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Every-Other-Day Valganciclovir Prophylaxis for Cytomegalovirus Prevention in Kidney Transplant Recipients: A Single-Center Experience

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Abstract

Background: Moderate-risk for Cytomegalovirus (CMV) infection includes patients with donor positive/recipient positive (D+/R+) or donor negative/recipient positive antibody status (D−/R+). Guidelines recommend high-dose daily Valganciclovir (VGCV) as prophylaxis, which may be due to the paucity of data on the efficacy of every-other-day VGCV.

Methods: Our experience of using every-other-day VGCV as a prophylactic strategy in moderate risk Kidney Transplant Recipients (KTR) has been described. We retrospectively reviewed 86 moderate-risk KTR in our institution between 2018 and 2020. CMV infection at 6 months post-transplant was the primary endpoint. Graft survival, biopsy-proven rejection, opportunistic infections, Haematological adverse events, and mortality were also evaluated.

Results: CMV infection occurrence at 6 months was zero in our cohort. Incidence of leukopenia was 13%, BPAR-31%, OI-33%, and mortality being 3.5%.

Conclusion: Every-Other-Day VGCV dosing can be an effective alternative in moderate risk KTR for CMV prevention.

Keywords: CMV prophylaxis; Valganciclovir; Kidney transplant recipients

Abbreviations

ATG-F: Anti-thymocyte globulin-Fresenius; BPAR: Biopsy Proven Acute Rejection; CD3: Cluster of Differentiation-3; CMV: Cytomegalovirus; D+/R-: Donor Positive/Recipient Negative; D-/R+: Donor Negative/Recipient Positive; D+/R+: Donor Positive/Recipient Positive; eGFR: Estimated Glomerular Filtration Rate; ug: Microgram; mg.h/L: Milligram.hours per Litre; MMF: Mycophenolate Mofetil; MPA AUC: Mycophenolic Acid Area under the Curve; ng/mL: Nanograms per millilitres; OI: Opportunistic Infection; PCR: Polymerase Chain Reaction; r-ATG: Rabbit Anti Thymocyte Globulin; TAC: Tacrolimus; VGCV: Valganciclovir; VZV: Varicella-zoster

Introduction

Cytomegalovirus (CMV) is a well-established opportunistic infection confronted in the post-transplant setting. Its impact on graft survival, morbidity, and mortality in renal transplant recipients has always remained very significant [1,2]. Anti-CMV Immunoglobulin G (IgG) is detected in plasma in renal donors with prior CMV exposure when being evaluated for transplantation and so it is one of the multiple factors that can influence CMV emergence, others being CMV serological status of the recipient, the usage of pre-emptive therapy or prophylaxis and immune-suppressants [3]. None of the given guidelines accepts the prescription of Every-Other-Day dose of VGCV for Cytomegalovirus (CMV) prophylaxis, which is partly due to the lack of published data [1]. However, in a survey conducted internationally, nearly 30-40% of centers have reported using the low-dose regimen of 450mg/day in the moderate-risk population [4]. The safety and efficacy of low-dose VGCV for CMV prophylaxis in 478 intermediate-risk Kidney Transplant Recipients (KTR) has been reported by Heldenbrand et al. [5], who found no significant difference in the 12-month incidence of CMV disease (3.4% *vs.* 3.5%), rejection (11.2% *vs.* 10.3%) or graft loss (6.7% *vs.* 5.0%) between patients receiving high *vs.* low-dose VGCV prophylaxis respectively. Khan et al. [6], also described a low incidence of CMV in 316 KTR i.e. 2.7% in D+/R+, 4% in the D-/R+ and 3% in R+, where they used 450mg/day (adjusted to renal functions) of VGCV as prophylaxis. We used even lower doses of VGCV prophylaxis (defined as 450mg on Every-Other-Day with renal dose adjustment if needed) in moderate risk KTR at our institution and have presented our findings.

Methods

A retrospective analysis utilizing our institutional electronic medical record system of a cohort of 86 CMV D+/R+ KTR between 2018 and 2020 was done. The analysis was conducted following the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice guidelines. Recipients included were live (related/directed - near and not near) or deceased complement-dependent cytotoxicity cross-match negative, HLA match or mismatch patients, along with ABO-incompatible recipients, who underwent desensitization. All transplant recipients received a single dose of Anti-thymocyte globulin - Fresenius (ATG-F) IV (2-5 mg/kg) as a part of induction therapy along with methylprednisolone 500mg IV on postoperative days 0, 1, 2 days as per unit protocol. Maintenance Immunosuppression included a combination of Anti-

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Table 1: Demographic and baseline characteristics.

	Alternative N (%)
Number	86
Age (Years)†	39.3 ± 12.20
Sex: Male	69 (80.0)
Weight (kg)†	60.76 ± 13.53
Allograft Type	
Live Donor	71 (82.5)
Deceased Donor	15 (17.5)
Live Donor	
ABO - incompatible	8 (9.3)
ABO - compatible	78 (90.7)
HLA Mismatch†	6.26 ± 2.37
CMV Serostatus	
D+/R+ (live)	71 (82.5)
R+	15 (17.5)
Induction r-ATG/ATG-F (mg/kg)†	3.44 ± 0.75
Immuno-suppression	
TAC/MMF	81 (94.2)
CSA/MMF	5 (5.8)
CD3 Level (cells/ml) †	224.5 ± 161.6

†Mean ± Standard Deviation; TAC: Tacrolimus; MMF: Mycophenolate Mofetil; CSA: Cyclosporine A; r-ATG/ATG-F: rabbit Anti-thymocyte globulin/Anti-thymocyte globulin - Fresenius.

proliferative agent i.e. mycophenolate mofetil (30mg/kg), Calcineurin inhibitor i.e. Cyclosporine (3-5 mg/kg) or Tacrolimus (0.15mg/kg) and Prednisolone (initially initiated at 20mg/day then was tapered to 2.5-5 mg/d at around 4 weeks post-transplant and remained the same during the study period.

The recipients received VGCV (defined as 450mg on every other day adjusted for renal function if needed) for CMV prophylaxis. Following transplantation, prophylaxis was given for the first 90-100 days. The primary endpoint being CMV infection incidence till 6 months (max incidence of CMV during this period) post-transplant defined as (i) Positive CMV Deoxyribonucleic acid (DNA) determination by Polymerase Chain Reaction (PCR) - which was performed based on clinical suspicion of the treating doctor (ii) Evidence of CMV with positive immunohistochemistry staining or viral inclusions on histology. The secondary endpoints included leucopenia episodes during the period of prophylaxis, graft survival, Biopsy-Proven Acute Rejection (BPAR), Opportunistic Infection (OI), and mortality.

Results

A total of 86 of moderate risk KTR were a part of our analysis. 80% of the patients were male and their mean age was 39 years (Table 1). All received VGCV prophylaxis for 90-100 days.

Efficacy

CMV infection: The incidence of CMV infection at 6 months after transplant was zero in both live and deceased KTR - moderate risk (Table 2).

Table 2: Primary and Secondary endpoints.

	Alternative N (%)
CMV-PCR (Tested) at 6th Month	7
Positive	0
Complications at 6th Month	
Diarrhea	2 (2.3)
Fever	16 (18.6)
Leukopenia	11 (12.8)
Opportunistic Infection	
Present	24 (32.5)
Absent	52 (67.5)
Mortality	
Month 1	1 (1.1)
Month 3	1 (1.1)
Month 6	1 (1.2)
Serum Creatinine(mg/dl) †	
Month 1	1.32 ± 0.86
Month 3	1.29 ± 0.41
Month 6	1.22 ± 0.39
Biopsy Proven Graft Dysfunction	
ATN	9 (10.0%)
Rejection	
ACR	15 (17.5%)
AMR	12 (13.9%)
Nil	59 (68.6%)

†Mean ± Standard Deviation; ATN: Acute Tubular Necrosis; ACR: Acute Cellular Rejection; AMR: Acute Antibody Mediated Rejection; CMV-PCR: Cytomegalovirus Polymerase Chain Reaction.

Safety and graft outcomes: The incidence of leukopenia was 13%, BPAR - 31%, OI - 33%, and mortality is 3.5% (Table 2). None of the biopsies showed immunohistochemistry staining, viral inclusions, or any other features suggestive of CMV.

Others: With regards to immunosuppression, r-ATG/ATG-F was used as induction (3.44±0.75 mg/kg). These patients received a baseline steroid dose of 3.29±1.34 mg/kg with a tacrolimus trough levels (10.51±2.48 ng/ml, 10.86±2.01 ng/ml and 10.21±1.76 ng/ml in 1st, 2nd, and 3rd months respectively), Cyclosporine levels (C0-176.8±39.78 ng/ml and C0- 157±30.75 ng/ml in the 1st and 3rd months respectively) and mycophenolic acid levels of 31.30±10.04 mg.h/l during the prophylaxis (Table 3).

Discussion

Our analysis adds to the growing evidence supporting the effectiveness of using low-dose VGCV in preventing CMV infection in moderate-risk KTR. Zero cases of CMV 6 months post-transplantation were seen in our cohort. Furthermore, the incidence of leukopenia also remained small. As stated previously, little evidence favoring very low-dose VGCV for prophylaxis is available but even after that none of the studies have used such low doses of 450mg on Every-Other-Day. Many Pharmacokinetic (PK) studies have demonstrated that GCV exposure levels at oral GCV 3g/day

Table 3: Characteristic of Immunosuppressive therapy in Patients during Follow-up.

	Alternative
Steroid dose	
Prednisolone (mg) †	3.29 ± 1.34
Mean TAC trough conc. (ng/ml) †	
Month 1	10.51 ± 2.48
Month 2	10.86 ± 2.01
Month 3	10.21 ± 1.76
Mean CSA trough conc. (ng/ml) †	
Month 1	176.8 ± 39.78
Month 3	157 ± 30.75
MPA AUC (mg.h/l) †	31.30 ± 10.04

†Mean ± Standard Deviation; TAC: Tacrolimus; CSA: Cyclosporine A; MPA-AUC: Mycophenolate Acid Area Under Curve.

dose can be achieved by low-dose VGCV. Our analyses inferred that low-dose VGCV can provide enough drug levels for effective CMV prophylaxis [7-9]. Kalil et al. demonstrated in a meta-analysis, that equivalent efficacy for CMV prophylaxis can be provided by either of the low or high-dose VGCV regimens (97% statistical power) [10]. With growing clinical evidence, which is supported by the PK data for the use of low-dose VGCV, the Moderate risk population can be reasonably evaluated by this regimen of Every-Other-Day dose.

Limitations

This is a single-center experience, hence may not apply to other transplant units. Data were retrospectively collected, hence did not have a group receiving the standard doses (as per guidelines) of VGCV as a comparison. In patients whose renal functions fluctuate, especially KTR, renal dosing of medication is a highly specific task that requires the use of elements beyond just serum creatinine and eGFR, these adjustments were made at the discretion of the treating doctor and hence not controlled. Finally, As CMV events are rare in our transplant population and testing was done based on clinical judgment; it limited our ability to get precise results. In summary, a low incidence of CMV infection, less adverse drug effects, and expected cost savings support the use of Every-Other-Day dosing of VGCV as CMV prophylaxis in moderate-risk KTR. Although a formal pharmaco-economic evaluation was never completed in our analysis, an undeniable superiority of the Every-Other-Day VGCV regimen was its cost advantage. Even though the cohort included patients of a moderate-risk group, all of them received ATG as induction therapy and were maintained on high CNI trough levels during the duration of valganciclovir prophylaxis in the post-transplant period hence they had a higher risk of developing CMV infection than the standard moderate risk group patients. In our opinion, such very low-dose VGCV prophylaxis in D+/R+ KTR can be considered as a viable option in future guidelines.

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