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Low dose valganciclovir as cytomegalovirus prophylaxis in post-renal transplant recipients induced with alemtuzumab: A single-center study

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ABSTRACT

Objectives: Alemtuzumab (Ale) is a recombinant monoclonal antibody which binds to CD52 causing profound lymphodepletion, thus allowing its use in renal transplantation induction therapy. However, patients may be at increased risk for opportunistic infections, such as Cytomegalovirus (CMV). We analyzed CMV infection in renal allograft recipients administered low-dose valganciclovir (VGCV) prophylaxis with alemtuzumab induction and steroid minimization.

Materials and methods: In this retrospective analysis, 678 kidney transplant recipients were evaluated, with 606 included for analysis. Patients were excluded for receiving induction therapy other than Ale, or for lack of follow-up within 1 year. VGCV prophylaxis was stratified by recipient CMV risk status and low-dose (450 mg) VGCV was given 3 times a week to low and moderate risk patients and daily to high risk individuals. Subject records were examined for recipient demographics, donor and recipient CMV serostatus, CMV viremia, and invasive infection.

Results: Of the 606 recipients, 154 were defined as low risk for CMV infection (donor and recipient both negative, or D−/R−), 236 as moderate risk without mismatch (D+/R+), 122 as moderate risk with mismatch (D−/R+), and 94 as high risk (D+/R−). Twenty-nine (29) individuals (4.8%) tested positive by PCR for CMV viremia and 10 (1.7%) patients developed invasive CMV disease, including colitis ($n = 4$), esophagitis ($n = 1$), enteritis ($n = 1$), nephritis ($n = 1$), and pneumonia ($n = 3$). High risk recipients (D+/R−) accounted for the majority of invasive CMV disease ($n = 5$), followed by moderate risk ($n = 4$). CMV viremia was also more common in high risk and moderate risk (D+/R+) individuals. Overall rejection rate for our study population was 27%.

Conclusion: In this institution's experience, CMV incidence was reduced compared to historically reported data by using low-dose (450 mg) VGCV prophylaxis in combination with Ale induction and steroid minimization. However, overall rejection rate was significantly higher in our population, possibly influenced by the degree of steroid minimization.

1. Introduction

Alemtuzumab (Ale) is a humanized, rat monoclonal antibody for CD52. The CD52 antigen is present on multiple immune cells, including T-cells, B-cells, macrophages, monocytes, and natural killer cells [1]. Although initially employed for the management of chronic lymphocytic leukemia (CLL), its potent and immediate depletion of lymphocyte cell lines rendered Ale an excellent candidate for immunosuppression in solid organ transplant [1,2]. The primary goal for incorporating Ale into induction therapy was to provide the potential of steroid-free maintenance regimens, while also minimizing the use of calcineurin inhibitors [3]. Ale has been demonstrated to provide satisfactory outcomes with relative steroid avoidance, allowing for circumvention of the negative effects of long-term steroid use [4–6]. Ale offers sustained suppression of the immune system, but it is often accompanied by additional risks, including an increase in the incidence of opportunistic infections [1,7,8].

Cytomegalovirus (CMV) is the most common opportunistic infection encountered in the post-transplant setting, with significant impacts on morbidity, mortality, and graft survival, especially in renal transplant

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recipients [9,10]. Delayed graft function, acute rejection, and increased rates of bacterial and fungal infections have all been linked to CMV [11]. Multiple factors can influence the emergence of CMV, including serostatus of the donor and recipient for CMV, immunosuppression, and the use of prophylaxis or pre-emptive therapy [11]. In order to minimize the risks to the patient and the allograft, appropriate prevention and/or surveillance measures must be employed.

Multiple prophylactic and pre-emptive therapy options exist for addressing CMV in post-renal transplantation. Prophylaxis aims at administering a course of antiviral therapy for a defined period of time, while pre-emptive therapy focuses on monitoring viral load and initiating antiviral therapy once a certain level has been reached [10]. Valganciclovir (VGCV) prophylaxis has been demonstrated as effective in the prevention of CMV in high (D+/R-) and moderate-risk (D−/R+ or D+/R+) renal transplant recipients both in low (450 mg) and high (900 mg) doses [12–14]. However, publications evaluating CMV incidence and various VGCV prophylaxis regimens rarely involve the utilization of Ale induction [12,13].

VGCV has demonstrated its potential as an effective agent in preventing CMV infection after Ale induction, though experiments have focused on Ale immunosuppression for leukemia, including CLL, rather than solid organ transplantation [15]. Overall, few manuscripts have been published relating CMV infection rates to VGCV dosing regimens after Ale induction for renal transplantation. The purpose of this retrospective investigation was to examine the effectiveness of lower dose VGCV (450 mg on Monday, Wednesday, and Friday for low/moderate risk and 450 mg daily for high risk) on preventing CMV infection in renal transplant recipients following Ale induction therapy with steroid minimization.

2. Materials and methods

2.1. Patients and data collection

This is a single center, Internal Review Board-approved retrospective analysis of Ale induction with steroid minimization. Three electronic medical record (EMR) systems were utilized to identify all renal transplant recipients starting on January 1, 2006, when Ale was first initiated as the primary induction therapy, to May 31, 2015. Clinical records were examined in full for details of donor and recipient CMV status, CMV prophylaxis prescribed, signs of CMV infection (including viremia, manifestations, and positive serology). Outcomes, such as rejection and graft failure, and their causes were also explored. Rejection incidences, including those leading to graft loss, were biopsy proven. A small set of patients had graft failure with clinically suspected rejection (not biopsy proven) and were labeled and grouped separately as “clinically suspected rejection” for cause of graft failure. Prophylactic drug administration was examined for any notes regarding completion and/or early termination of therapy. Patient records were explored for adherence to prophylaxis protocol based on recipient CMV serostatus, but individual patient compliance to medication, including VGCV prophylaxis, could not be ascertained.

Exclusion criteria included any patient who received induction therapy other than Ale or was lost to follow-up within a year following transplantation due to death, transfer of care to another facility, or non-adherence to follow-up visits. A total of 678 individuals were evaluated, with 606 included for analysis.

2.2. CMV disease

CMV serostatus of pre-transplant patients was determined by positive CMV antibody titer. Per institutional protocol, CMV DNA by PCR was employed in the post-transplant setting to confirm or rule out CMV infection in the presence of clinical suspicion of CMV syndrome or invasive CMV disease. Routine PCR testing for CMV DNA was not performed. CMV viremia was defined as a positive blood CMV DNA titer by PCR with or without any clinical symptoms. Invasive CMV disease was defined by a positive PCR and included CMV syndrome, commonly fever and malaise, and associated leukopenia and thrombocytopenia, as well as organ involvement such as pneumonitis, gastroenteritis, hepatitis, and retinitis. These definitions are consistent with criteria described by Ljungman et al. and utilized in other publications [16–18].

2.3. Immunosuppression and CMV prophylaxis

Per institutional protocol, transplant recipients received a single dose of Ale 30 mg IV (or 0.5 mg/kg if the patient was under 60 kg) with mycophenolate 540 mg, and methylprednisolone 500 mg IV prior to transplantation. Diphenhydramine 25 mg IV was provided as premedication prior to Ale. Tacrolimus was administered on post-operative day (POD) 1, and titrated to a goal trough of approximately 10 ng/ml initially. Mycophenolate sodium was initiated on the same day, starting at 540 mg per oral (PO) twice daily and titrated to 720 mg twice daily or as tolerated. For bacterial prophylaxis, sulfamethoxazole/trimethoprim double-strength tablets were administered three times a week, while clotrimazole 10 mg troches were utilized four times a day for fungal protection.

VGCV prophylaxis was stratified by recipient CMV risk status into high risk (CMV donor positive and recipient negative; D+/R−), moderate risk without mismatch (donor positive and recipient positive; D+/R+), moderate risk with mismatch (donor negative and recipient positive; D−/R+), and low risk (donor negative and recipient negative; D−/R−). 450 mg VGCV on Monday/Wednesday/Friday (MWF) was provided to low and moderate risk recipients both with and without mismatch, while 450 mg VGCV daily was utilized in high risk individuals. All immunosuppression and CMV prophylaxis regimens were consistent throughout the almost 10-year study period.

2.4. Statistical analysis

Continuous variables were presented in medians with standard deviation and were compared using *t*-tests or Mann-Whitney *U* test when appropriate. Categorical variables were presented in terms of percentage of the total number within the group. Differences in rejection, DCGS, and patient survival were assessed using the Kaplan-Meier model. They were compared with Pearson's Chi-square or Fisher's Exact Test. Type I error level was set at 0.05. All statistical analyses were conducted using IBM SPSS ver23 (IBM Corp., Armonk, NY).

3. Results

3.1. Demographics

In total, 678 patients were evaluated with 606 included for analysis. Two were excluded for receiving induction therapy other than Ale and seventy due to lack of follow up within one year. The median age was 53.4 ± 14.0 years. 18.5% were elderly (defined as > 65 years old), and 63.9% were male. The ethnic breakdown was 70% white, 23.1% black, 4.6% Hispanic, and 2.3% Asian. 23.3% had a history of a prior renal transplant (retransplant), and 18.2% had a panel reactive antibody (PRA) of > 20%. These demographics, as well as donor factors, are listed in Table 1. Demographics significantly associated with CMV viremia included retransplant ($p = .012$), extended criteria donor ($p = .018$), and donor diabetes mellitus ($p = .004$) (Table 2).

Recipients were stratified by risk category for CMV. 154 patients (25.4%) were defined as low risk for CMV infection (D−/R−), 236 (38.9%) as moderate risk without mismatch (D+/R+), 122 (20.1%) as moderate risk with mismatch (D−/R+), and 94 (15.5%) as high risk (D+/R−).

Table 1
Study demographics.

Age at transplant	53.4 ± 14.0
Elderly (> 65 yoa)	18.5%
Male sex	63.9%
White race	70.0%
Black race	23.1%
Hispanic race	4.6%
Asian race	2.3%
Retransplant	23.3%
PRA > 20%	18.2%
Deceased donor	73.9%
Extended criteria donor	11.7%
Donor deceased after cardiac death	9.0%
Donor age	39 ± 14.7
Donor HTN	20.2%
Donor DM	5.3%
Recipient DM	39%

Table 2
Demographic risk factors and viremia.

% Viremia	Risk factor	Control	Significance
Elderly (> 65 yoa)	6.4%	4.4%	0.454
Male sex	4.6%	5.1%	0.843
Black race	3.6%	5.1%	0.650
Recipient DM	6.0%	4.0%	0.329
Retransplant	9.1%	3.4%	0.012
PRA > 20	5.5%	4.7%	0.629
Cadaveric donor	5.3%	3.2%	0.385
ECD	13.2%	4.5%	0.018
DCD	7.5%	5.1%	0.461
Donor HTN	8.4%	3.9%	0.054
Donor DM	17.6%	4.0%	0.004
Private health insurance	4.3%	5.0%	0.847

3.2. CMV prophylaxis

Prophylaxis using 450 mg VGCV was generally daily or MWF dosing. MWF dosing was preferred for low risk (75.4%) and both moderate risk categories (73.5% and 83.5%), while 66.7% of high-risk individuals received daily dosing. Other possible outcomes included transitioning from MFW to daily dosing (0.8% of patients), from daily to MWF (4.3%), acyclovir dosing (0.5%), or no prophylaxis (1.3%). Intended CMV prophylaxis by risk status is outlined in Table 3 and actual prophylaxis regimens are detailed in Table 4.

No difference existed between risk groups regarding adherence to CMV prophylaxis protocol. Reasoning for deviating from the prescribed regimen included leukopenia (9.9% of patients), medication intolerance (0.5%), interruption of prophylaxis regimen for treatment of CMV viremia/disease (0.3%), or other reason (1%). Overall, 71 (11.7%) individuals deviated from the initially-assigned protocol.

359 of 606 patients (59.2%) were fully adherent, defined as not discontinuing the prophylaxis protocol for any reason. Retransplanted individuals were more likely to be fully adherent (24.8% vs. 13.8%, $p = .002$); no other tested factors were significant (Table 5). Adherence to prophylaxis did not affect risk of developing viremia (5.6% vs. 4.1% for full) or invasive disease (0% vs. 2%) (Table 6).

3.3. CMV viremia

29 (4.8%) individuals tested PCR positive for CMV viremia. The majority of these (21) received MWF prophylaxis; 11.7% of the high-risk group developed viremia vs 3.5% of others ($p = .002$). Six individuals developed viremia having received daily prophylaxis, and 1 viremia patient was initiated on daily prophylaxis, but was transitioned to MWF due to leukopenia. Prophylaxis dosing frequency was not a significant predictor of viremia (4.5% of daily vs 5.2% of MWF), nor was adherence (4.1% of full adherence vs 5.6%) (Table 6).

3.4. Invasive CMV disease

10 of the CMV PCR positive viremia patients developed invasive CMV disease, including colitis ($n = 4$), esophagitis ($n = 1$), enteritis ($n = 1$), nephritis ($n = 1$), and pneumonitis ($n = 3$). High-risk status transplants accounted for the majority of invasive CMV disease ($n = 5$), followed by moderate risk ($n = 4$). One individual, considered low risk pre-transplantation, developed CMV colitis. 50% of invasive disease cases occurred in high risk recipients (5.3% of group), while only 1% of the non-high-risk group were affected. Again, neither dosing scheme (2.2% of daily vs. 1.6% of MWF) nor adherence (2% of full vs 0%) were significant predictors of invasive disease (Table 6). Table 7 lists dosing schedule and invasion outcomes for risk status groups.

3.5. Outcomes

A statistically significant increase in the incidence of 3 and 5-year graft rejection was observed with viremia when measured against those without viremia. 3-year rejection was 45.3% with viremia and 26.3% without viremia ($p = .041$) while 5-year rejection was 53.2% for the viremia group compared to 28.3% in the control ($p = .021$). Graft rejection was also significant between individuals with invasive CMV disease and those without for 90-day (40.0% vs 15.4%; $p = .031$), 1-year (50.0% vs 22.0%; $p = .022$), and 3-year (50.0% vs 26.7%; $p = .046$) rejection. 5-year, but not 1 or 3-year, death-censored graft survival (DCGS) was significantly lower for both viremia (50.5% vs 87.6%; $p = .001$) and invasive disease groups (37.5% vs 86.9%; $p = .002$) as compared to the control. Overall graft rejection and patient survival were not significant for viremia or invasive disease versus control. Total DCGS was significantly less for both viremia (72.4% vs 87.4%; $p = .043$) and invasive disease (60.0% vs 87.1%; $p = .033$). However, overall (or total) graft rejection, DCGS, and patient survival inherently have some confounding variables and so should not be emphasized over the 1, 3 and 5-year results. Delayed graft function (DGF) and patient survival were not significantly influenced by viremia or invasive CMV disease (Table 8). Dosing scheme, adherence, and risk status showed no significant differences in rejection, DCGS, or patient survival.

Causes of graft failure included acute rejection, chronic rejection, graft thrombosis/allograft complication, death, recurrent disease, primary nonfunction, clinically suspected rejection, and other. No significant difference existed in any cause of graft failure for viremia or invasive disease compared to the controls (Table 9).

Table 3
Valganciclovir prophylaxis by CMV risk status.

CMV risk	Valganciclovir dose
Low risk (D−/R−)	450 mg on Monday, Wednesday and Friday for 6 months
Moderate risk (D−/R+ or D+/R+)	450 mg on Monday, Wednesday and Friday for 6 months
High risk (D+/R−)	450 mg daily for 1 year

Table 4
Valganciclovir prophylaxis dosing regimen.

CMV prophylaxis						
Risk status	None	MWF	Daily	Acyclovir QD	MWF - > daily	Daily - > MWF
D−/R−	3 (2.2%)	104 (75.4%)	22 (15.9%)	2 (1.4%)	2 (1.4%)	5 (3.6%)
D+/R+	5 (2.2%)	164 (73.5%)	41 (18.4%)	0	3 (1.3%)	10 (4.5%)
D−/R+	0 (0%)	91 (83.5%)	13 (11.9%)	0	0	5 (4.6%)
D+/R−	0 (0%)	22 (25.3%)	58 (66.7%)	1 (1.1%)	0	6 (6.9%)

p = .285.

Table 5
Prophylaxis adherence.

	Full adherence	Not full	Sig
Median age	51.8 ± 14.2	55.7 ± 13.4	0.789
Elderly	19%	16.5%	0.493
Black	25.7%	19.3%	0.094
Hispanic	4.1%	6.4%	0.237
Asian	1.6%	3.2%	0.244
Diabetes mellitus	37.9%	40.7%	0.527
Retransplant	24.8%	13.8%	0.002

3.6. Other infections

Incidences of other infections were analyzed in those with CMV viremia compared to the control. Variables analyzed included bacterial infection, fungal infection, parasitic infection, and BK viremia. A greater percentage of CMV viremia patients had at least one bacterial infection (58.6% vs. 31.7%; p = .004) and at least one fungal infection (13.8% vs. 3.5%; p = .023). One individual with CMV viremia had a parasitic infection, specifically cryptosporidium. Some recipients with CMV viremia also had BK viremia, but the two infections were not significantly associated (Table 10).

4. Discussion

Ale induction therapy offers the benefit of possible steroid-free maintenance regimens and decreased use of calcineurin inhibitors while providing sufficient immunosuppression. Kaufman et al. reported > 99% DCGS at 1 year and rejection rates below 15% with such a regimen, while Hanaway et al. found comparable or superior graft survival and rejection outcomes over multiple time points [4,5]. When compared to traditional induction regimens including basiliximab, recipients experienced a durable, sustained suppression of the immune system, but with additional risks. These risks included more opportunistic infection complications, such as cytomegalovirus (CMV) infections [1,7,8]. However, the overall CMV incidence at this institution using Ale induction appears to be less than historically reported with other therapies (4.8% vs. 8–32%) [1,17,19]. Consistent with historical literature, of those who experienced invasive CMV disease, gastrointestinal disease (colitis, enteritis, esophagitis) was the most common manifestation [20].

Multiple therapies currently exist for prophylaxis against CMV in renal transplant recipients. Several investigations have questioned the appropriate agent and duration of prophylactic therapy. End results have varied, with studies often involving short durations or small sample sizes [11,15,21–23]. VGCV prophylaxis, both in low-dose (450 mg) and high-dose (900 mg) regimens, has been demonstrated as effective in the prevention of CMV in renal transplant recipients, though most publications failed to evaluate those administered Ale [12–14]. Traditional prophylaxis regimens with high-dose VGCV (900 mg daily) require a higher pill burden with an increased risk of adverse drug events in a patient population where medication adherence is critical to graft function and survival. A meta-analysis by Kalil et al. indicated no difference in efficacy between high (900 mg) and low-dose (450 mg) VGCV prophylaxis. In fact, high-dose (900 mg)

Table 7
CMV risk status and manifestations of invasive CMV disease.

	High risk		Moderate risk (D+/R+)	Moderate risk (D−/R+)	Low risk
Renal				1 – MWF	
Pulmonary	1 - daily		1 - MWF	1 – MWF	
Gastrointestinal	1- daily	1- MWF	1 - MWF		1 - MWF
	1- daily	1- MWF			

Table 8
DGF, graft rejection, DCGS, and patient survival in viremia & invasive disease.*

Outcome	Viremia	Control	Significance	Invasive disease	Control	Significance
DGF	13.8%	9.5%	0.513	0.0%	9.9%	0.609
Graft rejection						
90 day	24.10%	15.40%	0.229	40.0%	15.4%	**0.031**
1 year	35.3%	21.9%	0.103	50.0%	22.0%	**0.022**
3 year	45.3%	26.3%	**0.041**	50.0%	26.7%	**0.046**
5 year	53.2%	28.3%	**0.021**	50.0%	29.0%	0.054
Overall	44.8%	26.8%	0.053	50.0%	27.3%	0.15
Death-censored graft survival						
1 year	96.6%	95.9%	0.903	90.0%	96.1%	0.323
3 year	75.8%	91.2%	0.052	75.0%	90.8%	0.173
5 year	50.5%	87.6%	**0.001**	37.5%	86.9%	**0.002**
Overall	72.4%	87.4%	**0.043**	60.0%	87.1%	**0.033**
Patient survival						
1 year	100.0%	97.0%	0.368	100.0%	97.1%	0.59
3 year	91.7%	91.2%	0.96	100.0%	91.1%	0.388
5 year	78.0%	85.7%	0.445	100.0%	85.2%	0.299
Overall	86.2%	85.5%	0.912	100.0%	85.3%	0.372

Bold indicates a statistically significant result, or P < 0.05
* DGF = Delayed Graft Function; DCGS = Death-Censored Graft Survival.

Table 6
Outcomes associated with prophylaxis and risk status.

	Dosing frequency			Adherence			Risk status		
	MWF	Daily	p	Full	Incomplete	p	Low/moderate	High	p
Viremia	5.2%	4.5%	0.822	4.1%	5.6%	0.708	3.5%	11.7%	0.002
Invasive disease	1.6%	2.2%	0.802	2%	0%	0.58	1.0%	5.3%	0.011

Table 9
Causes of graft failure.*

Cause of graft failure	Viremia	Control	Significance	Invasive Disease	Control	Significance
Acute rejection	27.3%	11.4%	$p > .05$	50.0%	11.5%	$p > .05$
Chronic rejection	9.1%	7.6%	$p > .05$	0.0%	7.9%	$p > .05$
Graft thrombosis/ complication	0.0%	4.5%	$p > .05$	0.0%	4.3%	$p > .05$
Death	27.3%	44.7%	$p > .05$	0.0%	44.6%	$p > .05$
Recurrent disease	9.1%	6.1%	$p > .05$	0.0%	6.5%	$p > .05$
PNF	0.0%	3.8%	$p > .05$	0.0%	3.6%	$p > .05$
Clinically suspected rejection	18.2%	8.3%	$p > .05$	25.0%	8.6%	$p > .05$
Other	9.1%	13.6%	$p > .05$	25.0%	12.9%	$p > .05$

* PNF = primary nonfunction.

Table 10
Other infections in CMV Viremia patients.

	Control	CMV viremia	Significance
Bacterial infection	31.7%	58.6%	0.004
Fungal infection	3.5%	13.8%	0.023
Parasitic (cryptosporidium)	0	3.4% ($n = 1$)	0.048
BK viremia	8.8%	10.3%	0.736

VGCV has been correlated with an increased risk of leukopenia when compared to low-dose (450 mg) [24]. In this institution's experience, successful CMV prophylaxis was achieved with less aggressive, low-dose VGCV regimens when used in combination with Ale induction therapy and steroid minimization.

Despite the abundance of published research on CMV infection in solid organ transplant, the association of various negative outcomes with CMV remains controversial. Studies have differed in CMV screening protocols, antiviral drugs used, and preemptive or prophylactic therapy of various durations, possibly contributing to the ambiguity [22,23]. In some investigations, CMV infection has been associated with acute and chronic rejection, chronic allograft changes, and/or decreased graft and patient survival [17,25,26]. Specifically, Erdbrugger et al. determined that CMV infection was associated with significantly reduced patient and graft survival ($p = .008$) and reduced graft survival censored for death ($p = .032$) [17]. While we determined that CMV infection (both viremia and invasive disease) was associated with some increased graft rejection and decreased long-term (5-year and overall) death-censored graft survival (DCGS), it had no significant impact on patient survival.

Many opportunistic infections, including CMV, are a major complication in renal allograft transplant recipients. Newer, more potent immunosuppressive therapy has been implicated in the increasing number of these infections in recent years. LaMattina et al. concluded that Ale was an independent risk factor for opportunistic infections and CMV infections. Their cumulative CMV infection rates in Ale-treated patients were 21.3% and 22.7% at 1 and 3 years. These exceed the overall CMV incidence of 4.8% determined for our population. While many discrepancies between LaMattina et al. and our investigation could account for this inconsistency, CMV prophylaxis is noteworthy. In their analysis, prophylaxis consisted of VGCV for CMV-negative recipients of CMV-positive donor organs as well as those receiving thymoglobulin induction, and acyclovir for all other donor-recipient combinations for 3 months. Further details, such as dose and frequency of administration (MWF versus daily), were not discussed [1]. Most notably, the duration of our VGCV administration was 6 months for low and moderate risk groups and 1 year for high risk. While given in low dose, the extended period of prophylaxis in our population (6 months to 1 year versus 3 months in LaMattina et al.) could account for the reduced rate of CMV infection observed.

Others have determined that CMV infection is frequently linked with other infections, especially hospital acquired and opportunistic pathogens [27,28]. Conclusions were similar within our cohort, as CMV infection was significantly associated with bacterial, fungal, and parasitic infections. CMV infection causes indirect effects via the inflammatory response, such as cytokine release and changes in the host immune responses. CMV replication also induces a state of immunosuppression within the host due to the functional changes it causes in monocytes and lymphocytes, thus impairing response capacity [28]. These changes, in addition to immunosuppressive medications, may explain the frequency of CMV with other infections. Theodoropoulos et al. found a positive relationship between CMV infection and BK virus nephropathy in Ale-induced patients [29]. However, Elfadawy et al. observed lower rates of CMV infection among transplant recipients with prior BK viremia, although the population in Elfadawy et al. was not induced with Ale [30]. Our analysis discovered no significance between CMV infection and BK viremia, consistent with an analysis of patients receiving non-Ale immunosuppression in Hirsch et al. [31]

One potential disadvantage of the steroid minimization used along with Ale induction may be under-immunosuppression. We achieved low rates of CMV disease with this regimen; however, we noted an overall rejection rate of 27%, higher than the national average and greater than other institutions utilizing Ale. Additionally, investigation into our rejection occurrences determined a relatively rapid onset and more severe rejection diagnoses, characterized by high Banff classification. In the face of these findings, our institution is experimenting with long-term steroid maintenance in individuals pre-operatively determined to be at greater risk for rejection. Whether this increased immunosuppression affects CMV incidence rates is a topic for future investigation.

Since 2015, CMV prophylaxis protocol has adjusted slightly. This institution now administers acyclovir instead of VGCV for low risk (D−/R−) patients. Donor and recipient CMV negative transplants carry no risk of CMV transmission or reactivation, eliminating the need for the most efficacious prophylaxis against this virus. Nevertheless, the risk of other viral infections still exists, necessitating the use of acyclovir. Decreased cost is the main incentive for acyclovir over VGCV in this group. However, during our entire study period, this was not yet the protocol in place. All patients in our investigation received VGCV regardless of risk category, with risk simply determining the regimen (MWF or daily dosing).

Potential limitations of this investigation include retrospective review and transition to a different electronic medical records software during the study period, which may have led to inconsistencies in documentation practice. While adherence to the prophylaxis protocol based on recipient CMV serostatus was recorded and analyzed, individual patient compliance with viral prophylaxis regimens could not be monitored and would ideally be considered when assessing incidence of disease. The major drawback of this study is lack of a control group. We attempted to overcome this through extensive enquiry and comparison to related publications. Our analysis also has several strengths. Unlike most other publications, we examined CMV prophylaxis specifically in Ale-induced patients with steroid minimization. This report also expanded upon results by others regarding low-dose VGCV (rather than high dose) as effective prophylaxis for CMV in renal

transplants. Additionally, a relatively large population was used with a rather consistent protocol between individuals.

5. Conclusion

This investigation effectively demonstrated a lower than reported incidence of CMV infection but also revealed the unfavorable outcome of increased rejection rates in our patient population. While it was difficult to account for all confounding variables, this retrospective analysis revealed that 450 mg VGCV prophylaxis alongside Ale induction therapy with steroid minimization offered the benefit of reduced CMV risk in our renal transplant population. This investigation confirms the effectiveness of low-dose VGCV and highlights important variables requiring further investigation in order to reduce the number of renal transplant patients suffering from post-transplant complications such as CMV infection or allograft rejection. Factors include the time period of VGCV prophylaxis, possibly influencing CMV infection rates, and the degree of steroid minimization, perhaps contributing to overall rejection. Further investigation should focus on balancing the benefits of steroid minimization in Ale induction with overall rejection rates, as well as minimizing the risk of CMV infection, using an effective low dose and extended time period of VGCV prophylaxis.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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