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Early Cytomegalovirus DNAemia and Antiviral Dose Adjustment in High versus Intermediate Risk Kidney Transplant Recipients

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Abstract

Background: Cytomegalovirus (CMV) infection continues to negatively affect outcomes for solid organ transplant recipients, despite the advent of strategies for preemptive surveillance and prophylaxis. The impact is especially great for CMV seronegative recipients of donor seropositive organs, who typically lack the ability to control CMV infection at the time of transplantation.

Methods: We reviewed episodes of CMV DNAemia in a modern cohort of kidney transplant recipients over a 3-year period at a high-volume transplant center to investigate the frequency of DNAemia during antiviral prophylaxis.

Results: Despite receipt of antiviral prophylaxis per current guidelines, 75 cases of CMV DNAemia were observed in the first 100 days after transplantation. For high risk patients, median time to DNAemia was 75 days after transplantation, and the majority of patients had experienced dose-reduction of valganciclovir due to renal insufficiency. Review of CMV seropositive intermediate risk patients demonstrated DNAemia occurring earlier after transplantation compared with high risk patients with a median time of 64 days (p= 0.029). The impact of valganciclovir dose adjustment was less notable in the intermediate risk group.

Conclusions: Guidelines recommend beginning routine surveillance for CMV after the completion of antiviral prophylaxis. Our findings suggest that closer monitoring may be beneficial, especially for high risk patients at risk for DNAemia. Patients requiring dose adjustment of valganciclovir due to renal insufficiency may be at increased risk for CMV DNAemia. Improved methods for CMV prophylaxis and evaluation of immunologic risk for CMV DNAemia and disease are needed to improve patient outcomes after kidney transplantation.

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Authors' contributions:

J.S. designed the study, performed data analysis and interpretation, and wrote the manuscript; T.S., E.L., E.F.R., and S.B. participated in research design and data interpretation; K.P., I.S., and T.D. contributed to performance of the research and assisted in writing of the manuscript.

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Keywords

Cytomegalovirus; Kidney Transplantation; Antiviral medication

Introduction

Widely accepted guidelines in the field of transplantation from the American Society of Transplantation and The Transplantation Society describe recommended approaches to prevent CMV disease in high risk (donor seropositive (D+) and recipient seronegative (R−)) and intermediate risk (recipient seropositive, R+) solid organ transplant recipients.[1,2] These guidelines recommend 6 months of valganciclovir (VGC) prophylaxis for high risk D+/R− kidney transplant recipients given the demonstrated benefit of 6 month compared with 3 month regimens.[3] For intermediate risk patients (R+), it is recommended to either perform regular surveillance testing with CMV PCR or to administer VGC prophylaxis for 3 months. In both cases, the recommendation is to perform surveillance testing after or instead of antiviral prophylaxis, not during the period prophylaxis, given the previously observed low levels of CMV DNAemia (18.7%) observed in previous studies.[3]

Viral load surveillance with PCR assays is recommended given the demonstrated link between CMV DNAemia and progression to disease and allograft damage, with increased risk for biopsy-proven graft rejection after CMV DNAemia in a modern cohort study (HR 1.58).[4,5] Both induction with antithymocyte globulin (ATG) and treatment of episodes of acute rejection have been shown to be associated with CMV primary infection or reactivation of latent CMV.[3,6] However, many studies of risk factors for CMV infection and reactivation are based on patient cohorts from the 1990s and early 2000s, with different methodologies for CMV PCR screening, antiviral prophylaxis, and management of immunosuppression.

VGC has demonstrated efficacy for CMV prophylaxis.[7] As it is renally excreted, the manufacturer recommends dose adjustment for patients with renal insufficiency based upon the creatinine clearance (CrCl) as measured by the Cockcroft-Gault equation. In addition, studies of T cell function have demonstrated a link between patients requiring dialysis and T cell immunosenescence.[8] Given the frequency of renal insufficiency occurring after kidney transplantation, the possible association between this complication and CMV DNAemia is important to further evaluate. We present here a review of high and intermediate risk patients with early CMV DNAemia in a recent cohort of kidney transplant recipients to determine patterns and clinical attributes in the setting of modern approaches for surveillance and antiviral prophylaxis. We hypothesized that CMV DNAemia would be found only after completion of CMV-active prophylaxis, but found instead many episodes of breakthrough CMV DNAemia in high risk patients. This investigation raises questions regarding the current recommendations regarding timing of testing for CMV DNAemia in kidney transplant recipients.

Methods

Under a UCLA IRB approved retrospective study, we reviewed microbiology laboratory data to obtain data on patients transplanted between 1/2/13–12/22/15 with positive CMV PCR testing results defined as >137 IU/ml in plasma (Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test). This study was restricted to the first 100 days after antiviral start given that during this time period, all microbiologic testing is done at the UCLA laboratory. All patients were followed clinically for a minimum of one year after transplantation. CMV PCR testing was performed for surveillance purposes every 2 weeks for the first 3 months after transplantation. All episodes of detectable CMV DNAemia >137 IU/ml led to cessation of prophylaxis, if applicable, and start of treatment dose intravenous ganciclovir or oral VGC. Length of DNAemia was defined as the time between positive CMV DNAemia results within the same episode of DNAemia. To avoid DNAemia lengths of zero days for those with only a single recorded date of DNAemia, we added 1 to the length of DNAemia result for each patient.

As previously described, in our patient population induction immunosuppression with antithymocyte globulin (ATG) 1.5 mg/kg was administered to patients at increased risk for rejection (panel-reactive antibodies >20%, history of donor specific antibodies, positive crossmatch, cold ischemia time > 24 hours, or donation after cardiac death).[9] Other patients not meeting these criteria received basiliximab. Tacrolimus, mycophenolate mofetil (MMF) 1g twice daily, and prednisone was used for maintenance immunosuppression at standardized doses and with similar target drug levels in each patient following the UCLA protocol. Tacrolimus goal trough level was 10–12 ng/mL for first 3 months after transplantation and then 6–10 ng/mL thereafter.

Patients received VGC prophylaxis for cytomegalovirus for 6 months for high risk (D+/R−) patients. Intermediate risk (R+) patients receiving ATG generally received 3 months VGC prophylaxis. R+ patients receiving induction with basiliximab and not placed on VGC were given acyclovir 400 mg once daily for 3 months for prophylaxis. VGC dose adjustment was performed according to the package insert, with some modification to try to address concerns of inadequate drug absorption and exposure: Patients with CrCl >60 mL/min received 900mg po daily. Patients with CrCl 25 – 59 mL/min were treated with 450mg po daily. Patients with CrCl 10 – 24 mL/min were treated with 450 mg po three times weekly. This practice differs only slightly from the package insert, which recommends that patients with CrCl 40–59 receive 450 mg po daily but that those with CrCl 25–39 receive 450 mg every other day. In addition the package insert recommends that patients with CrCl 10 – 24 mL/min receive 450 mg twice weekly. Cotrimoxazole sulfate was administered for the first year after transplantation.

Acute cellular rejection and antibody-mediated rejection were defined using Banff criteria.[10] Rejection was treated with steroid pulse, ATG, or plasmaphereis and IVIg following KDIGO guidelines.[11] Protocol kidney biopsies are not performed at our center.

For comparing the groups of interest, we first performed single variable analysis using the Mann-Whitney U-Test for continuous variables and for categorical variables Pearsons chi-

squared test. P<0.05 was used to define statistical significance. Statistical analysis was performed using JMP Pro 11 (SAS Software).

Results

Demographic characteristics

We identified a total of 75 patients who underwent kidney transplantation between 2013–2015 and had positive CMV PCR testing results within the first 3 months of transplant, as detected by routine clinical surveillance, for an overall incidence of 9.2% out of the 811 adult patients transplanted during this time period (Figure). Of these 75 patients, 11 were in the high risk group (D+/R−), and 64 were in the intermediate risk group (R+). Of the intermediate risk group, 55 were D+/R+ and 7 D−/R+. For 2 CMV seropositive patients, donor serology for CMV was not available. Demographic characteristics were similar between high and intermediate risk patients groups, including patient ages, sex and race distribution, and use of deceased versus living donors (Table 1). Although there was a trend towards high risk patients being more likely to receive ATG than intermediate risk patients, this difference did not reach statistical significance. Rates of rejection, both ACR and AMR, were also similar between groups. For all 8 patients experiencing rejection, rejection occurred prior to episodes of CMV DNAemia, ranging from 9 to 54 days after the first episode of rejection with a median time to DNAemia after rejection of 34 days. Of these 8 patients, 3 were diagnosed with AMR without ACR, and were treated with IVIG with or without plasmapheresis. Three had ACR (ACR1A or ACR2A) and 2 had borderline ACR, and were treated with either high dose steroids or ATG. Of the 3 patients who received ATG for treatment, one received ATG induction and two received basiliximab. Two of the patients with ACR were also concurrently diagnosed with AMR, and 2 patients had multiple episodes of rejection in the first year after transplantation despite treatment of the initial episode with ATG.

CMV DNAemia in the high risk patient group

Eleven high risk (D+/R−) patients developed early CMV DNAemia during the 3 year period of review, for an incidence of 8.4% (11/131). Analysis of these patients revealed that DNAemia occurred at a median time of 75 days (range 62–103 days) after transplantation (Table 2). Despite this relatively early time to detection, the majority of patients (8/11, 73%) were still receiving primary prophylaxis with VGC at the time of DNAemia detection. One patient had VGC on hold at the time of DNAemia due to leukopenia, 1 had completed the planned period of VGC prophylaxis, and 2 were on ACV, presumably due to VGC intolerance. Of the 8 patients on VGC, 1 patient was on full maintenance dose VGC at the time of DNAemia, while 7 had VGC dose-adjusted based on CrCl at the time of DNAemia (88%). The median time between dose adjustment and CMV DNAemia was 66 days (range 52–120 days). For patients receiving dose-adjusted VGC, there was a median of 69 days (range 52–119 days) on dose-reduced therapy prior to CMV DNAemia. Review of dose adjustment revealed that in each case, VGC dose had been adjusted correctly as described in the Methods section above. In the patient with no antiviral at the time of CMV DNAemia, the time between early termination of VGC prophylaxis and DNAemia was 31 days. Peak CMV PCR levels were similar in high risk patients (median 2240 IU/ml, interquartile (IQ)

range 624–6340) compared to intermediate risk patients (1495 IU/ml, IQ range 479–3874, p=0.423). A trend was observed towards longer episodes of CMV DNAemia in the high risk patient group (19 days in the high risk compared with 9 days in the intermediate risk patient group) (p=0.093) (Table 2). Both high and intermediate risk patients, however, had notable lymphopenia at the time of CMV DNAemia, with absolute lymphocyte count $<1.3 \times 10^3$/uL (Table 2), and 72.7% of high risk and 71.9% of intermediate risk patients are lymphopenic at DNAemia.

CMV DNAemia in the intermediate risk patient group

Sixty-four intermediate risk patients (R+) developed CMV DNAemia in the first 100 days after transplantation, for an incidence of 11.0% (64/584) and 10.5% out of the 715 patients at risk (either donor or recipient CMV seropositive) (75/715). 11 of these received ATG induction and were on VGC for at least some period of time after transplant; 53 received basiliximab induction, one of whom received VGC prophylaxis. Analysis of these patients revealed that DNAemia occurred relatively early after transplant, at a median of 64 days (range 9–99 days) after transplant (Table 2). This was statistically significantly shorter time to infection compared with the high risk patients (p=0.029). There was no difference in time to CMV positive in the intermediate risk patients based on donor status (p=0.509). Both the median first CMV PCR value and the highest recorded CMV PCR value trended lower than the high risk patients, although this difference did not reach statistical significance (Table 2).

For the intermediate risk patients, 8 were on VGC at the time of DNAemia, significantly fewer than the high risk patients (p<0.001). 4 patients who received VGC had VGC on hold at the time of DNAemia due to leukopenia (n=2) or elevation in liver function tests (n=2). Of the 8 patients on VGC at the time of DNAemia, 2 patients were on full-dose VGC, while 6 had VGC dose-adjusted for renal insufficiency (n=5) or elevation in liver function tests (n=1) at the time of DNAemia. In another 4 patients, VGC dose was decreased for renal insufficiency, and increased again after renal function improved and before DNAemia start. The median time between dose adjustment and CMV DNAemia was 61 days. As above for the high risk patients, dose adjustment for renal insufficiency was performed according to the package insert as described in the Methods section above. CrCl at the time of DNAemia was also similar between groups, with median 48 mL/min in the high risk (range 29–79) and 58 mL/min in the intermediate risk group (range 17–89) (p=0.239). There was no correlation between highest level of CMV DNAemia and history of VGC dose reduction (p=0.147). There was a trend towards a longer period of DNAemia in the high risk (median 19 days) compared with the intermediate risk patients (median 9 days) (p=0.090) (Table 2). Within the intermediate risk patients, no difference was seen in terms of length of DNAemia by donor serostatus (p=0.252). There was not statistically significant difference in incidence of CMV disease in high compared with intermediate risk patients.

VGC dose adjustment in patients at the time of CMV DNAemia was less common for the intermediate risk compared with the high risk patients (17% vs 77% respectively, p<0.001).

Discussion

We reviewed patterns of early CMV DNAemia in high risk (D+/R−) and intermediate risk (R+) patients on antiviral prophylaxis after kidney transplantation. We noted that early onset DNAemia was common despite receipt of VGC prophylaxis as recommended by AST and international guidelines. This revealed several interesting insights into patterns of CMV DNAemia in the setting of modern protocols prophylaxis and surveillance.

Despite years of progress in the field of kidney transplantation, cytomegalovirus (CMV) infection continues to cause negative impact on patient and allograft outcomes, especially for high risk patients where donor is CMV seropositive (D+) and recipient is CMV seronegative (R−).[12,13] The mechanism of deleterious effect on the kidney allograft remains unclear, with possibilities including inflammatory damage in the setting of direct infection, versus the stimulation of anti-allograft immune response via a heterologous immune mechanism.[14,15] In addition, latent CMV infection has been shown to be associated with progression of immune senescence in older patients,[16,17] which may explain the link between CMV and vulnerability to other opportunistic infections.[18]

One of the most surprising findings of our review was the prevalence of CMV DNAemia in high risk patients during VGC prophylaxis with 69% of high risk patients with DNAemia receiving VGC at the time of DNAemia start. The evidence of the effective use of the prophylaxis strategy was described by Humar et al. in the IMPACT study.[19] This is relevant to current practice given that most guidelines do not recommend monitoring for CMV DNAemia during prophylaxis periods.[1,2] This approach may lead to missing episodes of asymptomatic DNAemia, and may contribute to the negative impact of high risk CMV serology on allograft and patient outcomes. These patients noticeably also demonstrated a trend towards higher levels and longer periods of DNAemia (Table 2), emphasizing the immunologic vulnerability produced by the absence of CMV-specific immunity at transplantation. The observation that CMV DNAemia early after transplant may be an important issue for high risk kidney transplant recipients contrasts with the recent attention on the impact of late or delayed-onset disease, after the completion of prophyalxis.[20]

Another important conclusion from this study is the association between VGC dose adjustments for renal insufficiency in breakthrough CMV DNAemia in high risk patients. This occurred despite using higher doses than the package insert recommendations for adjustment based on CrCl. This observation suggests that the recommended dose adjustments may result in an inadequate dosing for many high risk patients. This is of special concern given the suspected association between low serum levels of antiviral drugs and development of antiviral resistance.[21,22] Additional studies would be instructive to determine whether monitoring of drug levels would be helpful during dose adjustment. Another possible mechanism behind this association between dose adjustment and CMV DNAemia is immune dysfunction associated with renal insufficiency. Even brief periods of renal insufficiency may negatively impact immune control and the development of an effective antiviral immune response.

We also observed that VGC was often held for leukopenia. This common practice was associated with development of CMV DNAemia in 6 patients, suggesting that careful viral surveillance during this period is required for both high and intermediate risk patients. Alternatively, filgrastim can be used to support bone marrow function during periods of ganciclovir or VGC administration. Future practice may include use of new antiviral agents such as letermovir without the effect of neutropenia.[23]

Another interesting finding was the relatively early time to DNAemia for the intermediate risk patients, with median time to CM DNAemia of 64 days, earlier than the high risk patients. This may reflect the fact that reactivation of secondary infection as seen in the recipient seropositive situation occurs more quickly than primary infection in the high risk patient. The rates of DNAemia noted in intermediate risk patients receiving simulect induction have led to the reconsideration of the use of acyclovir in this patient population. It remains unknown why some patients develop CMV DNAemia despite being CMV seropositive, while other patients on similar prophylaxis or preemptive regimens are free from CMV DNAemia and disease. A monitoring approach incorporating immunologic assessment provides the promise to better define patients at risk.[24]

Limitations of this study include its retrospective nature, which limits the amount of clinical information available regarding each episode of CMV DNAemia. Although our goal was to focus on breakthrough DNAemia in the setting of anti-CMV prophylaxis, we also included description of patients with CMV DNAemia during preemptive monitoring while receiving ACV, increasing the heterogenetiy of the population studied. In addition, this report represents a single center study, although the high volume of our institution has allowed us to obtain a relatively large number of cases in a short time period and furthermore permits analysis of a cohort of patients receiving identical protocols for immunosuppression, antiviral prophylaxis, and CMV monitoring. Future studies should be performed to monitor VGC levels in patients with and without need for dose adjustment to determine whether effective underdosing occurs when dose adjustment is performed according to the manufacturer’s instructions.

Our study demonstrates gaps in the current understanding of CMV DNAemia, especially in regard to renal dosing and detection during the recommended prophylaxis period. Additional studies on CMV specific T cell response in patients with and without development of CMV DNAemia, patterns of CMV infection, and pharmacological studies on dosing are needed to build on our current understanding of CMV in transplant recipients. Such data will aid in refining the current guidelines to better suit recipients in the modern era of transplantation.

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Abbreviations:

CMV	cytomegalovirus
VGC	valganciclovir

ATG	antithymocyte globulin
MMF	mycophenolate mofetil
CrCl	creatinine clearance

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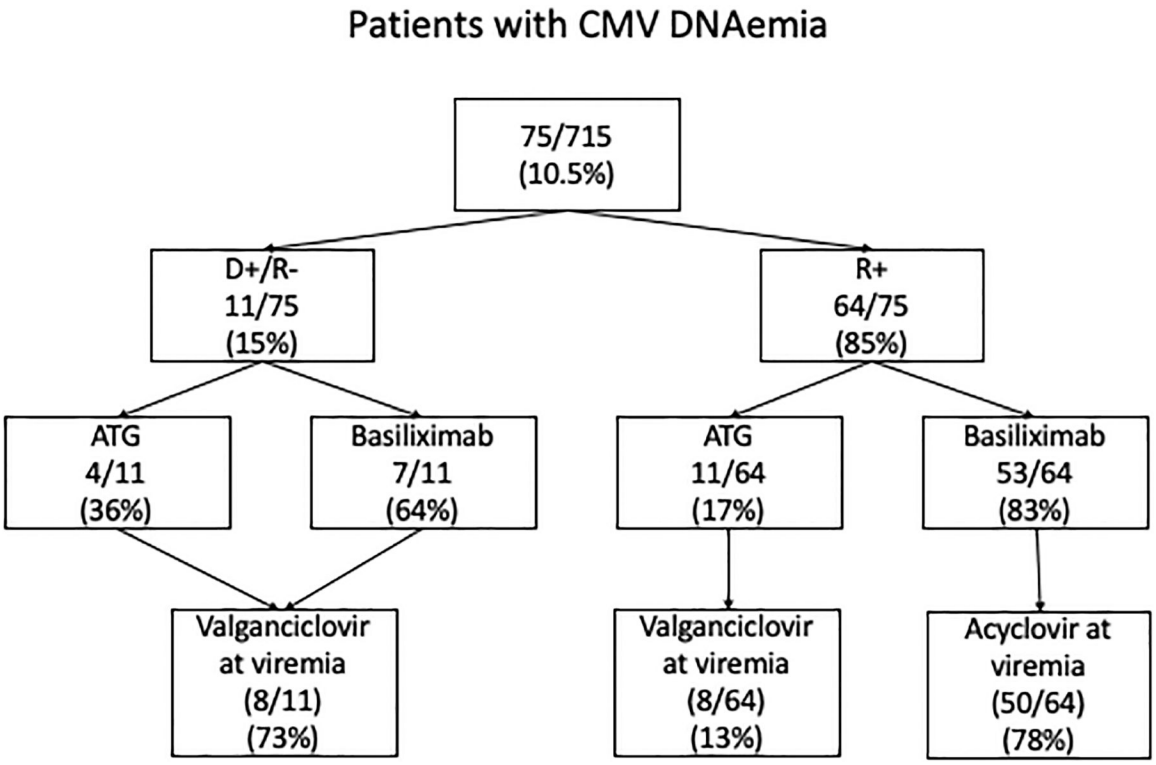

Figure:

Kidney Tansplant Patients with CMV DNAemia. Flowchart of patient analysis: Out of 811 patients transplanted with 715 at risk for CMV infection (donor or recipient seropositive), there were 75 cases of DNAemia identified in the first 100 days after transplantation. Of these, 11 were high risk and 64 intermediate risk. The percentages of patients with different types of induction and receiving Valganciclovir at the time of DNAemia are indicated.

Table 1

Demographic and clinical characteristics of CMV high (D+/R−) and intermediate (R+) risk kidney transplant recipients with CMV DNAemia detected in the first year after transplantation. P values represent nonparametric testing for numerical variables, and Pearson for categorical variables.

	High risk n=11	**Intermediate risk n=64**	**p-value**
Median age (range)	47.8 (21–71)	58.7 (24–75)	p=0.222
Male sex	64%	70%	0.657
White race	36%	27%	0.513
Hispanic	18%	27%	0.543
Deceased donor	64%	58%	0.717
Induction, ATG	36%	17%	0.142
Rejection (ACR or AMR)	9%	11%	0.852

Table 2

CMV DNAemia in the high (D+/R−) and intermediate risk (R+) kidney transplant recipients. P values represent nonparametric testing for numerical variables, and Pearson for categorical variables, and are bolded when p<0.05. Abbreviations: IQ, interquartile; VGC, valganciclovir; ALC, absolute lymphocyte count.

	High risk n=11	**Intermediate risk n=64**	**p-value**
Median days to DNAemia (range)	75 (62–103)	64 (9–99)	**0.029**
Median first PCR, IU (IQ range)	975 (473–2240)	709 (230–2682)	0.816
Median peak PCR, IU (IQ range)	2240 (624–6340)	1495 (479–3874)	0.423
Median DNAemia length, days (range)	19 (1–269)	9 (1–105)	0.093
On VGC at DNAemia	73% (8/11)	13% (8/64)	**<0.001**
Median GFR at DNAemia (range)	48 (29–79)	58 (17–89)	0.121
Median ALC at DNAemia (range)	0.93 (0.20–1.9)	0.80 (0.10–2.9)	0.928
CMV disease	9% (1/11)	2% (1/64)	0.274