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ORIGINAL RESEARCH

Effects of oral valganciclovir prophylaxis for cytomegalovirus infection in heart transplant patients

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Background: Cytomegalovirus (CMV) infection is a serious complication following heart transplantation. This study (June 2003-January 2010) retrospectively assessed the effects of oral valganciclovir prophylaxis in adult heart transplant recipients during the first year after transplantation.

Methods: In patients with normal renal function, 900 mg of oral valganciclovir was administered twice daily for 14 days after heart transplant followed by 900 mg per day for following 6 months. In the event of renal insufficiency, valganciclovir was adjusted according to the manufacturer's recommendations. Antigenemia testing for pp65 antigen and simultaneous polymerase chain reaction (PCR) were used to document exposure to CMV. From 2003 to 2010, 146 patients (74.0% men) of mean age 50.7 ± 10.3 years at the time of heart transplant were included.

Results: A total of 16 patients (11.0% of total, 75.0% male) had a positive pp65 and PCR result (ie, CMV infection) during the year following heart transplant; three of these patients had discontinued valganciclovir prophylaxis within the first 6 months following transplant because of leukopenia, including one patient developed CMV colitis. Two further patients developed CMV pneumonia during prophylactic valganciclovir therapy. Eight patients had positive pp65 and PCR tests in the 6–12 months after heart transplant following cessation of routine prophylaxis. One of these patients developed CMV pneumonia and another developed CMV colitis and CMV pneumonia. Thirty-seven of the 146 (25.3%) patients were CMV donor-seropositive/recipient-seronegative, and seven (18.9% of this subgroup) had a positive CMV test. In patients who were CMV donor-seropositive/recipient-seronegative, the risk of a positive CMV test (ie, CMV infection) was significantly elevated ($P = 0.023$).

Conclusion: CMV prophylaxis with oral valganciclovir for 6 months following heart transplant is clinically feasible. In line with previous studies, CMV donor-seropositive/recipient-seronegative patients have a significantly elevated risk of CMV infection. In patients who prematurely discontinue valganciclovir, close monitoring of CMV antigenemia appears warranted. No significantly elevated rate of CMV infection was observed after 6 months of valganciclovir prophylaxis.

Keywords: cytomegalovirus infection, heart transplantation, valganciclovir prophylaxis

Introduction

Epidemiological studies have demonstrated that cytomegalovirus (CMV) infection is a serious complication after heart transplantation. It remains one of the most important infectious complications in solid organ transplant recipients.[1–3] Even though CMV is generally treatable, it has been associated with increased mortality after transplantation.[1–3] Direct effects attributed to CMV infection include viral syndrome and tissue-invasive disease,[4] and indirect effects include an increased risk of allograft rejection[5] and opportunistic infections.[6] Seronegative recipients (R–) receiving an organ from a

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CMV-seropositive donor (D+) are at highest risk for developing CMV infection.[7] Furthermore, heavily immunosuppressed patients, such as those receiving antilymphocyte antibody treatment for treatment of acute rejection, are at risk.[1,7]

CMV prophylaxis is now widely used in the transplantation setting and has been associated with reduction in CMV disease, mortality, and graft rejection in high-risk patients.[8–10] Given that delays in diagnosis of CMV infection result from the fact that late-onset CMV disease is often associated with nonspecific or atypical symptoms,[11–13] the optimal duration of prophylactic therapy in patients after solid organ transplant is unclear.[11,14] Recurrence of CMV disease after prophylaxis and treatment is not uncommon after solid organ transplantation.[15] Relevant data are limited, particularly in heart transplant patients. The aim of this study was to determine the ability of oral valganciclovir prophylaxis for 6 months (180 days) to prevent CMV infection in heart allograft recipients.

Materials and methods

Study design and patient population

This retrospective single-center study assessed the effects of oral valganciclovir prophylaxis in adult heart transplant recipients in the year following transplantation. Heart transplant recipients transplanted from 2003 until January 2010 were included in the study. All study patients were routinely monitored at the Heidelberg Heart Transplant Center according to the center's clinical routine protocols. pp65 antigen and simultaneous CMV DNA testing was performed weekly during the first month following heart transplant and monthly thereafter until the end of the first year. According to the center's clinical protocol, patients with preserved renal function (glomerular filtration rate $>$ 30 mL per minute) received valganciclovir 900 mg twice daily for 14 days after the heart transplant, and 900 mg/day thereafter until the end of month 6, at which point valganciclovir was routinely stopped. In the event of advanced renal insufficiency (ie, a glomerular filtration rate $<$ 30 mL per minute), the valganciclovir dose was adjusted according to the manufacturer's recommendations (Roche Pharma AG, Grenzach-Wyhlen, Germany). Oral valganciclovir prophylaxis was reduced or discontinued routinely in patients with side effects, eg, leukopenia.

In accordance with previous studies,[16] CMV infection was defined as CMV viremia identified by routine simultaneous quantitative polymerase chain reaction (PCR) and pp65 antigen detection. CMV disease was defined as CMV infection with at least one of the following symptoms: fever $>$ 38°C, severe malaise of new onset; leukopenia on two successive measurements separated by at least 24 hours defined as a white blood cell count of $<$3500 cells/μL if presymptomatic count was $>$4000 cells/μL or a decrease of $>$20% if the presymptomatic count was $<$4000 cells/μL; atypical lymphocytosis of $>$5%; and thrombocytopenia or elevation of hepatic transaminases to more than twice the upper limit of normal. Tissue-invasive CMV was defined as evidence of localized CMV infection in a biopsy or other appropriate specimen (ie, bronchial lavage or cerebral spinal fluid) and symptoms of organ dysfunction.

Quantitative CMV PCR was performed according to the manufacturer's instructions (light cycler, Roche Diagnostics, Mannheim, Germany), and 10^3 copies/mL was used as the qualitative detection limit, ie, a positive CMV PCR result versus a negative CMV PCR result. Nucleic acid was extracted from 200 μL of whole blood, and pp65 antigen testing was performed as previously described.[17] Quantitative real-time Epstein-Barr virus PCR was performed monthly up to month 6 after heart transplant and bimonthly from months 6 to 12 thereafter, as previously described.[18]

Myocardial biopsies were performed weekly during the first month after heart transplant, biweekly during the second month, once a month until month 6, and bimonthly until month 12 following transplant.

All patients received a combination of a calcineurin inhibitor and mycophenolate mofetil as baseline immunosuppression. Target trough levels for cyclosporin A were 175–225 μg/L at month 1, 125–175 μg/L at months 3–6, and 110–140 μg/L at months 7–12; and target trough levels for tacrolimus were 12–14 μg/L at month 1, 10–12 μg/L at months 3–6, and 8–10 μg/L at months 7–12. The target predose level of mycophenolate mofetil was 1.5–4.0 mg/L. Steroids were routinely administered for 6 months following heart transplant. All patients received post-transplant antithymocyte globulin as induction therapy. Dosage and duration of therapy were adjusted according to CD4 T cell counts, which were monitored daily by flow cytometry during the first week after heart transplant, aiming at an absolute CD4 T cell number below 50/μL.[19]

All patients gave their written informed consent prior to study inclusion and the study was approved by the ethics committee of the University of Heidelberg, so was performed in accordance with the ethical standards laid down in the 2008 Declaration of Helsinki.

The primary outcome parameter was the number of patients testing positive for CMV by PCR or pp65 antigenemia within the year following heart transplant. Vital signs, laboratory results, adverse events, and opportunistic infections were documented during routine clinical assessments.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences software (version 14.0, SPSS Inc, Chicago, IL). A two-sided *P* value of <0.05 was considered to be statistically significant. The Student's *t*-test was used for normally distributed variables and the Mann–Whitney test for other variables. Categorical variables were compared using the Chi-square test. Kaplan–Meier analyses were used to show the proportion of patients who tested positive and continuously tested negative for CMV.

Results

Patients

Included in this study were 146 patients who underwent heart transplantation at Heidelberg Heart Transplant Centre between 2003 and January 2010 and had complete follow-up data available. All patients were followed up locally for at least one year after transplantation at the center. Forty of the 146 patients were female (27.4%) and 106 were male (72.6%). Mean patient age at the time of heart transplant was 50.6 ± 10.5 years. Heart transplant was performed for dilated cardiomyopathy in 75 patients (51.4%), coronary artery disease in 40 (27.4%), valvular heart disease or congenital defects in two (1.3%), amyloidosis in 23 (15.8%), and for other reasons in six (4.1%). The mean donor age was 53.5 ± 9.2 years, with 104 of the donors being female (72.2%). The mean duration of ischemia was 3.6 ± 1.2 hours (Tables 1 and 2). All 146 patients were grouped according to CMV donor/recipient serostatus (D+/R–, D+/R+, D–/R–, or D–/R+). For further statistical analysis, the patients were divided in two groups, ie, those testing positive for CMV (n = 16) and those testing continuously negative for CMV (n = 130, Figure 1).

CMV test results

Sixteen patients tested positive for CMV during the first 12 months after heart transplantation (Figure 1). Eight patients (50.0% of this subgroup) tested positive for CMV within the first 6 months after their transplant, and the remaining eight patients (50.0%) tested positive in months 6–12 after transplant.

When analyzing separately the patients who tested positive for CMV during the first 6 months after heart transplant, three (37.5% of this subgroup) tested positive after prematurely discontinuing valganciclovir prophylaxis due to leukopenia. All of these patients were in the high-risk CMV group (ie, D+/R–), with one of the three patients developing CMV colitis. Five further patients tested positive for CMV during CMV prophylaxis (mean daily valganciclovir dose: 692.9 ± 489.9 mg, as valganciclovir prophylaxis was reduced in two patients). None of these patients belonged to the high-risk CMV group, and two of them developed CMV pneumonia. Eight patients tested positive for CMV at months 6–12 following their heart transplant, with one patient (D+/R–) developing CMV pneumonia and one patient (D–/R+) developing both CMV colitis and CMV pneumonia (Table 4). The time points at which these patients tested positive for CMV during the year after heart transplant is shown in Figure 2.

Survival

Total mortality during the year following heart transplant was not affected by CMV test status. Of the 16 patients who tested positive for CMV, one (6.3% of this subgroup) died during

Table 1 Patient characteristics at baseline

	Patients continuously testing CMV-negative, n = 130 (89.0% of total)	Patients testing CMV-positive at months 1–6, n = 8 (5.5% of total)	Patients testing CMV-positive at months 6–12, n = 8 (5.5% of total)
Male, n (%)	94 (72.3% of subgroup)	6 (75.0% of subgroup)	6 (75.0% of subgroup)
Mean age, years ± SD	53 ± 8.5	44 ± 3.5	44 ± 3.5
Death (during first 12 months post transplant), n (%)	18 (13.8% of subgroup)	1 (12.5% of subgroup)	0 (0.0% of subgroup)
Immunosuppression, n (%)			
CSA + MMF	44 (33.8% of subgroup)	4 (50.0% of subgroup)	4 (50.0% of subgroup)
TAC + MMF	86 (66.2% of subgroup)	4 (50.0% of subgroup)	4 (50.0% of subgroup)
D/R status, n (%)			
D+/R+	31 (23.8% of subgroup)	1 (12.5% of subgroup)	1 (12.5% of subgroup)
D+/R–	30 (23.1% of subgroup)	3 (37.5% of subgroup)	4 (50.0% of subgroup)
D–/R+	35 (26.9% of subgroup)	2 (25.0% of subgroup)	1 (12.5% of subgroup)
D–/R–	34 (26.2% of subgroup)	2 (25.0% of subgroup)	2 (25.0% of subgroup)

Abbreviations: CSA, cyclosporine A; MMF, mycophenolate mofetil; TAC, tacrolimus; D/R, donor/recipient status.

Table 2 Laboratory parameters

Mean ± SD	CMV– month 1	CMV+ month 1	*P* value	CMV– month 6	CMV+ month 6	*P* value	CMV– month 12	CMV+ month 12	*P* value
Creatinine (mg/dL)	1.5 ± 1.0	1.1 ± 0.7	0.519	1.5 ± 1.0	1.4 ± 0.6	0.292	1.5 ± 0.8	1.3 ± 0.4	0.276
Urea (mg/dL)	74.0 ± 37.59	73.4 ± 52.5	0.798	64.6 ± 36.5	56.4 ± 23.0	0.686	62.1 ± 30.0	62.7 ± 22.8	0.630
Cholesterol (mg/dL)	196.9 ± 51.9	205.1 ± 56.8	0.596	187.3 ± 44.3	187.5 ± 41.7	0.923	185.2 ± 49.3	166.4 ± 54.7	0.125
HDL (mg/dL)	57.3 ± 20.6	60.2 ± 17.5	0.715	51.6 ± 18.2	50.0 ± 21.1	0.707	50.4 ± 18.7	42.9 ± 19.9	0.133
LDL (mg/dL)	101.5 ± 33.8	109.5 ± 31.2	0.966	100.3 ± 33.3	105.2 ± 27.2	0.324	99.1 ± 31.5	93.6 ± 37.5	0.965
Triglycerides (mg/dL)	167.1 ± 74.3	167.3 ± 78.6	0.934	189.6 ± 194.8	177.0 ± 79.8	0.713	185.1 ± 162.5	199.3 ± 136.8	0.673
Hemoglobin (g/dL)	11.2 ± 1.4	11.8 ± 1.1	0.045	10.8 ± 1.3	11.0 ± 1.4	0.735	11.8 ± 1.5	11.0 ± 1.7	0.164
White blood cells (n/µL)	9.1 ± 4.8	11.5 ± 3.9	0.0002	4.7 ± 2.2	4.4 ± 2.3	0.855	5.9 ± 2.0	6.5 ± 5.9	0.644
Platelets (n/µL)	290.9 ± 131.9	242.4 ± 88.1	0.307	248.6 ± 89.2	213.8 ± 72.2	0.297	239.9 ± 62.1	230.8 ± 103.2	0.309
CK (U/L)	46.4 ± 61.8	34.3 ± 24.8	0.757	77.5 ± 73.9	56.3 ± 43.2	0.210	140.7 ± 135.7	76.2 ± 72.4	0.056
GGT (U/L)	217.8 ± 216.2	164.1 ± 159.8	0.739	133.0 ± 196.1	79.1 ± 78.1	0.586	106.0 ± 153.4	107.5 ± 105.8	0.189
GOT (U/L)	24.6 ± 18.1	23.6 ± 14.7	0.382	23.2 ± 13.2	22.7 ± 8.7	0.271	26.4 ± 14.1	35.9 ± 28.8	0.095
GPT (U/l)	44.7 ± 41.5	47.6 ± 26.1	0.467	26.8 ± 25.9	24.9 ± 14.5	0.219	25.2 ± 15.2	38.7 ± 34.2	0.134
AP (U/L)	117.2 ± 79.9	105.1 ± 99.0	0.635	94.1 ± 77.5	90.1 ± 43.9	0.348	111.4 ± 71.0	122.9 ± 52.4	0.155
Body weight (kg)	71.9 ± 13.3	73.2 ± 22.2	0.704	70.7 ± 14.2	72.2 ± 20.3	0.957	71.6 ± 14.2	70.0 ± 19.6	0.693
Blood pressure (mmHg)	117.4 ± 16.4/	118.4 ± 14.3/	0.702	122.4 ± 17.7/	124.0 ± 13.1/	0.417	121.8 ± 15.8/	120.0 ± 15.2/	0.712
	71.4 ± 11.3	73.4 ± 8.7	0.937	74.5 ± 10.4	74.7 ± 10.3	0.079	76.0 ± 11.9	76.3 ± 14.6	0.407

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; CK, creatine kinase; GGT, gamma-glutamyltransferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; AP, alkaline phosphatase; SD, standard deviation.

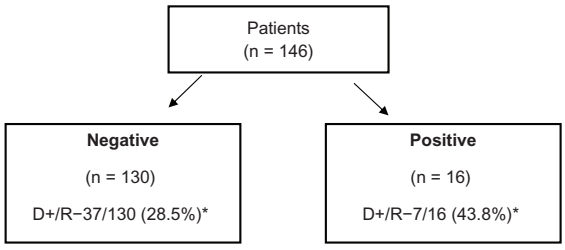

Figure 1 CMV testing results throughout the study.
Note: *$P < 0.001$.
Abbreviations: CMV, cytomegalovirus; D, donor; R, recipient.

the first year after heart transplant, whereas in the 130 patients who continuously tested negative for CMV, 18 (13.9%) died during the first 12 months after transplant (Figure 3). Of the 130 patients who continuously tested negative for CMV, 11 (8.5%) died during prophylaxis, seven (5.4%) of whom died after routine cessation of prophylaxis. Nine (6.9%) of the 130 patients who continuously tested negative for CMV and none of the patients who tested positive for CMV died as a result of infectious complications. Three (2.3%) of 130 patients who continuously tested negative for CMV and none of the patients who tested positive for CMV died because of acute rejection.

Effects of immunosuppression

Previous research has demonstrated an increased risk of CMV infection in patients with high calcineurin inhibitor levels.[20] All patients received a combination of calcineurin inhibitor and mycophenolate mofetil as their baseline immunosuppression. Steroids were routinely administered for 6 months following heart transplant. At the time of testing positive for CMV, absolute levels of immunosuppression (see Materials and methods section) were elevated in nine of 16 patients (56.3%, $P < 0.001$) when compared with levels in those who continuously tested negative for CMV. Because all patients received antithymocyte globulin, we did not evaluate the effects of induction therapy in the present study.

Side effects

The overall incidence of leukopenia in this study was 14.4% (n = 21). Subgroup analysis revealed that three (18.8%) of the 16 patients who tested positive for CMV developed leukopenia compared with 18 (13.9%) of 130 of the patients who continuously tested negative for CMV. No significant increase in concomitant infections was seen in the patients who tested positive for CMV (Table 3). No Epstein-Barr virus coinfection was observed.

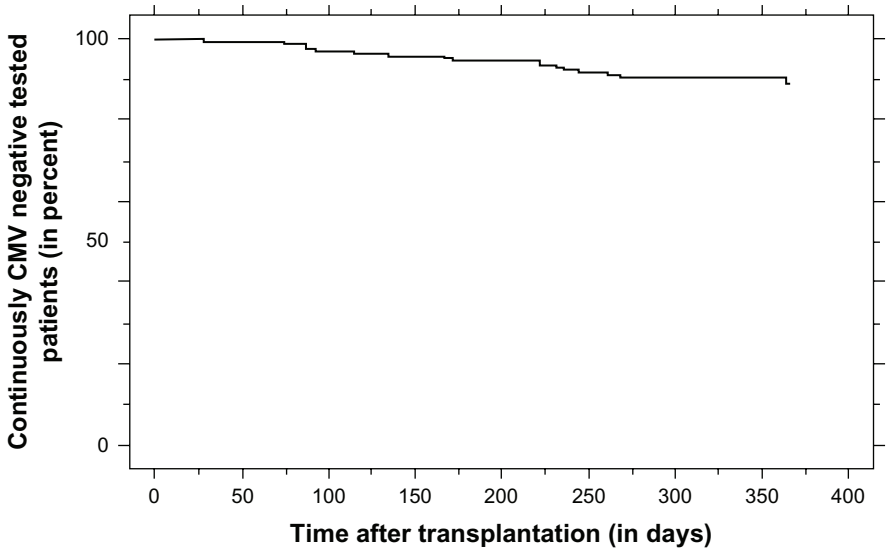

Figure 2 Kaplan–Meier curve showing percentage of patients who continuously tested negative for CMV.
Abbreviation: CMV, cytomegalovirus.

Acute rejection episodes and graft function

Significantly more acute rejection episodes requiring treatment were observed in patients who tested positive for CMV during the first year after heart transplant (occurring in three (18.8%) of 16 CMV-positive patients and in 14 (10.8%) of 130 patients who continuously tested negative for CMV, $P < 0.001$). After 12 months, left ventricular ejection fraction was normal in all 15 patients who tested positive for CMV and in 108 (96.4%) of 112 patients who continuously tested negative for CMV.

Discussion

CMV infection is a serious complication after heart transplant. Due to its availability in an oral formulation, valganciclovir is being increasingly used as CMV prophylaxis. However, the optimal recommended duration of CMV prophylaxis for heart transplant patients is currently unclear. According to our center's protocol, valganciclovir is routinely given for 6 months after transplantation in the absence of contraindications, eg, renal insufficiency or leukopenia.[15]

Our data show that CMV prophylaxis with oral valganciclovir for 6 months after heart transplant is clinically feasible.

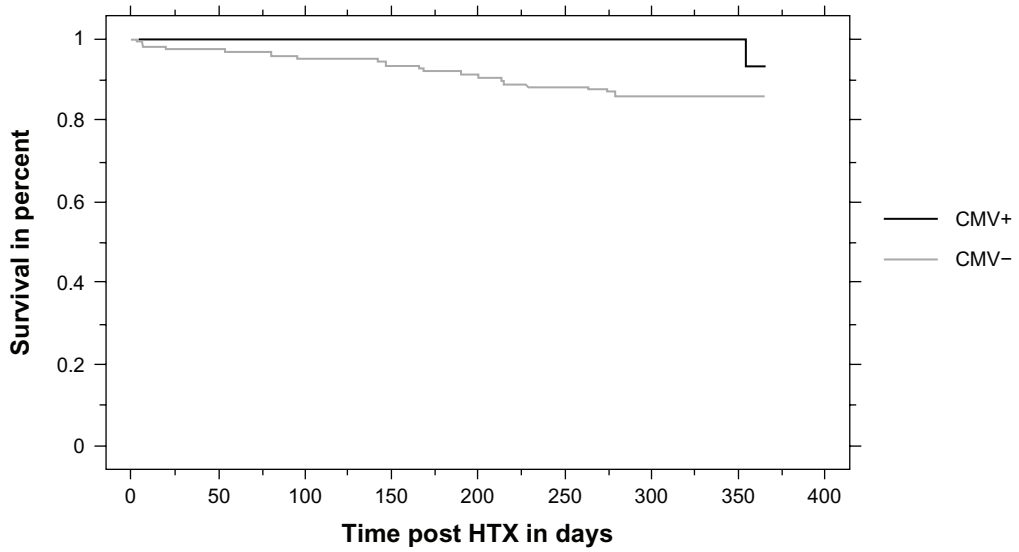

Figure 3 Kaplan–Meier curve describing the survival during the first year post HTX (P = NS).
Abbreviations: CMV, Cytomegalovirus; HTX, heart transplantation; CMV+, patients with CMV infection during post-op year 1; CMV–, patients without CMV infection during post-op year 1.

Table 3 Opportunistic infections in patients who tested CMV-negative and CMV-positive during the first year post heart transplantation

Non-CMV pneumonia		Zoster infections	
Patients testing CMV-negative n = 130 n (%)	Patients testing CMV-positive n = 16 n (%)	Patients testing CMV-negative n = 130 n (%)	Patients testing CMV-positive n = 16 n (%)
9 (6.9%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
$P = 0.277$		$P = 0.438$	

Abbreviation: CMV, cytomegalovirus.

However, in case of premature valganciclovir discontinuation (ie, <6 months following heart transplant), increased rates of CMV infection could be observed; in such patients, close monitoring for CMV infection appears warranted. In line with previous reports,[7,15] D+/R– patients have a significantly elevated risk of testing positive for CMV. Although we did observe patients developing CMV disease after routine cessation of CMV prophylaxis, no statistically significant elevated rate of a positive CMV test result or of symptomatic disease was found during months 6–12 after heart transplant. Mortality in the year following heart transplant was not affected by a positive CMV test result. In CMV-positive patients, more acute rejections requiring therapy were documented during the year following heart transplant ($P < 0.001$), whereas left ventricular ejection fraction was unchanged.

Further, in patients who tested positive for CMV, an association with quantitative immunosuppression was observed. However, given that all patients received dual immunosuppression consisting of a calcineurin inhibitor and mycophenolate mofetil (and steroids for 6 months post transplant), the potential effects of mTOR inhibitors could not be addressed.

Previously published studies have raised concerns that prolonged CMV prophylaxis may cause resistance to valganciclovir,[16] but no cases of valganciclovir resistance were observed at our center. All patients who tested positive for CMV responded promptly to valganciclovir therapy. In comparison with previous studies,[21] the proportion of patients who tested positive for CMV after transplant was generally low (16 of 146 patients, 11.0%) which might be attributed to the target levels of immunosuppression used. Furthermore, the rate of CMV disease (five of 146 patients, 3.4% of total) was acceptable.[21] In contrast with previously published data, there was no statistically significant difference with regard to opportunistic infections between patients who tested positive for CMV and those who did not.[21]

Table 4 Time point of positive CMV testing

	Before month 6	After month 6
Infection	5	6
Disease	3[a,b,b]	2[a+b,b]

Notes: [a]CMV colitis; [b]CMV pneumonia.
Abbreviation: CMV, cytomegalovirus.

The retrospective nature of this analysis carries the limitations of any such study design. Additionally, this study was from a single center and lacked a control group without valganciclovir prophylaxis. Further, different durations of CMV prophylaxis were not compared. Because all patients received antithymocyte globulin, the effects of induction therapy could not be evaluated in the present study.

Conclusion

The present study demonstrates that CMV prophylaxis with oral valganciclovir for 6 months post heart transplant is clinically feasible. No increase in positive CMV testing (ie, CMV infection) after 6 months of valganciclovir prophylaxis was observed. However, close monitoring after premature valganciclovir discontinuation appears to be warranted. In line with previous studies, D+/R– patients have a significantly elevated risk for a positive CMV test result. However, these single-center data should be confirmed by a large, double-blind, multicenter study assessing various durations of prophylactic valganciclovir. In our opinion, despite the higher costs of prophylactic therapy after heart transplant, our data support a prophylactic approach, in line with previously published data.[22]

Disclosure

The authors report no conflicts of interest in this work.

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