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Impact of Prophylactic Versus Preemptive Valganciclovir on Long-term Renal Allograft Outcomes

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Abstract

Background—Both prophylactic and preemptive oral valganciclovir therapy are effective for management of cytomegalovirus (CMV) post renal transplantation in the short-term. The long-term effect of either strategy is less well-defined.

Methods—We analyzed data on 115 adult recipients previously enrolled in a prospective randomized controlled trial of prophylaxis versus preemptive therapy for CMV. The primary outcome was a composite of freedom from acute rejection, graft loss, or death. Secondary outcomes included individual primary outcomes, post-transplant cardiovascular events, new-onset diabetes mellitus after transplant (NODAT), achievement of goal blood pressure, change in body mass index (BMI), interstitial fibrosis/tubular atrophy (IF/TA) and change in renal function. The analysis period was a 48-months post-transplant or date of death/graft loss, whichever was earlier.

Results—The primary outcome was similar between groups (83% prophylactic versus 81% preemptive, $p = 0.754$). The secondary outcomes showed similarities between the prophylactic and preemptive groups. Four patients in the prophylactic group (8%) compared to none in the preemptive group (0%) died with a functioning graft, $p=0.043$.

Conclusions—Within the limitations of sample size, our data suggest that either strategy for the management of CMV immediately post-transplantation appears effective for patient and graft survival in the long-term. CMV-management is one of many therapeutic strategies incorporated into a renal transplantation protocol which often differs among institutions, and the decision as to which approach to use remains center and resource specific. The increased incidence of death in the prophylactic group requires further investigation.

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Keywords

Cytomegalovirus; kidney transplantation; preemptive; prophylactic; valganciclovir

Introduction

Cytomegalovirus (CMV) infection and disease are two of the most significant infectious complications affecting renal allograft recipients (1). CMV has direct effects such as CMV syndrome or tissue-invasive disease including retinitis, pneumonitis, hepatitis, and gastrointestinal disease (2). CMV also has indirect effects including increased incidence of opportunistic infections, allograft rejection, and reduction in allograft and patient survival (3–6). Without preventative therapy, symptomatic CMV infection can occur in 20–60% of renal transplant recipients (7). Even asymptomatic CMV has been associated with adverse health outcomes such as new onset diabetes after transplantation (NODAT) (8).

Management strategies for CMV include prophylactic, preemptive or deferred therapy (9–16). Comparative studies have found all strategies equally effective in the short-term (9,13). Two recent studies have investigated the long-term impact of these management strategies. Sagedal, et al, studied the impact of CMV infection and disease within the first 100 days post-transplant on long-term graft and recipient survival (5,6). Kliem et al conducted a randomized trial of patients who received either oral ganciclovir prophylaxis or preemptive treatment with intravenous ganciclovir and examined the effect on 4-year graft survival (15).

Both studies used intravenous ganciclovir for treatment. Historically, intravenous ganciclovir has been the drug of choice for treatment of symptomatic CMV and oral ganciclovir for the prevention of CMV (2,12). Recently, valganciclovir, the oral pro-drug of ganciclovir, has been introduced for prevention of CMV. Valganciclovir has approximately ten times the bioavailability of oral ganciclovir, with an equivalent safety and efficacy profile for CMV -prevention (11,17). Valganciclovir has also been used for treatment of CMV lessening the costs, inconveniences and risks of intravenous therapy (13,18).

We previously compared prophylactic to preemptive oral valganciclovir therapy for CMV management in a prospective, randomized, controlled trial of 119 renal transplant recipients (13). Of 119 enrolled subjects, 99 were at-risk for CMV (donor or recipient seropositive). Of these, 50 were randomized to prophylaxis and 49 to preemptive therapy. One patient in the prophylactic group had primary non-function the first week and was excluded from the analysis. Thus, we analyzed 98 CMV at-risk patients. The remaining 20 patients were donor and recipient CMV seronegative (D-/R-) and were treated similar to the preemptive group. We found both strategies to be equally effective in preventing symptomatic CMV with similar overall costs at one-year (13). Although not significant, we did note the occurrence of several symptomatic CMV infections in the prophylactic group that occurred shortly after the discontinuation of prophylaxis.

The purpose of the present analysis was to examine the long-term (minimum 4-year) consequences of prophylactic versus preemptive valganciclovir in kidney transplant recipients participating in the prospective trial. We performed an analysis of the at-risk CMV patients in the original trial and the non-CMV at-risk D-/R- group as a comparator. The analysis followed patients from transplant up to a minimum of 48 months post-transplant, death or graft loss, whichever was earlier. The primary outcome was a composite of freedom from acute rejection, graft loss, and death. Secondary outcomes included: individual primary outcomes, post-transplant cardiovascular events, NODAT, achievement

of goal blood pressure, change in body mass index (BMI), change in renal function, and interstitial fibrosis/tubular atrophy (IF/TA).

Results

Patients' characteristics

There were 98 patients analyzed in the initial study at-risk for CMV and 20 D-/R- not CMV at-risk. Their demographic characteristics have been previously reported (13). After excluding 3 lost to follow-up, there were 95 at-risk and all 20 D-/R- patients (97% of the original cohort) eligible for analysis. Demographic characteristics of the eligible patients are presented in Table 1.

There was no significant difference between the groups for episodes of acute rejection (n=4 prophylactic vs n=8 preemptive, $p=0.203$) when analyzed separately. The time to acute rejection post-transplant was similar and ranged from 1–52 months in the prophylactic group and 5–52 months in the preemptive group.

Neither graft loss nor death-censored graft loss differed between the prophylactic and preemptive groups (n=6 vs n=4, $p = 0.526$ and n=2 vs n=4, $p=0.385$ respectively), Figure 1. The time to graft loss post-transplant ranged between 3–52 months in the prophylactic group and 10–51 months in the preemptive group.

The difference in the incidence of death with graft function was significant. Four patients in the prophylactic group (8%) compared to none in the preemptive group (0%) died with a functioning graft, $p=0.043$. The causes of death of the four patients in the prophylactic group were colon cancer, esophageal cancer, and unknown causes (two patients), while natural and unknown causes were recorded as cause of death for the two patients in the preemptive group; both of whom previously experienced graft loss. Survival analyses for the composite endpoint, death-censored graft loss, and graft loss are shown in Figure 1. There were no differences in survival from these endpoints ($p = 0.754, 0.395$ and 0.565 respectively) between the groups.

Correlation of CMV DNAemia and long-term outcomes

We previously reported 29 patients in the preemptive group and 3 patients in the prophylactic group experienced a positive CMV DNAemia test at < 100 days post-transplant while no patients in the preemptive group and 11 patients in the prophylactic group yielded a positive test between days 100–365 post-transplant (13). Continuing from day 366 to follow-up, 1 patient in the preemptive group and 2 patients in the prophylactic group had a positive CMV DNAemia test. Of all CMV positive patients, seven preemptive patients and four prophylactic patients did not meet the long-term composite endpoint.

Incidence of other secondary endpoints between treatment groups

Several secondary endpoints were compared between those in the prophylactic group versus the preemptive group (Table 2). There were no significant differences between the groups for any of the secondary endpoints examined. Post-transplant cardiovascular events were comprised of five specific sub-types. There was not a significant difference in the incidence of the individual events between the two groups; however, there were fewer total events in the prophylactic group compared to the preemptive group in every sub-type.

The D-/R- group

The D-/R- group (n=20) was included in the initial study and treated with valganciclovir only after a positive CMV DNAemia test or the presence of symptoms. Only two patients

developed CMV DNAemia within the first year post-transplant with one most likely a false positive as repeat CMV-PCR of the original sample was negative (13). This patient received preemptive treatment and was considered to have been CMV-positive for all analyses. The primary and secondary end points in this group at follow-up are shown in Table 3. Of the four patients who did not meet the composite primary endpoint, one was a positive CMV DNAemia patient. The outcome rates in the D-/R- group were similar to the prophylactic and preemptive groups with no significant differences between groups overall.

Discussion

Our long-term follow-up of renal allograft recipients managed either prophylactically or preemptively for CMV showed that both treatments were equally effective in the combined prevention of acute rejection, graft loss, and death up to 48-months post-transplant. This study is one of only a few to follow the long-term effects of patient and allograft survival relating to CMV infection and its management (6,15).

Sagedal et al studied long-term recipient and kidney graft survival after early onset CMV infection and disease in 397 first transplant patients (6). No induction therapy was used and patients were maintained on cyclosporine, mycophenolate mofetil, and prednisone. Patients had CMV-antigenemia tests at least every 2 weeks for the first 100 days. Despite no induction therapy, over 60% developed CMV-antigenemia. Only symptomatic patients were treated with a reduction in immunosuppression and intravenous ganciclovir in a deferred strategy; no prophylaxis strategy was utilized. Median time of follow-up was 66.6 months. Hazard ratios for death were 2.90 for asymptomatic CMV-antigenemia, 2.50 for symptomatic CMV disease, and 7.88 for graft loss. All three variables were shown to be independent risk factors of mortality after 100 days (up to seven years post-transplant).

Kliem and colleagues compared the long-term renal graft survival between oral ganciclovir prophylaxis versus IV ganciclovir preemptive therapy in 130 patients four years post-transplant (15). Approximately 11% in each group received anti-thymocyte globulin (ATG) induction. Patients were maintained on a calcineurin inhibitor, mycophenolate mofetil, and steroids. Prophylaxis therapy consisted of 1000 mg oral ganciclovir for 90-days. Preemptive treatment was 5 mg/kg IV ganciclovir for a minimum of 10-days until two DNA test-results of < 100 copies/mL, followed by secondary prophylaxis of 1000 mg oral ganciclovir t.i.d. for 14-days. There was a non-significant trend for fewer acute rejection episodes in the prophylactic group compared to the preemptive arm (19% vs 28%, respectively), no differences in patient survival at 12-months, but a significant difference in graft survival (uncensored for death) in favor of the prophylactic group (92% vs 78%, p=0.04).

We observed lower incidences of acute rejection (13% vs 59%), death censored graft loss (6% vs 11%), and death (6% vs 21%) compared to Sagedal et al. When compared to Kleim et al, our strategies also had a lower incidence of acute rejection (13% vs 24%) and uncensored for death graft survival (89.5% vs 85.5%). Kleim et al did not present long-term patient survival data.

Another notable aspect of our study is we examined the relationship of post-transplant cardiovascular events to the type of CMV management therapy. Cardiovascular disease and events are the leading cause of graft loss and death in renal allograft recipients (19). CMV infection and its effects on atherosclerosis have been implicated in coronary re-stenosis post-angiography (20) and adverse renal allograft events (21). In this study there were numerically increased cardiovascular disease or events such as NODAT, MI, PCI, CHF, CAD and arrhythmias in the preemptively treated renal transplant patients but none were

statistically significant. Our study groups were relatively small, and it is possible that a real difference was not demonstrated because of inadequate statistical power.

One surprising finding was that death with graft function was significantly more common among those who received prophylactic therapy. Malignancy was the cause of death in half of the patients in the prophylactic arm. Our observation is hypothesis generating since, recently and paradoxically, CMV infection and disease have been reported to be associated with decreased incidences of solid malignancies (22).

Transplantation protocols vary among centers and warrant consideration along with CMV management strategies. Only 11% of patients in the Kliem study received ATG induction and none received induction in the Sagedal study. In our present study, 91 of 94 patients (97%) received 3–5 days of induction therapy with rabbit-ATG-Thymoglobulin. Previous studies have shown that Thymoglobulin, compared to ATGAM induction, was associated with less acute rejection, CMV disease and more event-free survival at one year (23). The Thymoglobulin benefit continued through ten years post-transplantation (24). In a multicenter, international trial of Thymoglobulin compared to basiliximab, in deceased donor transplant recipients, acute rejection rates ($p=0.02$) and CMV ($p=0.02$) were both lower with Thymoglobulin (25). Three month prophylaxis with oral ganciclovir for D+/R– patients was prescribed for this trial. A five-year follow-up of the 183 enrolled U.S. patients showed that freedom from the composite endpoint of death, graft loss ($p=0.04$), acute rejection ($p=0.03$), and CMV disease ($p=0.04$) was lower with Thymoglobulin (26). The use of Thymoglobulin in this study may have decreased the incidence of acute rejection and thus CMV leading to less graft loss and deaths in both groups. A notable finding was the low incidence of late onset (after 12 months) CMV in any group. This may be attributable to the use of relatively low maintenance immunosuppression allowed by the use of Thymoglobulin.

The primary limitation of our study was sample size. A major difficulty of a retrospective follow-up study is pre-determined sample size. The original sample size was based on a hypothesized pharmacoeconomic advantage of prophylaxis that was not observed at one-year after transplantation (13).

The most appropriate CMV-therapy post-renal transplantation remains debatable. Our initial study concluded that both prophylactic and preemptive approaches were effective to manage CMV for the first year post-transplant. The studies by Kleim et al suggest potential long-term graft and patient benefits with CMV prophylaxis. Contrary to their conclusions, our 48-month follow-up suggests that either approach continues to be effective in the long-term for patient and allograft. It is highly improbable that long-term benefits are solely due to the CMV-management strategy. Unlike the other two studies, our use of Thymoglobulin as induction therapy is probably accountable for the lowest incidence of acute rejection post-transplant among the studies, which in turn, may affect other long-term outcomes. We conclude that while many aspects of transplant protocols will continue to vary and remain resource and center specific, the use of either prophylactic or preemptive CMV management will be equally effective.

Materials and Methods

Patients and study design

The study was approved by the Washington University Human Research Protection Office. The patient population included all adults who received a kidney transplant at Washington University Medical Center between March 1, 2003 and June 30, 2004. This population of 118 patients was analyzed in a randomized, prospective study comparing prophylactic

versus preemptive oral valganciclovir for cytomegalovirus management as previously reported (13). Three were lost to follow-up, defined as not having a routine laboratory work-up or clinical follow-up within the last 12-months at time of data collection, yielding 95 CMV at-risk patients and 20 D-/R- graft recipients eligible for long-term follow-up (Figure 2).

The current retrospective cohort study used data extraction through review of both physical and electronic records. Sources included: the Washington University Kidney Transplant Research (WUKTR) database, the electronic Organ Transplant Tracking Record (OTTR, Hickman-Kenyon, Omaha, NE), in-patient admission and discharge summaries, laboratory reports, pathology reports, and clinic follow-up dictation notes. Data were collected from March 1, 2003 through July 15, 2008 allowing a minimum four-year follow-up for all surviving patients. Final follow-up was defined as the date of most recent follow-up clinic visit, most recent laboratory work-up, graft loss, or death; whichever was earlier at time of data collection. Follow-up duration was the time between date of transplantation and time of final follow-up. The initial inclusion and exclusion criteria have been previously described (13).

Cytomegalovirus Testing and Treatment

All patients were monitored with CMV polymerase chain reaction (PCR) tests to detect CMV DNAemia in whole blood specimens collected before transplantation, weekly for 16 weeks after transplantation, at months 5, 6, 9 and 12 and for cause as previously described (13). The absolute lowest limit of detection was 200 copies/mL with accurate quantification ≥ 2000 copies/mL. For purposes of instituting preemptive therapy and analysis, positive CMV DNAemia was defined as the detection of ≥ 2000 copies/mL of CMV DNA in ≥ 1 -specimen. First positive specimens from each patient were retested. Those which were negative upon retesting in the absence of symptoms were considered false positives (13).

Follow-up

All patients are followed with a minimum of monthly laboratory evaluations after the first year including complete blood count (CBC), renal panel, and calcineurin-inhibitor level. Quarterly laboratory evaluations include: a complete metabolic panel (CMP), fasting lipid panel, uric acid, creatinine kinase, and magnesium. Patients with a diagnosis of diabetes or an elevated random or fasting blood glucose (>200 mg/dL and >126 mg/dL respectively) also have a hemoglobin A1c obtained quarterly. Patients are seen at least annually after the first transplant year.

Outcomes and definitions

This study's primary outcome was a comparison between prophylactic and preemptive groups from freedom of the composite endpoint of acute rejection, graft loss, and death.

Acute rejection was defined as rejection confirmed by biopsy using Banff criteria for allograft pathology. All patients with suspected rejection underwent allograft biopsy. Graft loss was defined as return to chronic dialysis, allograft removal, or re-transplantation. Death was defined as date of expiration.

Secondary outcomes included individual primary outcomes (acute rejection, graft loss [including death censored], and death [including death with graft function]), incidence of NODAT, incidence of post-transplant cardiovascular events, blood pressure control at follow-up, changes in BMI, changes in renal function, and incidence of IF/TA.

NODAT was defined as any single hemoglobin A1c level of > 6.0% post transplant, any single random blood glucose level of ≥ 200 mg/dl post-transplant, or initiation of either an oral anti-diabetic or injectable insulin post-transplant. Post-transplant cardiovascular events included: MI, PCI, CHF, CAD, or arrhythmias. All events were defined as physician diagnosis or a troponin I or T level of > 0.09 ng/ml for MI, documented evidence of coronary angioplasty or PCI procedure, an ejection fraction of < 40% determined by echocardiogram or nuclear stress test for CHF, history/diagnosis of any one of MI, angina, PCI, abnormal angiographic results, or coronary artery bypass graft (CABG) for CAD, and an electrocardiogram reading for arrhythmias. Blood pressure control at follow-up was defined as the average of the most recent two blood pressure readings at time of data collection. The designation of controlled versus uncontrolled blood pressure was defined by the JNC 7 goal classifications (27). Median percent change in BMI was defined as the median difference between BMI at the time of transplant and the time of final follow-up. Median percent change in renal function was defined as the median difference between estimated glomerular filtration rate (GFR) at one month post-transplant and the time of final follow-up. The GFR was calculated using the abbreviated modification of diet in renal disease (MDRD) equation (28). Interstitial fibrosis/tubular atrophy, including chronic allograft nephropathy (CAN) and “chronic rejection”, was defined as confirmation by biopsy evidence using the Banff criteria.

Statistical analyses

Data were entered and analyzed using Stata software version 11.0 (StataCorp, College Station, TX, USA). Univariate analysis used Student's *t*-test or Mann-Whitney *U*-test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables. Kaplan-Meier was used for survival analysis. A significance level of 0.05 was set for all tests.

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Figure 1.
Kaplan-Meier curves indicating proportion of patients meeting composite endpoint (A) death censored graft survival (B) and patient survival (C) in months post-transplantation.

Figure 2.
Study population flowchart

Table 1

Demographic, baseline, and follow-up characteristics

	Prophylactic N (%)	Preemptive N (%)	D-/R- Group N (%)	p-value ^a
Patients	48	47	20	
Age at FU, mean (SD)	55.1 (13.9)	50.6 (16.2)	50.4 (13.5)	0.150
Time of FU mos., mean (SD)	50.9 (11.1)	51.8 (9.5)	53.7 (4.8)	0.674
Gender				0.914
Male	23 (48)	22 (47)	13 (65)	
Female	25 (52)	25 (53)	7 (35)	
Race				0.232
Caucasian	40 (83)	43 (91)	19 (95)	
African-American	8 (17)	4 (9)	0 (0)	
Other	0 (0)	0 (0)	1 (5)	
CMV serostatus				0.695
D-/R+	10 (21)	12 (26)		
D+/R+	21 (44)	22 (47)		
D+/R-	17 (35)	13 (27)		
Allograft Type				0.334
Deceased donor	27 (56)	20 (44)	5 (25)	
Living related	13 (27)	13 (28)	11 (55)	
Living unrelated	8 (17)	13 (28)	4 (20)	
HLA mismatch, mean				
HLA-A	0.77	1.06	0.75	0.050
HLA-B	1.13	1.26	1.15	0.401
HLA-DR	0.71	0.74	0.75	0.819
HLA-Total	2.61	3.06	2.65	0.167
Immunosuppression CNI/SIR				0.818
FK	38 (79)	39 (83)	17 (85)	
CSA	2 (4)	1 (2)	1 (5)	
SIR	0 (0)	2 (4)	0 (0)	
None	8 (17)	5 (11)	2 (10)	
Antimetabolite				0.726
AZA	9 (19)	6 (13)	1 (5)	
MMF	22 (46)	23 (49)	16 (80)	
None	17 (35)	18 (38)	3 (15)	
Prednisone	48 (100)	44 (96)	20 (100)	0.297
Thymoglobulin	47 (98)	45 (98)	19 (95)	0.545

^aComparison of prophylactic and preemptive groups

N, number of patients; FU, follow-up; SD, standard deviation; mos., months; CMV, cytomegalovirus; D, donor; R, recipient; HLA, human leukocyte antigen; FK, tacrolimus; CSA, cyclosporine A; CNI, calcineurin inhibitor; SIR, sirolimus; AZA, azathioprine; MMF, mycophenolate mofetil

Incidence of acute rejection, graft loss, and death between treatment groups

Incidence of the primary composite endpoint and individual components between CMV management groups are shown in Table 2 and Figure 1. There was no difference in the composite endpoint: 40 (83%) receiving prophylaxis vs 38 (81%) treated preemptively, $p = 0.752$.

Table 2

Comparison of composite primary endpoint and secondary endpoints between prophylactic and preemptive treatment groups

Endpoint at follow-up	Prophylactic N=48 (%)	Preemptive N=47 (%)	p value
<i>Freedom from</i> acute rejection, graft loss, or death	40 (83)	38 (81)	0.752
Acute rejection	4 (8)	8 (17)	0.203
Graft loss	6 (13)	4 (9)	0.526
Death censored graft loss	2 (4)	4 (8)	0.385
Death with graft function	4 (8)	0 (0)	0.043
Incidence of NODAT ^a	6 (18)	11 (30)	0.275
Incidence of blood pressure not at goal	30 (63)	27 (57)	0.615
Incidence of post-transplant cardiovascular events	9 (19)	11 (23)	0.622
Incidence of MI	2 (4)	6 (13)	0.131
Incidence of PCI	1 (2)	5 (11)	0.09
Incidence of CHF	0 (0)	3 (6)	0.117
Incidence of CAD	2 (4)	3 (6)	0.700
Incidence of arrhythmias	3 (6)	5 (11)	0.486
Median % change in BMI, kg/m ² (IQR)	+11(3,18)	+12(-1,20)	0.513
Median % change in GFR, ml/min/1.73m ² (IQR)	60 (48,71)	53(36,66)	0.118
Incidence of IF/TA	4 (8)	2 (4)	0.677

^aN=34 for prophylactic group and 37 for preemptive group who were non-diabetic pre-transplant.

NODAT, new onset diabetes mellitus after transplant; MI, myocardial infarction; PCI, percutaneous intervention; CHF, congestive heart failure; CAD=coronary artery disease; BMI, body mass index; IQR, interquartile range; GFR, glomerular filtration rate; IF/TA =, interstitial fibrosis/tubular atrophy.

Table 3

Incidence of primary and secondary endpoints in D-/R- group

Endpoint at follow-up	N=20 (%)
<i>Freedom from</i> acute rejection, graft loss, or death	16 (80)
Acute rejection	3 (15)
Graft loss	1 (5)
Death censored graft loss	1 (5)
Incidence of NODAT ^a	4 (27)
Incidence of post-transplant cardiovascular events	4 (20)
Incidence of blood pressure not at goal	10 (50)
Median % change in BMI, kg/m ² (IQR)	+8.0(−4,16)
Median % change in GFR, ml/min/1.73 m ² (IQR)	−1 (−28,22)
Incidence of IF/TA	0

^aN=15 for D-/R- group who were non-diabetic pre-transplant

NODAT, new onset diabetes mellitus after transplant; BMI, body mass index; IQR, interquartile range; GFR, glomerular filtration rate; IF/TA, interstitial fibrosis/tubular atrophy.