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Comparison of universal prophylaxis and preemptive treatment with valganciclovir in management of cytomegalovirus infection in heart transplant recipients

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ABSTRACT

Background: Cytomegalovirus (CMV) is a major cause of infection in the early period after heart transplantation (HTx). There are limited data comparing universal prophylaxis with preemptive treatment of CMV infection in HTx recipients. Therefore, the goal of this study was to evaluate efficacy and safety of both strategies.
Methods: A total of 17 HTx recipients were prospectively enrolled in the universal prophylaxis group. This study cohort was matched with 18 HTx recipients who had the same immunosuppressive regimen and received preemptive therapy for CMV infection. All patients were CMV-seropositive. The study group received oral valganciclovir in a dose of 900 mg daily for 100 days. The second group was treated in case of CMV viraemia higher than 500 copies/ml. The incidence of CMV infection, other opportunistic infections and acute graft rejection and adverse events were evaluated at 3th, 6th and 12th months post-transplant.
Results: Universal prophylaxis was well tolerated in 87.5% of the patients for a period of 100 days. Leukopenia was the most frequent side-effect that appeared in 25% of this group. This strategy decreased the rate of asymptomatic CMV infection during the first three months after HTx (11.7% vs 55.6%, $p = 0.006$) compared with preemptive therapy. This positive effect was associated with lower incidence of acute graft rejection at 12 months of follow up (6.3% vs 41.2%, $p = 0.015$).
Conclusion: Universal prophylaxis with valganciclovir in CMV-seropositive HTx recipients was acceptably safe and compared with preemptive therapy of CMV infection reduced the incidence of asymptomatic CMV infection and of acute graft rejection.

Klíčová slova:
Cytomegalovirus
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Valganciclovir

SOUHRN

Kontext: Cytomegalovirus (CMV) je jedním z hlavních původců infekce v časném pooperačním období po transplantaci srdce (OTS). V současnosti existují pouze omezená data srovnávající univerzální profylaxi s preemptivní terapií CMV infekce u pacientů po OTS. Cílem naší prospektivní studie bylo posoudit účinnost a bezpečnost obou metod.
Metody: Do skupiny s univerzální profylaxí bylo zařazeno celkem 17 příjemců OTS. Kontrolní skupinu tvořilo 18 pacientů, kterým byla podána preemptivní terapie. Všichni pacienti měli zavedenou stejnou imunosupresivní léčbu a byli CMV sérologicky pozitivní. Za účelem univerzální profylaxe byl podán perorální valganciclovir v dávce 900 mg denně po dobu 100 dnů. Ve skupině s preemptivní terapií byla zahájena léčba

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CMV infekce při průkazu CMV viremie > 500 kopií/ml. Ve 3., 6., a 12. měsíci po transplantaci byla sledována incidence CMV infekce, oportunních infekcí a rejekce štěpu.
Výsledky: Univerzální profylaxe byla dobře tolerovaná u 87,5 % pacientů po dobu 100 dnů. Leukopenie jako nejčastější nežádoucí účinek vznikla u 25 % pacientů. Tato strategie ve srovnání s preemptivní terapií vedla ke snížení výskytu asymptomatické CMV infekce v průběhu prvních tří měsíců po OTS (11,7 % vs. 55,6 %, p = 0.006). Rovněž byla zaznamenána nižší incidence akutní rejekce štěpu v průběhu ročního sledování (6,3 % vs. 41,2 %, p = 0,015).
Závěr: Univerzální profylaxe s valganciclovirem u CMV sérologicky pozitivních příjemců po OTS je bezpečnou a účinnou metodou redukce výskytu asymptomatické CMV infekce a akutní rejekce štěpu.

Introduction

Cytomegalovirus (CMV) is a major cause of infection in the first months after heart transplantation (HTx). The reported incidence of CMV disease ranges between 10 and 60% depending on donor-recipient mismatch in CMV serology and on intensity of immunosuppression [1–3]. Besides to direct sequalae of infection, CMV viral load has been associated with indirect effects as an increased risk of opportunistic infections [1–3], high incidence of acute graft rejection and/or cardiac allograft vasculopathy [4–6]. Intravenous ganciclovir has been shown to prevent CMV disease both in CMV-seronegative [7] and CMV-seropositive [8] HTx recipients. The invention of valganciclovir a valine ester prodrug of ganciclovir with improved bioavailability has facilitated easier and more widespread use of CMV prophylaxis in these patients. As a universal prophylaxis in CMV-seronegative recipients of organs from seropositive donors, valganciclovir at dosage of 900 mg daily is equivalent to oral ganciclovir administered at a dose of 1,000 mg three times daily [9]. Valganciclovir has also been studied in the setting of preemptive therapy in HTx recipients [10]. In such case the HTx recipients are monitored for early evidence of CMV replication and treated with antiviral therapy in case of documented viraemia.

Universal prophylaxis might be more effective way preventing both direct and indirect effects of CMV infection than preemptive therapy. On the other hand, preemptive therapy could reduce drug costs and toxicity. However, there are limited data about efficacy of universal prophylaxis with valganciclovir in CMV-seropositive HTx recipients. Similarly, direct comparison of universal prophylaxis and preemptive therapy is not available in this population. Therefore, we conducted a prospective cohort study comparing the efficacy and safety of the universal CMV prophylaxis with the preemptive treatment in HTx recipients at risk of CMV infection.

Methods and materials

1. Study protocol

This was a prospective single-centre, case-control study. The inclusion criteria were as follows: *de novo* HTx, age of recipient above 18 years and an increased risk of CMV infection. The following combinations of CMV serology in a donor (D) and a recipient (R) were included: R+/D–, R+/D+ and R–/D+. We excluded individuals who deceased before the 10th postoperative day. The other exclusion criteria comprised acute renal or liver failure, severe leukopenia or trombocytopenia and known hypersensitivity to ganciclovir or valganciclovir.

2. Study groups

In total, 44 individuals who underwent *de novo* HTx between November 2007 and December 2008 were screened. Out of this cohort, 41 patients were at risk of CMV infection (85%). Three individuals died early after HTx and another three refused to participate in the study. A total of 35 patients participated in the study. Seventeen HTx recipients at risk of CMV infection were prospectively enrolled in the universal prophylaxis group. The remaining 18 individuals received preemptive treatment of CMV infection. The whole study group had the same induction therapy with polyclonal anti-human thymocyte immunoglobulin (Thymoglobuline, Genzyme Polyclonals S.A.S, Marcy L'Étoile, France) 1.25 mg/kg.day administered at the time of surgery and in the following 3–7 days until target through levels of tacrolimus were reached. Standard immunosuppressive regimen consisted of tacrolimus with a target through level of 10–15 ng/ml, mycophenolate mophetil 2,000 mg daily, and prednisone at an initial dose of 1 mg/kg.day with subsequent tapering to less than 0.3 mg/kg.day at one month and 0.1 mg/kg.day at 12 months after HTx. Both groups were followed using the same schedule of clinical and laboratory controls, as well as the institutional protocol of endomyocardial biopsy (EMB). Acute allograft rejection episodes ≥ grade Banff 3A were treated with intravenous methylprednisolone 1,000 mg for 3 consecutive days.

3. Study treatment

The universal prophylaxis group was treated with 900 mg of oral valganciclovir once daily for 100 days starting within the first ten days after HTx. The group of preemptive therapy was closely monitored to detect CMV viraemia and received valganciclovir only in case of CMV viraemia higher than 500 copies/ml. The terapeutic dosage of valganciclovir was 900 mg twice daily for 2–3 weeks until clearance of CMV viraemia followed by a prophylactic dose for next 3 months. Individuals with tissue invasive CMV disease were treated with intravenous ganciclovir 5 mg/kg twice daily for 3 weeks followed by a prophylactic dose of valganciclovir for next 3 months. In cases of

impaired renal function, dosages of valganciclovir and ganciclovir were adjusted appropriately.

4. Follow-up

Presence of CMV disease, CMV viraemia, other infections and acute graft rejection, as well as adverse effects were analyzed at 3th, 6th and 12th months post-transplant.

EMB were planned and performed according to the institutional protocol. In brief, patients underwent EMB every week until 30 days post-transplant, every 2 weeks until 3 months, every one month until 6 months, followed by EMB at 9th and 12th months after HTx. Biopsies were graded according to 1990 ISHLT classification (Banff classification) using the following scale: 0, 1A, 1B, 2, 3A, 3B, 4 [11]. Each EMB was accompanied with a clinical and laboratory control. Laboratory analysis included measurements of CMV-viraemia, blood count, serum creatinine and liver function tests (aspartate amino-transferase, alanine amino-transferase, γ-glutamyl-transferase, alkaline phosphatase).

The pre-transplant CMV serology status of recipients and donors was assessed using a commercial enzyme-linked immunoassay detecting specific IgG and IgM antibodies. CMV viraemia was measured in peripheral venous blood samples obtained into tubes containing ethylenediaminetetraacetic acid. The measurement of CMV DNA concentration was performed using a commercially available real-time polymerase chain reaction (Artus™ CMV RG PCR kit, Qiagen, Hilden, Germany).

5. Definitions

CMV infection was defined as presence of CMV viraemia > 500 copies/ml regardless of symptoms. For the purpose of statistical analysis, we divided CMV infection into asymptomatic CMV viraemia (a positive CMV PCR without signs or symptoms) and CMV disease (detectable CMV PCR with attributable symptoms). Leukopenia referred to white blood cell count of less than 4.0×10^9/liter and trombocytopenia to platelet count of less than 150×10^9/liter.

6. Statistical methods

Categorical data were expressed as percentages and compared using chi-squared analysis. Continuous variables were expressed as a mean and standard deviation. They were compared using the Student t test for paired and unpaired data or by the non-parametric Mann-Whitney test when appropriate. A p-value < 0.05 was considered statistically significant. Analysis was performed using the statistical software SPSS (Chicago, Illinois, USA) for Windows, version 17.0.

7. Ethics

The investigation conformed to the principles outlined in the Declaration of Helsinki. It was approved by the local human ethics committee. All subjects gave their written informed consent prior to the participation in the study.

Results

Table 1 shows the study population characteristics. The universal prophylaxis group and the preemptive therapy group were well matched. All recipients were CMV-seropositive. There was no case of D+/R-CMV mismatch which indicated an intermediate risk of post-transplant CMV infection in our study group. Two patients died during follow-up. In the universal prophylaxis group, one patient died of intracerebral hemorrhage on the 16th postoperative day which was not related to treatment with valganciclovir. In the preemptive therapy group, one patient died of sepsis of unknown origin in the 6th postoperative week. The remaining 33 patients completed 12 months of follow-up.

Efficacy of treatment

Compared with the preemptive therapy, universal prophylaxis with valganciclovir resulted in significant reduction of asymptomatic CMV viraemia during the first three

Table 1 – The study group characteristics.

	Universal prophylaxis n = 17 pts	Preemptive therapy n = 18 pts	*P*-value
Age (years)	49.5 ± 12.8	50.4 ± 10.5	NS
Gender	12 males (74%) 5 females (26%)	14 males (77.8%) 4 females (32.2%)	NS
Aethiology of heart failure	CAD 4 pts (23%) DCM 7 pts (42%) Other 6 pts (35%)	CAD 9 pts (50%) DCM 5 pts (28%) Other 4 pts (22%)	NS
Immunosuppression	Tacrolimus 17 pts (100%) MMF 17 pts (100%) Prednisone 17 pts (100%)	Tacrolimus 18 (100%) MMF 18 (100%) Prednisone 18 (100%)	NS
CMV serology	D+/R– – 0 D–/R+ – 5 pts (29%) D+/R+ – 12 pts (71%)	D+/R– – 0 D–/R+ – 2 pts (17%) D+/R+ – 15 pts (83%)	NS

CAD – coronary artery disease; CMV – cytomegalovirus; D – donor; DCM – dilated cardiomyopathy; MMF – mycophenolate mophetil; NS – not significant; pts – patients; R – recipient.

Table 2 – Efficacy of the universal prophylaxis with valganciclovir compared with preemptive therapy. Table shows number of patients who experienced CMV infection, other opportunistic infections and acute graft rejection.

Time period	Study group	CMV viraemia	CMV disease	Other opportunistic infections	Acute rejection Banff 2	Acute rejection Banff 3A–3B
0–3 months	UP	2	0	2	0	1
	n = 17	(11.7%)		(11.7%)		(5.9%)
	PT	10	2	0	5	1
	n = 18	(55.6%)**	(11.1%)		(27.8%)*	(5.6%)
4–6 months	UP	2	0	0	1	0
	n = 16	(12.5%)			(6.3%)	
	PT	2	2	2	1	0
	n = 17	(11.7%)	(11.7%)	(11.7%)	(5.9%)	
7–12 months	UP	2	0	0	0	0
	n = 16	(12.5%)				
	PT	2	0	0	1	0
	n = 17	(11.7%)			(5.9%)	

PT – preemptive treatment; UP – universal prophylaxis.
P-value for comparison between the universal prophylaxis group and the preemptive therapy group during each period of follow-up was coded: $p < 0.05$ *, $p < 0.01$ **.

months of follow-up: 2 pts (11.7%) vs 10 pts (55.6%), $p = 0.006$ (Table 2). The relative risk reduction reached 80%. In addition, four individuals (22%) from the preemptive therapy group experienced a CMV tissue invasive disease which was not observed in the universal prophylaxis group. These four cases included histologically proven CMV gastritis and CMV myocarditis (0–3 months of follow-up) and histologically proven CMV colitis and interstitial pneumonia with detection of CMV and pneumocystis jiroveci in bronchoalveolar lavage specimens (4–6 months of follow-up). Importantly, there was no increase in late-onset CMV infection after completion of valganciclovir prophylaxis. Three months after HTx, asymptomatic CMV infection affected about 12% of patients in both groups in each time period (Table 2).

During the follow-up period, four cases of opportunistic infection were observed. Two of them occurred in the universal prophylaxis group. The first case was pneumocystis jiroveci pneumonia diagnosed at 7 weeks after HTx that resolved after cotrimoxazol treatment. The second case was pneumocystis jiroveci pneumonia complicated by invasive pulmonary aspergilosis at 8 weeks after HTx. It was successfully treated with cotrimoxazol and voriconazol. The remaining two cases of opportunistic infection appeared in the preemptive therapy group. One case comprised mixed CMV and pneumocystis jiroveci interstitial pneumonia at 4 months of follow-up, treated again with a combination of cotrimoxazol and voriconazol. The second case was invasive pulmonary aspergilosis diagnosed at 4 months of follow-up, successfully treated with itraconazol.

Interestingly, during the first three months of follow-up, the universal prophylaxis group presented with lower incidence of acute cellular rejection grade Banff 2 compared with the preemptive therapy group (0 pts vs 5 pts [27.8%], $p = 0.019$). Within 12 months of follow-up, only one patient (6.3%) from the universal prophylaxis group experienced one episode of acute cellular rejection, grade Banff 2. On the contrary, 7 pts (41.2%) from the preemptive therapy group had within the same time period a total of 10 episodes of acute cellular rejection grade Banff 2 ($p = 0.015$).

Safety

Universal prophylaxis with valganciclovir was well tolerated by 14 individuals (87.5%) for the entire treatment period of 100 days. Valganciclovir had to be discontinued in 2 patients (12.5%) due to significant leukopenia and neutropenia on the 57th and 85th day of prophylaxis. In these two patients, the count of leukocytes and neutrophils reached 2.2×10^9/l and 3.3×10^9/l, and 1.52×10^9/l and 1.83×10^9/l, respectively. Another two individuals experienced leukopenia that resolved after dose reduction of valganciclovir to 450 mg daily (Table 3). The first case appeared on the 79th day (leukocytes 3.5×10^9/l, neutrophiles 2.13×10^9/l), while the second case was diagnosed on the 83rd day (leukocytes 3.9×10^9/l, neutrophiles 2.11×10^9/l). In the first three months, the prevalence of leukopenia in the universal prophylaxis group was higher (25%) than in the preemptive therapy group (0%). However, this difference did not reach statistical significance ($p = 0.089$).

Table 3 shows the other parameters of safety. We observed a mild elevation of aspartate amino-transferase in the universal prophylaxis group at three months. However, this elevation was only mild and did not exceed the upper limit of normal values in any patient. No other drug-related side-effects were observed.

Discussion

The main findings of our study can be summarized as follows. First, universal prophylaxis was significantly more effective than preemptive treatment in reduction of subclinical CMV infection. Second, universal prophyla-

xis with valganciclovir was safe and tolerated by 83% of the study group for the entire treatment period of 100 days. Third, universal prophylaxis reduced incidence of acute graft rejection Banff 2 during the first three months post-transplant.

Comparison with previous studies

The first experience with preemptive treatment of CMV infection with valganciclovir was reported by Devyatko et al. in 2004 [9]. Subsequently, Potena el al. demonstrated in a cohort study that universal prophylaxis with valganciclovir compared with preemptive intravenous ganciclovir reduces CMV viral burden and prevents progression of cardiac allograft vasculopathy [12]. In another study by the same author, an aggressive CMV prophylaxis in CMV R–/D+ HTx patients decreased risk of CMV infection, acute graft rejection and progression of cardiac allograft vasculopathy below levels seen in CMV- seropositive HTx patients receiving standard prophylaxis [13]. The aggressive prophylaxis protocol consisted of CMV hyperimmune immunoglobulin plus four weeks of treatment with intravenous ganciclovir followed by two months of valganciclovir. Standard prophylaxis consisted of intravenous ganciclovir administered for 4 weeks. A direct comparison of universal prophylaxis and preemptive therapy with valganciclovir was performed by Khoury et al. in a randomized study in renal transplant recipients [14]. The study demonstrated greater efficacy of prophylactic valganciclovir given for 100 days to suppress subclinical CMV infection for 12 months than preemptive therapy. However, 22% of patients in the universal prophylaxis group experienced late-onset CMV viraemia. This occurred more frequently in individuals with pre-transplant serology CMV D+/R– (in 38%). A randomized trial in 364 CMV D+/R– solid organ transplant recipients compared valganciclovir 900 mg once daily with oral ganciclovir 1,000 mg three times a day for 100 days [9]. Valganciclovir provided greater reduction of CMV viraemia associated with reduced occurrence of acute graft rejection. Nevertheless, this study demonstrated high incidence of late-onset CMV infection which appeared approximately in 50% of these high risk patients after completion of prophylaxis.

Our study extends the available evidence by direct comparison of universal prophylaxis and preemptive therapy with valganciclovir in CMV-seropositive HTx recipients. It confirms results of previous studies in terms of reduced incidence of CMV infection and acute allograft rejection achieved through universal prophylaxis. However, its results may not be applicable to individuals with pretransplant CMV serology D+/R–. These recipients have a high risk of CMV infection and may need a combination of prophylactic approaches or prolonged prophylaxis with valganciclovir. Further studies are needed to elucidate the best management in these individuals. Moreover, prognostic impact of universal CMV prophylaxis can only be assessed in large randomized trials.

CMV infection as a trigger of acute graft rejection and cardiac allograft vasculopathy

There is a growing evidence supporting association between CMV infection, acute graft rejection and cardiac

Table 3 – Safety of the universal prophylaxis compared with the preemptive therapy. Leukopenia was defined as white blood cells count less than 4,000 × 10^9/l.

Time period	Group	Bilirubin (μmol/l)	AST (μkat/l)	ALT (μkat/l)	S-Cr (μmol/l)	Leukopenia number of patients (%)	WBC (× 10^9/l)	Hb (g/l)	Platelets (× 10^9/l)
10th day	UP n = 17	16.3 ± 9.0	0.54 ± 0.61	0.90 ± 0.35	74.9 ± 18.2	0	11.0 ± 5.2	102.6 ± 26.7	267.5 ± 101.3
	PT n = 18	16.7 ± 9.0	0.38 ± 0.22	0.88 ± 0.44	78.4 ± 22.9	0	11.5 ± 3.3	105.4 ± 19.4	246.9 ± 73.1
3 months	UP n = 16	12.2 ± 8.2	0.44 ± 0.11*	0.77 ± 0.29	93.3 ± 28.0	4 (25.0%)	6.3 ± 2.2	129.7 ± 7.9*	208.3 ± 56.9
	PT n = 17	12.5 ± 6.4	0.35 ± 0.14	0.57 ± 0.24	98.6 ± 24.5	0	7.1 ± 2.0	121.1 ± 13.8	196.1 ± 51.5
6 months	UP n = 16	13.2 ± 8.9	0.39 ± 0.10	0.61 ± 0.24	100.6 ± 38.3	0	7.4 ± 1.4*	132.1 ± 14.2	188.2 ± 51.0
	PT n = 17	11.8 ± 3.8	0.43 ± 0.18	0.65 ± 0.28	109.4 ± 25.4	3 (17.6%)	6.0 ± 1.9	126.2 ± 14.4	185.1 ± 51.3
12 months	UP n = 16 n = 16	13.4 ± 6.3	0.42 ± 0.14	0.56 ± 0.16	107.2 ± 47.4	0	7.7 ± 2.6	132.0 ± 16.3	199.3 ± 58.0
	PT n = 17	13.2 ± 7.1	0.41 ± 0.12	0.58 ± 0.18	121.4 ± 30.0	1 (5.8%)	7.2 ± 2.9	128.2 ± 17.8	173.1 ± 57.3

ALT – alanine amino-transferase; AST – aspartate amino-transferase; PT – preemptive therapy; S-Cr – serum creatinine; UP – universal prophylaxis; WBC – white blood cells count.
P-value for comparison between the universal prophylaxis group and the preemptive therapy group at each period of follow-up was coded: $p < 0.05$ *, $p < 0.01$ **.

allograft vasculopathy. These complications are called indirect effects and belong to the main causes of death and retransplantation in HTx patients.

CMV infection is known to increase the risk of acute cellular rejection. Several mechanisms have been implicated in the inflammatory response to allograft triggered by CMV. They include altered expression of growth factors and cytokines, up-regulation of proinflammatory adhesion molecules and/or modulation of the nitric oxide synthase pathway [3,15–19]. Even latent CMV infection has been shown in a murine model to be associated with disruption of allograft tolerance and increased intramyocardial expression of proinflammatory genes in allografts but not in isografts [20]. The resulting inflammatory response of the host contributes to endothelial cell injury and development of cardiac allograft vasculopathy [21].

We observed a significant increase in incidence of acute allograft rejection grade Banff 2 in individuals receiving preemptive therapy of CMV. It seems that frequent subclinical CMV infection in this subgroup may have contributed to impaired allograft tolerance. Grade Banff 2 of acute cellular rejection is characterized by detection of one lymphocytic infiltrate with focal myocyte damage in EMB. This grade of acute rejection usually does not cause acute dysfunction of the allograft. However, destruction of myocytes at this stage may stimulate native and adaptive immune response and trigger higher grades of acute allograft rejection and/or cardiac allograft vasculopathy.

Study limitations

This study has several limitations. First, relatively small sample size and non-randomized study design may decrease the applicability of the results. Second, only CMV-seropositive HTx recipients were studied. Therefore, the study results should be applied in similar population. Third, the study design did not include quantitative assessment of cardiac allograft vasculopathy with intravascular ultrasound. Therefore, we cannot comment on the effects of CMV management on progression of cardiac allograft vasculopathy.

Conclusions

In comparison with preemptive anti CMV therapy, universal prophylaxis with valganciclovir in CMV-seropositive HTx recipients reduced more effectively incidence of CMV infection and acute allograft rejection grade Banff 2 during the first three months after transplantation. Prophylactic treatment was well tolerated and safe.

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References

[1] American Society of Transplantation. Cytomegalovirus. Am J Transplant 2004;4(Suppl.10):51–8.

[2] Kotton CN, Kumar D, Caliendo AM, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 2010;89:779–95.

[3] Snydman DR, Limaye AP, Poten L, Zamora MR. State-of-art management of cytomegalovirus infection and disease following thoracic organ transplantation. Transplant Proc 2011;43:S1–17.

[4] Emery V. Facing the facts: the indirect effects of cytomegalovirus. Transplantation 2007;84:S7–10.

[5] Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. JAMA 1989;261:3561–6.

[6] Fateh-Moghadam S, Bocksch W, Wessely R, Jager G, Hetzer R, Gawaz M. Cytomegalovirus infection status predicts progression of heart-transplant vasculopathy. Transplantation 2003;76:1470–4.

[7] Richens D, Harvison A, Kaan AM, et al. A double-blind placebo-controlled trial of low-dose ganciclovir to prevent cytomegalovirus disease after heart transplantation. J Heart Lung Transplant 1995;14(1, Part 1):32–8.

[8] Bristow MR, Starnes V, O'Connel JB, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med 1992;326:1182–6.

[9] Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valgancilovir vs oral ganciclovir for the prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplan 2004;4:611–20.

[10] Devyatko E, Zuckermann A, Ruzicka M, et al. Pre-emptive treatment with oral valganciclovir in management of CMV infection after cardiac transplantation. J Heart Lung Transplant 2004;23:1277–82.

[11] Billingham ME, Cary NR, Hammond ME, Kemnitz J, Marboe C, McCallister HA, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant 1990;9:587–93.

[12] Potena L, Grigioni F, Magnani G, et al. Prophylaxis versus preemptive anti-cytomegalovirus approach for prevention of allograft vasculopathy in heart transplant recipients. J Heart Lung Transplant 2009;28;461–7.

[13] Potena L, Holweg CT, Chin C, et al. Acute rejection and cardiac allograft vascular disease is reduced by suppression of subclinical cytomegalovirus infection. Transplantation 2006;82:398–405.

[14] Khoury JA, Storch GA, Bohl DJ, et al. Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. Am J Transplant 2006;6:2134–43.

[15] Borchers AT, Perez R, Kaysen G, Ansari AA, Gershwin ME. Role of cytomegalovirus infection in allograft rejection: a review of possible mechanisms. Transpl Immunol 1999;7:75–82.

[16] Tuder RM, Weinberg A, Panajotopoulos N, Kalil J. Cytomegalovirus infection amplifies class I major histocompatibility complex expression on cultured human endothelial cells. J Heart Lung Transplant 1994;13:129–38.

[17] Arbustini E, Morbini P, Grasso M, et al. Human cytomegalovirus early infection, acute rejection, and major histocompatibility class II expression in transplanted lung. Molecular, immunocytochemical, and histopathologic investigations. Transplantation 1996;61:418–27.

[18] Kloover JS, Soots AP, Krogerus LA, et al. Rat cytomegalovirus infection in kidney allograft recipients is associated with increased expression of intracellular adhesion molecule-1 vascular adhesion molecule-1, and their ligands leukocyte function antigen-1 and very late antigen-4 in the graft. Transplantation 2000;69:2641–7.

[19] Compton T, Kurt-Jones ES, Boehme KW, et al. Human cytomegalovirus activates inflammatory cytokine responses via CD14 and Toll-like receptor 2. J Virol 2003;77:4588–96.

[20] Cook CH, Bickerstaff AA, Wang JJ, et al. Disruption of murine cardiac allograft acceptance by latent cytomegalovirus. Am J Transplant 2009;9:42–53.

[21] Valantine HA. The role of viruses in cardiac allograft vasculopathy. Am J Transplant 2003;4:169–77.