n = 397)	3 (4.1%) (n = 74)	0.781
Month 3	57 (14.4%) (n = 395)	15 (22.7%) (n = 66)	0.099
Month 6	19 (5.2%) (n = 367)	2 (4.7%) (n = 43)	1.000
Month 9	11 (3.0%) (n = 362)	5 (12.2%) (n = 41)	0.016
Month 12	19 (5.2%) (n = 369)	0 (0%) (n = 41)	0.239
Thrombocytopenia (platelets <150 K/μL)			
Month 1	51 (12.8%) (n = 398)	12 (13.6%) (n = 88)	0.861
Month 2	38 (9.6%) (n = 397)	9 (12.2%) (n = 74)	0.526
Month 3	35 (8.9%) (n = 395)	11 (16.7%) (n = 66)	0.072
Month 6	40 (10.9%) (n = 367)	6 (14.0%) (n = 43)	0.607
Month 9	38 (10.5%) (n = 362)	4 (9.8%) (n = 41)	1.000
Month 12	47 (12.8%) (n = 368)	5 (12.2%) (n = 41)	1.000
Platelets (K/μL)			
Month 1	247.8 ± 100.4 (n =	246.6 ± 97.2 (n = 88)	0.839
Month 2	398)	230.4 ± 65.1 (n = 74)	0.888
Month 3	231.6 ± 72.9 (n = 397)	225.6 ± 82.4 (n = 66)	0.417
Month 6	230.8 ± 75.5 (n = 395)	208.9 ± 61.0 (n = 43)	0.280
Month 9	217.6 ± 63.2 (n = 367)	219.3 ± 62.4 (n = 41)	0.783
Month 12	216.7 ± 64.4 (n = 362)	208.3 ± 66.4 (n = 41)	0.477
	214.2 ± 64.9 (n = 368)		
Early VGCV* discontinuation	21 (5.28%)	3 (3.4%)	0.594
VGCV discontinuation related to leukopenia	9 (2.3%)	10 (11.2%)	<0.001
VGCV dose reductions secondary to adverse events	10 (2.5%)	9 (10.1%)	0.003

Use of G-CSF for treatment of leukopenia during VGCV therapy	28 (7.0%)	17 (19.1%)	0.001
Serum creatinine (mg/dL)			
Month 12	1.4 ± 0.8 (n = 369)	1.6 ± 0.7 (n = 41)	0.005
eGFR (mL/min/1.73m^2)			
Month 12	52.9 ± 20.0 (n = 369)	45.9 ± 19.8 (n = 41)	0.011
CrCl (mL/min)			
Month 12	52.8 ± 19.4 (n = 368)	48.2 ± 17.1 (n = 41)	0.146

*One patient had missing actual VGCV duration.

VGCV, valganciclovir; G-CSF, granulocyte colony-stimulating factor; eGFR, estimated glomerular filtration rate (via MDRD formula); CrCl, creatinine clearance.

TABLE 5 Odds ratios of cytomegalovirus in the 12 month post transplant, estimated using logistic regression

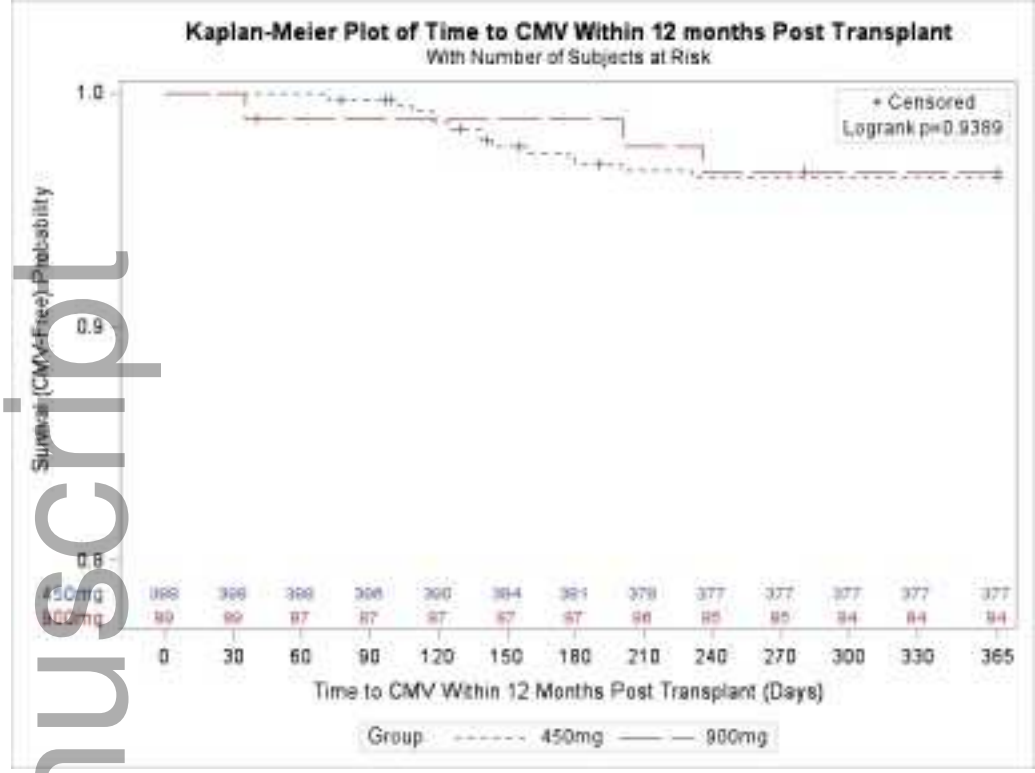
	Odds ratio	95% CI	P-value
Group (ref = 450 mg)	1.56	0.41–5.89	0.513
Nonwhite (ref = White)	0.88	0.32–2.39	0.800
Donor type (ref = LD)			
SCD	0.38	0.13–1.15	0.376
Other types	0.41	0.08–2.07	0.603
rATG induction	2.64	0.72–9.67	0.143
Early VGCV discontinuation	5.29	1.35–20.87	0.017

CI, confidence interval; ref, reference; LD, living donor; SCD, standard criteria donor; rATG, rabbit anti-thymocyte globulin; VGCV, valganciclovir.

TABLE 6 Hazard ratio of cytomegalovirus in the 12 months post transplant: estimated using Cox regression

	Hazard ratio	95% CI	P-value
Group (ref = 450 mg)	1.52	0.42–5.50	0.527
Nonwhite (ref = White)	0.86	0.33–2.28	0.767
Donor type (ref = LD)			
SCD	0.39	0.13–115	0.088
Other types	0.42	0.09–2.02	0.280
rATG induction	2.42	0.68–8.62	0.173
Early VGCV discontinuation	5.43	1.51–19.58	0.010

CI, confidence interval; ref, reference; LD, living donor; SCD, standard criteria donor; rATG, rabbit anti-thymocyte globulin; VGCV, valganciclovir.



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