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The Efficacy and Safety of 200 Days Valganciclovir Cytomegalovirus Prophylaxis in High-Risk Kidney Transplant Recipients

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Late-onset cytomegalovirus (CMV) disease is a significant problem with a standard 3-month prophylaxis regimen. This multicentre, double-blind, randomized controlled trial compared the efficacy and safety of 200 days' versus 100 days' valganciclovir prophylaxis (900 mg once daily) in 326 high-risk (D+/R–) kidney allograft recipients. Significantly fewer patients in the 200-day group versus the 100-day group developed confirmed CMV disease up to month 12 posttransplant (16.1% vs. 36.8%; $p < 0.0001$). Confirmed CMV viremia was also significantly lower in the 200-day group (37.4% vs. 50.9%; $p = 0.015$ at month 12). There was no significant difference in the rate of biopsy-proven acute rejection between the groups (11% vs. 17%, respectively, $p = 0.114$). Adverse events occurred at similar rates between the groups and the majority were rated mild-to-moderate in intensity and not related to study medication. In conclusion, this study demonstrates that extending valganciclovir prophylaxis (900 mg once daily) to 200 days significantly reduces the incidence of CMV disease and viremia through to 12 months compared with 100 days' prophylaxis, without significant additional safety concerns associated with longer treatment. The number needed to treat to avoid one additional patient with CMV disease up to 12 months posttransplant is approximately 5.

Key words: Antivirals, cytomegalovirus (CMV), prophylaxis, valganciclovir

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Introduction

Cytomegalovirus (CMV) remains one of the most important infections in solid organ transplant (SOT) recipients and is associated with significant morbidity and occasional mortality (1–3). Direct effects attributed to CMV infection include viral syndrome or tissue invasive disease (4). Indirect effects may include an increased risk of allograft rejection (5), opportunistic infections and posttransplantation diabetes mellitus (6). The risk of CMV disease is highest in seronegative recipients (R−) of seropositive donors (D+), and in patients who are heavily immunosuppressed such as those receiving antilymphocyte antibody therapy as induction or for treatment of rejection (1,7).

CMV prophylaxis is now widely used in the transplantation setting and has been associated with reductions in CMV disease, mortality and graft rejection in high-risk patients (8–10). Until recently, the emphasis on prophylaxis with these agents has focused on early disease occurring <3 months after transplantation, with the duration of prophylaxis typically no longer than 3 months (7). However, it is well recognized now that standard courses of antiviral prophylaxis are associated with a significant incidence of late-onset CMV disease. This is generally defined as CMV disease occurring after 3 months posttransplant. Late-onset CMV disease has the potential to cause significant morbidity and has been associated with increased mortality (11). In addition, these patients may present with nonspecific or atypical symptoms, resulting in delays in diagnosis (12–14).

With a standard 3-month course of prophylaxis, late-onset disease generally occurs between months 3 and 6. Therefore, prolongation of prophylaxis to 6 months or longer has been proposed as a potential strategy to decrease the incidence of CMV disease (12,15,16). This study was undertaken in order to compare the efficacy and safety of 200 days of valganciclovir prophylaxis with 100 days of prophylaxis for prevention of CMV disease in high-risk (D+/R–) kidney allograft recipients.

Methods

Study design and patient population

This was a multicentre, double-blind, randomized placebo-controlled study comparing the efficacy and safety of 200 days' valganciclovir prophylaxis with 100 days' valganciclovir prophylaxis (900 mg once daily adjusted for renal function in both cases) for the prevention of CMV disease in high-risk (D+/R−) kidney allograft recipients. All patients provided signed informed consent. The study was conducted in full accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and adhered with local and national regulatory requirements and laws. The trial was registered at clinicaltrials.gov (NCT00294515).

Eligible patients were kidney allograft recipients aged ≥16 years who were seronegative for CMV prior to transplant and who received an organ from a CMV seropositive donor (D+/R−). All patients were required to have adequate hematological assessments and renal function (defined as a creatinine clearance >10 mL/min by day 10 posttransplant), and be able to tolerate and commence oral study medication within 10 days of their transplant. Reasons for exclusion from the study included: suspected CMV disease at enrolment, HIV, hepatitis B or hepatitis C; use of anti-CMV therapy within 30 days prior to study; multiple organ transplantation; allergies or previous adverse reactions to acyclovir, valacyclovir, ganciclovir or valganciclovir; severe uncontrolled diarrhea or evidence of malabsorption; liver function tests >3 times the upper level of normal (ULN); serious psychiatric or medical disorder; male with a pregnant partner; or lactation. Women of childbearing potential were required to have a negative pregnancy test at screening and to use effective birth control throughout the study. Male patients were advised to use a barrier method of contraception during the study and for at least 90 days following cessation of study medication.

Patients were randomized sequentially in 1:1 ratio at each study centre in the order in which they were enrolled to receive valganciclovir 900 mg daily for 200 days, or for 100 days followed by 100 days of placebo. Treatment with the study drug was initiated as soon as the patient was able to tolerate oral medication following surgery, but no later than 10 days posttransplant, and was continued to Day 200 posttransplant. Intravenous ganciclovir (5 mg/kg/day) was permitted for patients initially unable to tolerate oral medication and could be administered until Day 10 posttransplant or until the patient could tolerate oral medication, whichever was sooner.

Study treatment was initiated at the recommended dosage of two 450 mg tablets once a day with doses to be taken within 30 min of breakfast. Patients with reduced renal function based upon calculated creatinine clearance (CrCl; calculated from serum creatinine using the Cockcroft–Gault formula) had dosages adjusted in accordance with standard recommendations. Patients with CrCl <10 mL/min or who required dialysis had their study medication interrupted, but could resume medication once CrCl increased to ≥10 mL/min provided they had not missed >14 consecutive days of study medication, or more than 21 days in any given 28-day period.

In this study, patients with either CMV viral syndrome or tissue invasive CMV were considered to have CMV disease. Patients with suspected CMV disease had a blood sample taken, which was divided and analyzed locally and at a central laboratory. Patients found to have CMV disease, were treated in accordance with local practice. CMV syndrome was defined as CMV viremia identified by quantitative PCR (or pp65 antigenemia and other sponsor-approved CMV assays) and at least one of the following: a fever ≥38°C; new onset severe malaise; leukopenia on two successive measurements separated by at least 24 hours (defined as a white blood cell [WBC] count of <3500 cells/μL if presymptomatic count was ≥4000 cells/μL or a decrease in WBC of >20% if the presymptomatic count was <4000 cells/μL); atypical lymphocytosis of ≥5%; thrombocytopenia (defined as a platelet count of <100,000 cells/μL if the prior count was ≥115,000 cells/μL or a decrease of >20% if the prior count was <115,000 cells/μL); or elevation of hepatic transaminases to ≥2 × ULN. Tissue invasive CMV was defined as evidence of localized CMV infection (CMV inclusion cells, *in situ* detection of CMV antigen, cell culture or DNA by immunostain or hybridization, respectively) in a biopsy or other appropriate specimen (e.g. bronchoalveolar lavage, cerebral spinal fluid) and symptoms of organ dysfunction. Definitions of CMV disease were consistent with current AST guidelines for use in clinical trials (17). No routine monitoring for CMV viremia was allowed during the study, unless as part of the management of an established CMV infection. However, plasma samples were collected at monthly intervals for the first 12 months posttransplant and for cause viral load assessment in case of suspect CMV disease; these were sent to a central laboratory for viral load testing (Roche Cobas Amplicor). The data were used for retrospective analysis, but not revealed to the investigators.

Efficacy

The primary efficacy parameter was the proportion of D+/R− patients who developed CMV disease (CMV syndrome or tissue invasive CMV) within the first 52 weeks. Secondary efficacy parameters included the proportion of patients with CMV disease at 6 and 9 month posttransplant, the proportion of patients with CMV viremia, the proportion of patients who experienced biopsy-proven acute rejection (BPAR), the proportions of patients with graft loss, the proportion of patients surviving, the proportion of patients with opportunistic infections and the proportion of patients experiencing posttransplantation diabetes mellitus.

Safety

Safety was evaluated by clinical assessment including vital signs, laboratory analyses, adverse events and opportunistic infections.

Statistical methods

Sample size was calculated as follows. A two-group continuity-corrected chi-square test with a 0.05 two-sided significance level has 80% power to detect a difference between the two groups if the CMV disease rate in the 200-day valganciclovir prophylaxis group was 15% and that in the 100-day valganciclovir prophylaxis group was 30% (odds ratio 0.412) when the sample size in each group is 134 patients. Assuming a premature termination rate of approximately 15%, 158 patients per arm (316 patients in total) would be required in the study to ensure 134 patients per arm complete the full course of treatment with 52 weeks follow-up or reach primary endpoint.

The patient populations analyzed included the intent-to-treat (ITT) population (all patients who were randomized, who were D+/R− and who received at least one dose of study drug) and the safety population (all patients who were randomized, who received at least one dose of study medication and who had at least one postrandomization safety assessment).

The null hypothesis of no difference in the proportion of patients responding in each treatment group was tested using the stratified

Cochran–Mantel–Haenszel analysis for the primary endpoint. No adjustments were made for multiple statistical testing. Secondary endpoints measured as time to event were summarized using life table methods and Kaplan–Meier curves and tested for significance using the two-sided log-rank test.

Results

Patients

Figure 1 outlines the trial flow for all randomized patients; 326 patients were randomized from 65 centers in 13 countries. The groups were well balanced with respect to patient baseline demographics (Table 1). All patients were between the ages of 17 and 77 years, with more men than women randomized in both treatment groups. A total of 123/160 (76.9%) patients in the 200-day group and 94/166 (56.6%) patients in the 100-day group completed the entire course (approximately 200 days) of prophylaxis with study medication (100 days of valganciclovir followed by 100 days of either valganciclovir or placebo): 33 (21.1%) and 70 (42.7%) patients withdrew from treatment, respectively, with the difference between groups mainly due to a high rate of insufficient treatment response in the 100-day group (i.e. development of CMV disease) (4 vs. 47 patients). Overall, 25 and 26 patients, respectively, prematurely withdrew from the study by week 52.

Although the two groups were well balanced with respect to use of intravenous ganciclovir during the period up to 10 days posttransplant, the majority of the safety population did not receive intravenous ganciclovir (120 [77%] vs. 130 [79%]). Of those that did receive intravenous ganciclovir (36 [23%] and 34 [21%]), 13 patients in the 200-day group had 5 or more days of intravenous ganciclovir treatment compared with 17 patients in the 100-day group.

Efficacy

CMV disease: The Kaplan–Meier curve showing the time to development of CMV disease is shown in Figure 2. The incidence of CMV disease by 12 months posttransplant was 25/155 (16.1%) in the 200-day compared to 60/163 (36.8%) in the 100-day group; $p < 0.0001$. The lower incidence of CMV disease in the 200-day group was evident at 6 and 9 months posttransplant ($p < 0.0001$ at both time points) (see Table 2). The vast majority of CMV disease was classified as CMV syndrome (83/85 [97.6%] total disease cases). CMV syndrome was rated by the investigator as mild-to-moderate in severity in most cases (20/24 [83.3%] in the 200-day group and 45/59 [76.3%] in 100-day group). The most common presenting symptoms were fever, malaise and leukopenia in both groups. All 24 patients with CMV syndrome in the 200-day group and 96.6% (57/59) of those with CMV syndrome in the

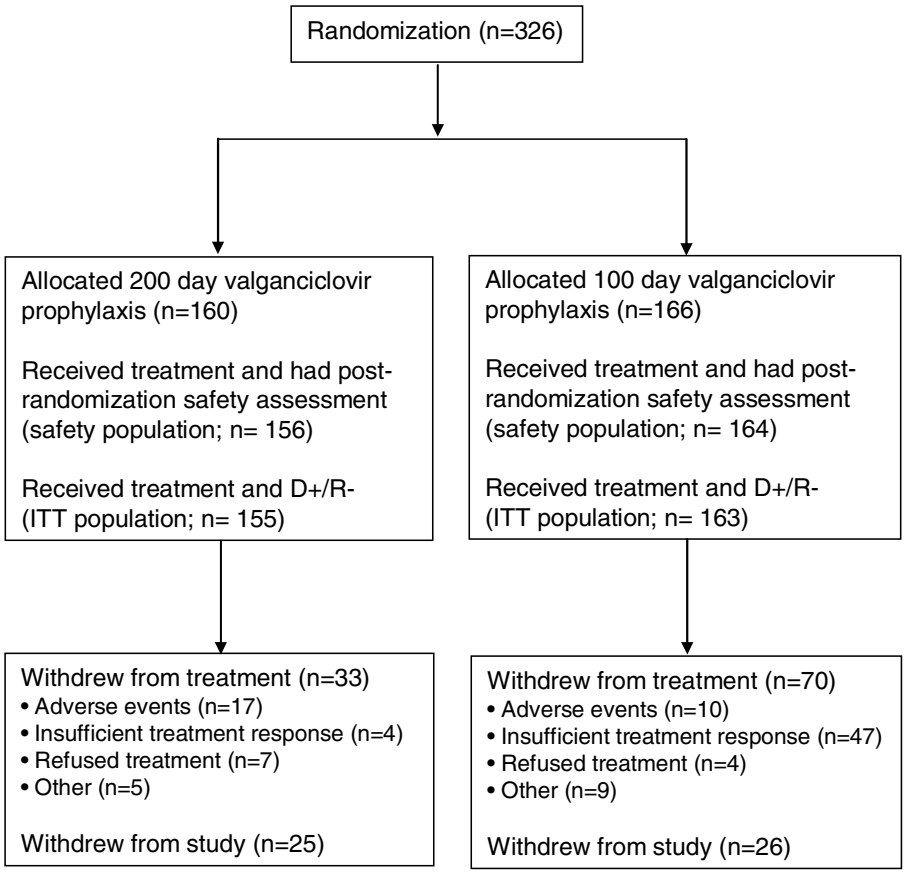

Figure 1: Patient flow through the study.

Table 1: Patient characteristics at baseline (safety population)

	Valganciclovir 200 day (n = 156)	Valganciclovir 100 day (n = 164)
Male, n (%)	116 (74%)	119 (73%)
Ethnicity, n (%)		
White	138 (89%)	141 (87%)
Mean age, years (SD)	47.0 (13.5)	48.5 (13.8)
Primary reason for transplant, n (%)		
Glomerulonephritis	22 (14%)	32 (20%)
Cystic/polycystic kidney disease	20 (13%)	24 (15%)
Diabetes mellitus	24 (15%)	23 (14%)
Hypertension	19 (12%)	21 (13%)
Pyelo/interstitial nephritis	7 (4%)	9 (5%)
Other	64 (41%)	55 (34%)
Primary transplant	145 (93%)	149 (91%)
Induction therapy at transplant[1]	127 (81%)	123 (75%)
Anti-interleukin-2 receptor antibodies	79 (51%)	72 (44%)
Antilymphocyte antibodies	52 (33%)	52 (32%)
Delay to start of study medication		
No delay	103 (66%)	119 (73%)
Delayed graft function	30 (19%)	25 (15%)
Unable to tolerate study medication	6 (4%)	6 (4%)
Other	17 (11%)	14 (9%)

SD = standard deviation.
[1]Some patients may have received both.

100-day group received treatment for their symptoms. Tissue invasive disease was uncommon. Only one patient in the 200-day group and two patients in the 100-day group had biopsy-confirmed tissue invasive CMV disease (on day 215 and days 119 and 132, respectively). All three cases of tissue invasive disease were gastrointestinal (one case of gastroenteritis in each group, and colitis and duodenitis). All cases of tissue invasive CMV disease resolved with treatment with intravenous ganciclovir or valganciclovir.

CMV viremia: CMV viremia analysis was performed using all central laboratory viral load data including for-cause viral loads and regular (i.e. blinded) interval viral load testing. The time to onset of viremia (viral load >600 copies/mL) was longer in the 200-day group than in the 100-day group ($p < 0.001$; Figure 3). The incidence of CMV viremia by 12 months posttransplant was significantly lower in the 200-day group ($p = 0.015$) compared to the 100-day group (Table 2). Viremia was also significantly lower in patients in the 200-day group as early as 6 months ($p < 0.0001$) posttransplant and at 9 months ($p = 0.013$). In general, the peak CMV viral load was lower in the 200-day group compared with the 100-day group (Figure 4); the proportion of patients with the highest peak in viral load (>100 000 copies/mL) was 2.6% and 11.0% in the two groups, respectively. The incidence of asymptomatic viremia (i.e. patients who had viral load >600 copies/mL, but were not reported by the investigator as having CMV disease because they had no symptoms) was similar in both groups: 34 patients (21.9%) versus 30 patients (18.4%) in the 200-day versus the 100-day groups, respectively.

Acute rejection and graft function: There was a trend toward less BPAR in the 200-day group versus the 100-day group (11% vs. 17%, respectively, $p = 0.114$) (Table 2). Most patients experienced BPAR before 100 days in both treatment groups: 10 out of 17 versus 15 out of 28 in the 200-day versus the 100-day group, respectively, and the rest of the cases were spread throughout the remaining time to 12 months. Very few patients experienced graft loss during the study and the rate was similar for both treatment arms ($p = 0.934$). The two treatment groups were broadly similar with respect to renal function.

Serum creatinine levels declined for both treatment groups over the first 4 weeks posttransplant and then remained stable thereafter (Figure 5). Significantly impaired renal function, defined as serum creatinine level of >2.5 mg/dL (221 μmol/L), was observed in 14% and 17% of patients, respectively, up to 28 days after completion of study medication.

Safety

The majority of patients (97%) reported at least one adverse event during the treatment phase and, in general, occurred at similar rates between the two groups (Table 3). These adverse events were in most cases (85%) considered by the investigator not related to study medication and the majority (91%) were rated mild-to-moderate in intensity. A total of 39 adverse events (25 in the 200-day group and 14 in the 100-day group) were considered probably related to study medication, mainly hematologic, including leukopenia.

The overall reported incidence of leukopenia (regardless of whether it was thought to be related to study medication or not) was 38% in the 200-day group versus 26% in the 100-day group (Table 3). However, the median laboratory WBC counts were similar between the two groups, even when the 100-day patient group converted to placebo for the later 100 days. Furthermore, the incidences of reported neutropenia, febrile neutropenia, agranulocytosis, anemia, thrombocytopenia and pancytopenia were comparable between the two groups. The majority of leukopenia cases resolved with or without treatment or study medication adjustment. However, 4% of patients (7/156) in the 200-day group had leukopenia that led to discontinuation of study medication compared with <1% of patients (1/164) in the 100-day group. Of the 113 reported cases of leukopenia, 16 (14%) were classified as grade

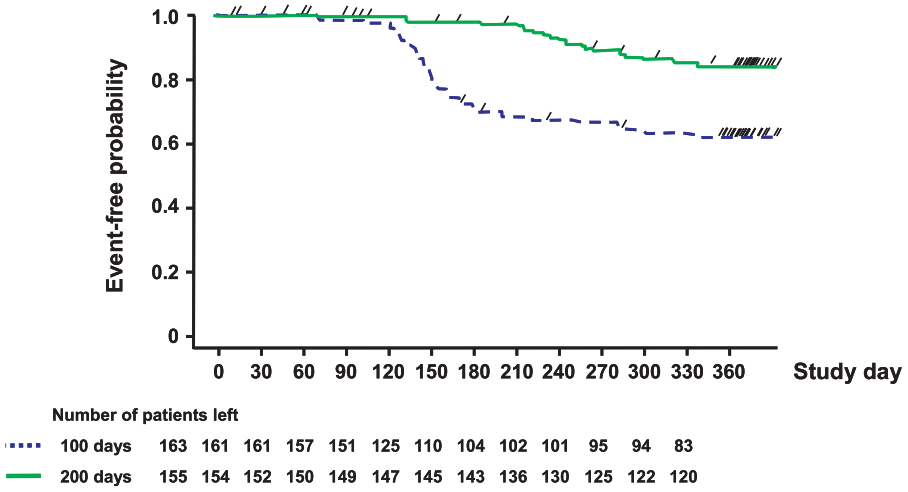

Figure 2: Kaplan–Meier plot of time to cytomegalovirus disease up to month 12 posttransplant.

3 or 4 according to their laboratory values. Overall, the use of granulocyte-colony stimulating factor (G-CSF) was similar between the two groups 14% (22/156) versus 13% (22/164).

The incidence of neutropenia was comparable between the groups overall and from study day 100 onward, when patients in the day-100 group were taking placebo tablets (15% in both groups overall [Table 3], and 5% (n = 8) in the 200-day group and 3% (n = 5) in the 100-day group after study day 100).

The incidence of gastrointestinal disorders in the two groups was 61% (95/156) and 52% (85/164), respectively, with the majority being diarrhea (Table 3). Interestingly, the incidence of gastrointestinal disorders was similar from study day 100 onward, when patients in the 100-day group were taking placebo tablets (21% (32/156) and 19% (31/164) in the two groups, respectively). Table 4 summarizes the common adverse events (occurring in ≥5% in either group) experienced from study day 100 onward in both groups.

Other outcomes

The proportion of patients in the ITT population with confirmed opportunistic infection (other than CMV disease) up to 12 months posttransplant was significantly lower in

Table 2: Primary and selected secondary endpoints at 12 months (unless otherwise stated) after transplantation (intent-to-treat population)

Endpoint	Valganciclovir 200 day (n = 155)	Valganciclovir 100 day (n = 163)	p-Value
Direct effects, n (%)			
Cytomegalovirus (CMV) disease	25 (16.1%)	60 (36.8%)	p < 0.0001
CMV disease at 9 months	22 (14.2%)	57 (35.0%)	p < 0.0001
CMV disease at 6 months	11 (7.1%)	51 (31.3%)	p < 0.0001
CMV disease (including assumed cases)[1]	36 (23.2%)	71 (43.6%)	p < 0.0001
CMV viremia	58 (37.4%)	83 (50.9%)	p = 0.015
CMV viremia at 9 months	55 (35.5%)	80 (49.1%)	p = 0.013
CMV viremia at 6 months	29 18.7%	73 (44.8%)	p < 0.0001
Indirect effects, (%)			
Biopsy-proven acute rejection	17 (11.0%)	28 (17.2%)	p = 0.114
Opportunistic infections	20 (12.9%)	44 (27.0%)	p = 0.001
BK virus infection[2]	7 (4.5%)	5 (3.0%)	
Oral candidiasis[2]	3 (1.9%)	8 (4.9%)	
Human polyomavirus infection[2]	2 (1.3%)	5 (3.0%)	
Oral herpes[2]	2 (1.3%)	5 (3.0%)	
Candidiasis[2]	0	4 (2.4%)	
Graft loss	3 (1.9%)	3 (1.8%)	p = 0.934
Posttransplant diabetes mellitus[3]	15 (12.4%)	13 (10.6%)	p = 0.815

[1]Patients without appropriate CMV disease status at the relevant time point and without a prior event were 'assumed' to have CMV disease.
[2]Safety population.
[3]15/121 and 13/123: Patients reporting diabetes mellitus at screening were excluded from the analysis of posttransplant diabetes mellitus.

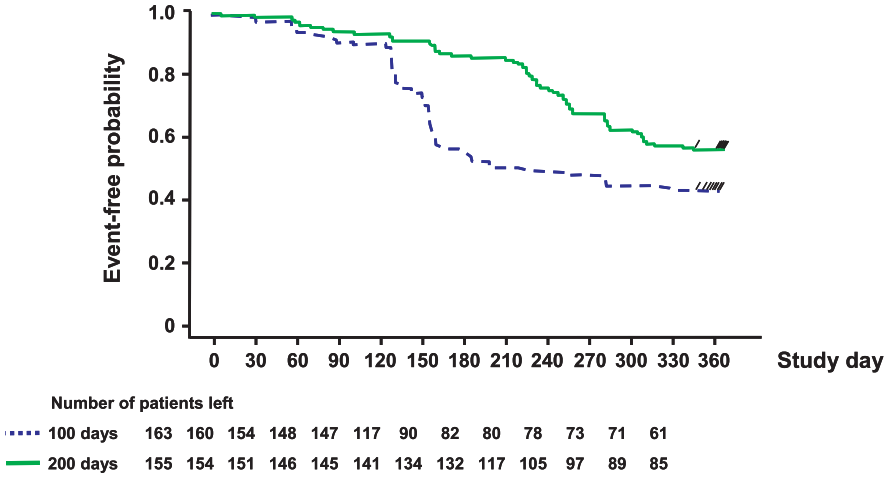

Figure 3: Kaplan–Meier plot of time to cytomegalovirus viremia up to month 12 posttransplant.

200-day group ($p = 0.001$; Table 2). This difference appears mainly due to an imbalance in occurrence of opportunistic infection during the first 50 days of therapy (0% [0/155] vs. 31.8% [14/163] of the overall opportunistic infections in the 200 days vs. 100 days groups, respectively). The proportion of patients with confirmed posttransplantation diabetes mellitus was similar ($p = 0.815$) between the groups up to month 12 (Table 2).

While the number of hospitalizations and the duration of the hospitalization stay were comparable between the groups (Table 5), the number of hospitalizations due to CMV was lower in the 200-day group (10% vs. 21%). All patients in the 200-day group survived to Month 12 posttransplant, but there were four deaths in the 100-day group, which were considered to be unrelated to study medication. Two patients died of septic shock on days 96 and 229 posttransplant, respectively, one patient died on day 335 posttransplant due to hemorrhage, and one patient died of sepsis on day 169 posttransplant.

Discussion

Late-onset CMV disease (occurring >3 months) is an increasingly recognized problem following a standard 3-month prophylaxis regimen. These data show a clear efficacy benefit for the prevention of CMV disease by using a 200-day prophylaxis regimen compared with the standard 100 days' prophylaxis in D+/R− kidney transplant recipients. The relative and absolute risk reduction observed with prolonged prophylaxis was 56% and 21%, respectively. This corresponds to a number needed to treat of approximately 5 in order to prevent each case of CMV disease up to 12 months posttransplant.

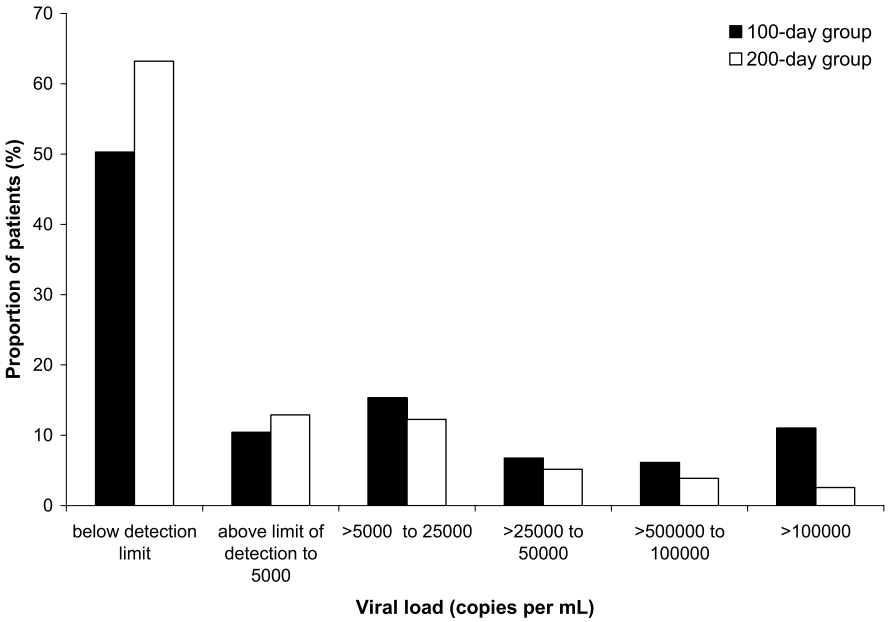

Figure 4: Peak cytomegalovirus viral load up to month 12 posttransplant (intent-to-treat population).

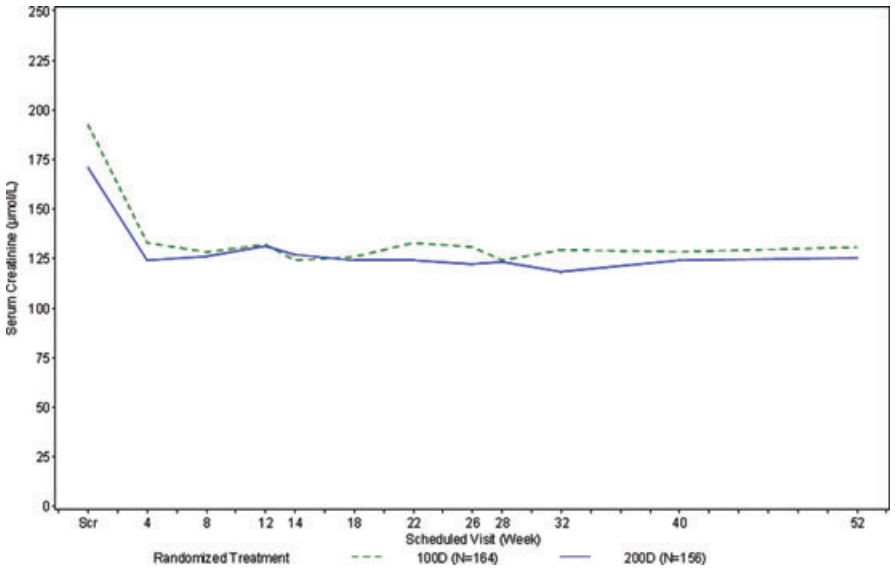

Figure 5: Median serum creatinine over time (μmol/L) (safety population).

The extended duration of prophylaxis was associated with a generally similar safety and tolerability profile compared with the standard 100-day regimen. There were no new safety concerns associated with the extension of valganciclovir CMV prophylaxis from 100 days to 200 days in kidney transplant patients at high risk (D+/R-). However, there are concerns that resistance may develop with prolonged exposure to ganciclovir (18). Genotypic resistance testing is currently being undertaken on all samples to evaluate the incidence of resistance.

The CMV disease rates (36.8% for confirmed cases) seen in this study at 12 months posttransplant for 100 days' prophylaxis are higher than those previously reported in the pivotal PV16000 study (committee agreed: 17.2%) (19). This difference may primarily relate to the definition of CMV disease used on the two studies. This study used a definition based on the AST recommendation for use in clinical trials that more accurately reflects CMV disease presentation in the modern era (i.e. many patients with viral syndrome do not have fever) (17). The rate of investigator-treated CMV disease in PV16000 was 30.5%, which is more comparable to the rate observed in this study. Tissue invasive disease was uncommon in this study with only two cases (1.2%) occurring in the 100-day group, but occurred in 9.2% of patients in the PV16000 study (data not specified by type of organ transplant). This may reflect current management strategies around CMV disease, which generally allow for rapid diagnosis through blood tests rather than needing a biopsy sample.

An alternative approach to prophylaxis is a preemptive strategy with regular laboratory monitoring and treatment of asymptomatic CMV viremia. In a randomized study, both preemptive and prophylactic (100 days) valganciclovir therapy were shown to have similar effectiveness in the prevention of symptomatic CMV disease after renal transplantation (20). However, very few D+/R- patients were evaluated. Late-onset CMV disease appears to be less of a problem with preemptive strategies, possibly because the low-level viremia that occurs with preemptive therapy may facilitate CMV-specific immune reconstitution and thus mitigate the risk of late-onset CMV disease (21). However, the possibility that preemptive strategies may be associated with poorer long-term graft survival compared with prophylaxis is worrisome (22).

The possibility of merely pushing the disease onset progressively further out after transplantation, while not affecting the actual incidence, is a significant concern with extended duration of prophylaxis. However, this study demonstrates a reduction in CMV disease incidence rather than merely a delay in onset with the 200-day prophylactic valganciclovir regimen. This finding is in line with data from other studies that have suggested increasing the duration of prophylaxis beyond the currently recommended 90–100-day window decreases the incidence of late-onset CMV disease (12–14).

The study was not powered to detect differences in the secondary endpoints of graft loss, BPAR or posttransplantation diabetes mellitus. There were no significant differences between the groups in these endpoints. However, there was a moderate trend toward less BPAR with 200 days of therapy versus 100 days of therapy (11% vs. 17%, respectively, $p = 0.114$). This trend has been reported previously in other clinical trials, as was a study comparing preemptive versus prophylaxis strategies in which the prophylaxis was associated with improved kidney graft survival 4 years posttransplant (22,23). A difference in opportunistic infections (other than CMV) was observed, but this should be interpreted with caution as the difference appears mainly due to an imbalance in occurrence during the first 50 days of therapy (0% vs. 31.8% of the overall

Table 3: Overview of safety and common adverse events (incidence ≥10% in either treatment group) (safety population)

	Valganciclovir 200 day (n = 156)	Valganciclovir 100 day (n = 164)
Overview of safety		
Patients with any adverse event, n (%)	152 (97)	158 (96)
Patients with a drug-related adverse event, n (%)[1]	93 (60)	86 (52)
Patients with serious adverse events, n (%)	78 (50)	94 (57)
Patients with a drug-related serious adverse events, n (%)[2]	13 (8)	13 (8)
Deaths during treatment (up to 28 days after study medication end)	0	1
Deaths during follow-up (more than 28 days after study medication end)	0	3
Common adverse events,[3] n (%)		
Leukopenia	59 (38)	43 (26)
Diarrhea	49 (31)	43 (26)
Peripheral edema	30 (19)	35 (21)
Urinary tract infection	34 (22)	26 (16)
Anemia	24 (15)	30 (18)
Neutropenia	23 (15)	25 (15)
Tremor	26 (17)	19 (12)
Hypertension	19 (12)	21 (13)
Constipation	14 (9)	25 (15)
Hypophosphatemia	18 (12)	20 (12)
Increased blood creatinine	16 (10)	21 (13)
Hyperkalemia	15 (10)	20 (12)
Nausea	17 (11)	18 (11)
Pyrexia	14 (9)	20 (12)
Nasopharyngitis	12 (8)	17 (10)
Hypomagnesemia	10 (6)	17 (10)
Headache	9 (6)	16 (10)
Cough	7 (4)	17 (10)

[1]Events judged by the investigator to be remotely, possibly or probably related to study treatment.
[2]Includes intercurrent illness.
[3]Occurring in ≥10% of patients between time of first drug intake and 28 days after last drug intake. Multiple occurrences of same adverse event in one patient counted only once.

opportunistic infections in the 200 days vs. 100 days groups, respectively), when both groups of patients were receiving the same prophylaxis regimen.

An important finding was that the number of hospitalizations for CMV disease was reduced by half, while hospitalizations for other reasons (including adverse events) were similar between the groups. In those who developed

Table 4: Common adverse events (incidence ≥5% in either treatment group) occurring after Day 100 (safety population)

Adverse events,[1] n (%)	Valganciclovir 200 day (n = 156)	Valganciclovir 100 day (n = 164)
Leukopenia	30 (19)	7 (4)
Diarrhea	15 (10)	18 (11)
Urinary tract infection	11 (7)	11 (7)
Nasopharyngitis	10 (6)	7 (4)
Pyrexia	6 (4)	10 (6)
Upper respiratory tract infection	11 (7)	4 (2)
Cough	4 (3)	9 (5)
Neutropenia	8 (5)	5 (3)

[1]Occurring in ≥5% of patients between time of first drug intake and 28 days after last drug intake. Multiple occurrences of same adverse event in one patient counted only once.

detectable viremia, peak CMV viral loads were generally lower in the 100-day group compared with the 200-day group. In addition, the median length of hospital stay per patient was reduced by around 1 day. These results suggest that extending prophylaxis to 200 days may have favorable economic benefits. Indeed, 6 months' prophylaxis with valganciclovir combined with a one-time assessment of viremia has been shown to be cost-effective from a US societal perspective in reducing CMV infection and disease in D+/R− kidney transplant recipients (24). A formal pharmacoeconomic analysis of the data from this study is currently in progress.

There are some limitations to this study. First, immunosuppressive regimens were not controlled as part of the trial and were at the discretion of the investigator. However, no investigational immunosuppression agents were permitted and so the regimens used likely reflect current

Table 5: Summary of hospitalization data up to Month 12 (safety population)

	Valganciclovir 200 day (n = 156)	Valganciclovir 100 day (n = 164)
Hospitalizations per patient, n (%)		
0	55 (35.3)	62 (37.8)
1	58 (37.2)	39 (23.8)
2	16 (10.3)	37 (22.6)
3	12 (7.7)	13 (7.9)
4	6 (3.8)	8 (4.9)
5	5 (3.2)	3 (1.8)
>5	4 (2.6)	2 (1.2)
Hospitalization duration (days) per patient, median (min, max)	4.0 (0, 108)	5.0 (0, 93)
Principal reason for each hospitalization episode, n (%)		
N	202	216
Cytomegalovirus	21 (10.4)	45 (20.8)
Adverse event	145 (71.8)	146 (67.6)
Other	36 (17.8)	25 (11.6)

practice. It should be noted that no large multicenter randomized trial of CMV prevention has ever mandated specific immunosuppression regimens. Second, HLA matching was not analyzed in our study. Poor HLA-B and -DR matching (i.e $\leq$2 matching) has been shown to significantly reduce the incidence of CMV infection in SOT recipients (16,25). Nonetheless, the randomization procedures undertaken in our study would have minimized HLA-matching bias between the two groups. Third, since this trial was restricted to kidney transplant recipients, it is unknown if these results can be extended to other transplant recipients or other risk categories such as D+/R+. In addition, data on discontinuation of antimetabolite use for drug-induced leukopenia or CMV viremia were not assessed in our study. Although total G-CSF used was captured, a detailed analysis of its use was not assessed. This information may have helped better understand the clinical consequences of drug-related adverse effects. Strengths of this trial include the large sample size, the randomized double-blinded design, and the use of more current definitions for CMV disease.

In conclusion, this study demonstrated that extending valganciclovir prophylaxis (900 mg once daily) to 200 days in high-risk patients significantly reduces the incidence of CMV disease and viremia up to 12 months compared with 100 days of prophylaxis. The extended duration of prophylaxis had a generally similar tolerability and safety profile. Based on these results, extending CMV prophylaxis to approximately 6 months in high-risk kidney transplant patients is a reasonable recommendation that appears to provide a significant benefit.

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