Transpl Int (1994) 7 [Suppl 1]: S385–S388




M. Cantarovich
P. René
D. Latter

# Is the incidence of cytomegalovirus disease following heart transplantation decreased by prophylactic ganciclovir and CMV-hyperimmunglobulin?

M. Cantarovich (✉) · P. René
Department of Medicine,
Royal Victoria Hospital and Center for Clinical Immunobiology
and Transplantation, McGill University,
687 Pine Ave West,
Montreal, Quebec, H3A 1A1, Canada

D. Latter
Department Surgery,
Royal Victoria Hospital,
and Center for Clinical Immunobiology
and Transplantation, McGill University,
687 Pine Ave. West,
Montreal, Quebec, H3A 1A1, Canada

**Abstract** Ganciclovir (DHPG) was used for the prophylaxis of CMV disease after heart transplantation (HTx) in 20 patients (aged 52 ± 8 years old). DHPG was used during the first 2 weeks post HTx, and during antirejection therapy with OKT3 or thymoglobulin (ATG), at a dosage of 3 mg/kg q 12 h in the case of a CMV+ donor (D) and/or CMV+ recipient (R). CMV-hyperimmunglobulin (−Ig, 1 ml/kg per week for 6 weeks) was added in the case of a CMV+ donor.
A historical control group included 18 HTx patients (aged 53 ± 10 years old). We excluded the combination of CMV− donor and CMV− recipient. Both groups received the same immunosuppression with methylprednisolone (MP), azathioprine, ATG, and cyclosporine A.
The global incidence of CMV disease was 15% (3/20 patients) in the study group and 11% (2/18 patients) in the control group.
Similar results were observed in the D+/R− combination (study group 40%, 2/5 patients; control group, 25%, 2/8 patients) and in cases of R+ irrespective of D status (study group, 7%, 1/15 patients; control group 0%, 0/10 patients). No difference was observed in both groups with respect to the incidence of CMV disease after antirejection therapy either with MP or with OKT3/ATG. At 1 year post HTx, no difference was found in the incidence of acute rejection, coronary artery disease or other etiology of infection or mortality.
All patients CMV disease responded to a 14-day course of DHPG (5 mg/kg q 12 h). No relapsing disease was observed, and no patient died from CMV. Our results suggested that at the doses and time-scale used, DHPG, with or without CMV-Ig did not reduce the incidence of CMV disease after HTx.

**Key words** CMV disease
Ganciclovir (DHPG) · Heart transplantation

## Introduction

Ganciclovir (DHPG) has dramatically changed the pattern of cytomegalovirus (CMV) infection in immunocompromized patients [1]. After its introduction into clinical transplantation, DHPG was only used in cases of life-threatening CMV infections [2, 3]. Since then, the indications for DHPG in patients with CMV infection have been enlarged, and it is infrequent to see life-threatening CMV infections when patients with less severe infections are promptly treated [4]. The use of biological agents such as OKT3, thymoglobulin (ATG), or lymphoglobulin

(ALG) has been associated with a significant increase in the incidence of CMV infection after organ transplantation [5–9]. It has been reported that CMV infection increases the risk of acute rejection and graft atherosclerosis following heart transplantation (HTx) [8, 10–13] possibly because of an homology with, or an upregulation of MHC class II antigens [14].

During the last 3 years, DHPG has been considered for CMV prophylaxis after organ transplantation [7, 9, 10, 15] during the early post-operative course, or concomitant to the use of biological agents for the therapy of episodes of acute rejection [7, 9]. Controversial results have been obtained with the use of CMV-Ig in kidney, bone-marrow [16], and HTx [17]. The purpose of this retrospective study was to assess if DHPG, with or without CMV-Ig, could reduce the incidence of CMV disease following HTx.

## Materials and methods

The study group included 20 patients (19 male, 1 female, mean age 52 ± 8 years) transplanted between November 1990 and December 1991. DHPG (3 mg/kg q 12 h) was used for CMV prophylaxis when donor (D) and/or recipient (R) were CMV positive (+) as detected by an agglutination test. DHPG was given during the first 14 days after HTx and during antirejection therapy with ATG or OKT3 (11 patients). In addition, CMV-Ig (1 ml/kg q week for 6 weeks) was used when D was CMV+. An historical control group included 18 patients (15 male, 3 female, age 53 ± 10 years), transplanted between June 1988 and October 1990. No CMV prophylaxis was used in this group.

No significant difference was observed with respect to the primary disease: ischemic cardiomyopathy (study group, 16/20 patients, 80%; control group, 14/18 patients, 78%), idiopathic cardiomyopathy (study group, 3/20 patients, 15%; control group 2/18 patients, 11%), and other (study group, 1/20 patients, 5%; control group, 2/18 patients, 11%). There was no difference in the different combinations according to D and R CMV status: study group: D+/R−, 5/20 patients (25%); D+/R+, 6/20 patients (30%); D−/R+, 9/20 patients (45%); R+, 15/20 patients (75%); control group: D+/R−, 8/18 patients (50%); D+/R+, 3/18 patients (17%); D−/R+, 5/18 patients (28%); unknown D status/R+, 2/18 patients (11%); R+, 10/18 patients (56%).

Both groups received the same immunosuppressive protocol including azathioprine (1.5 mg/kg per day), ATG (1.5 mg/kg per day for seven days), methylprednisolone (1.5 mg/kg per day for four days), then prednisone rapidly tapered to 0.3 mg/kg per day within 1 month post-HTx, and cyclosporin A (started on day 2, at 2 mg/kg per day, and progressively increased aiming for whole blood trough levels of 250–300 ng/ml by RIA monoclonal specific). Acute rejection (International Society for Heart and Lung Transplantation score ≧ 2), was treated with methylprednisolone (500 mg IV for 3 days). Ongoing or recurrent rejection was treated with TMG, ALG, or OKT3.

CMV disease was defined as fever (> 38 °C) for more than 3 days, in the absence of any other explanation for fever, and a positive buffy coat, and one of the following: leukopenia, increase transaminase, or evidence of organ involvement proven by biopsy. No routine virological tests were performed. CMV buffy coat in blood was performed only in cases of unexplained fever. Routine bacteriological cultures (blood, urine) were done when clinically indicated. Chi-square test and Students-*t*-test were used for statistical analysis, and significance was considered at $P < 0.05$.

## Results

The global incidence of CMV disease was 15% (3/20 patients) in the study group and 11% (2/18 patients) in the control group. No statistically significant difference in the incidence of CMV disease was found when comparing the D+/R− combination (study group, 2/5 patients, 40%; control group, 2/8 patients, 25%) and the R+ irrespective of donor status (study group, 1/15 patients, 7%; control group, 0/10 patients, 0%).

The incidence of CMV disease following antirejection therapy was similar in both groups (study group: postmethylprednisolone, 2/16 patients, 12.5%; post-ATG, 0/2 patients, 0%; post-OKT3, 1/10 patients, 10%; control group: postmethylprednisolone, 1/18 patients, 6%; post-ATG/ALG, 1/7 patients, 14%; post-OKT3, 0/5 patients, 0%). CMV disease was observed within 4 weeks following antirejection therapy. In the study group, all patients presented with fever, leukopenia, and a positive buffy coat. In addition, the patients presented with hepatosplenomegaly, duodenitis, and pneumonitis, respectively. In the control group, two patients presented with fever, leukopenia, and a positive buffy coat, and in one patient, hepatitis was observed. All patients responded to a 14-day course of DHPG (5 mg/kg q 12 h), and there was no relapsing disease or death secondary to CMV.

Within 1 year after HTx, there was no difference in the incidence of the following: acute rejection episodes (study group, 16/20 patients, 80%; control group, 18/18 patients, 100%), coronary artery disease (study group, 1/7 patients, 14%; control group, 3/15 patients, 20%), infections, including other herpes virus (study group, 2/20 patients, 10%; control group, 2/18 patients, 11%), bacteria (study group, 3/20 patients, 15%; control group, 2/18 patients, 11%), fungus (study group, 2/20 patients, 10%; control group, 2/18 patients, 11%), and protozoa (study group, 0/20 patients, 0%; control group, 2/18 patients, 11%), and mortality (study group, 1/20 patients, 5%; control group, 4/18 patients, 22%). The incidence of leukopenia (WBC $< 4000/mm^3$) and neutropenia (PMN $< 1000/mm^3$) was similar in both groups (study group, 2/20 patients, 10% and 0/20 patients, 0%; control group, 1/18 patients, 6% and 0/18 patients, 0%, respectively). The incidence of thrombocytopenia

(PLT < 100000/mm$^3$ or < 50000/mm$^3$) was also similar (study group 7/20 patients, 35% and 2/20 patients, 10%; control group, 8/18 patients, 44% and 3/18 patients, 17%, respectively). Acute renal dysfunction (100% increment from baseline serum creatinine) was observed in 1/18 patients (6%) in the control group, whereas no case of renal dysfunction was seen in the study group. The incidence of leukopenia and neutropenia during prophylaxis with DHPG in cases of antirejection therapy with OKT3 or ATG was 18% (2/11 patients) and 0% (0/11 patients), respectively. Serum creatinine, bilirubin, and transaminase remained stable. No gonadal tests were performed.

## Discussion

CMV infection in immunocompromized patients may predispose to potentially lethal superinfections [9], and may increase the risk of acute rejection and graft atherosclerosis after HTx [8, 10–13]. The use of DHPG at a dose of 5 mg/kg q 12 h for 14 days, then 6 mg/kg per day, 5 days per week for 1 month posttransplant has been associated with a significant decrease in the urinary excretion of CMV during the first 3 months after HTx. In the same study, there was a significant decrease in the incidence of CMV infection when the R was CMV+. On the other hand, when the R was CMV−, no difference was seen when compared to placebo [15]. In our study, we found the same negative results with respect to the D+/R− combination. In the present study, the use of CMV-Ig in addition to DHPG for the D+/R− or D+/R+ combinations did not reduce the incidence of CMV disease.

Our results are in agreement with a recent report [6], but at variance with others, with respect to the negative impact of CMV disease in the course of HTx patients [8, 10–13]. The possibility that an asymptomatic seroconversion could have played a role in the incidence of acute rejection or coronary artery disease cannot be answered by the present study because no systematic serologic tests were performed, and the number of patients was small. Our study suggested that DHPG (at the dosage and timescale used), in combination or not with CMV-Ig, did not reduce the incidence of CMV disease after HTx. The fact that the inhibition of viral replication is probably maintained for only a short period of time after a prophylactic course of DHPG [15], suggests that long-term therapy with higher (therapeutic) doses of DHPG (5 mg/kg q 12 h) might be required in order to reduce the incidence of CMV disease, especially in the D+/R− combination. This will be difficult to achieve until an oral preparation of DHPG becomes available. Early diagnosis and prompt therapy with DHPG remain cricital in the adequate management of HTx patients with CMV disease.

## References


1. Collaborative DHPG treatment study group (1986) Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl)guanine in patients with AIDS and other immunodeficiencies. N Engl J Med 314:801–805
2. Creasy T, Flower AJE, Veitch PS (1986) Life-threatening cytomegalovirus infection treated with dihydropropoxymethylguanine. Lancet I:675
3. Erice A, Jordan MC, Chace BA, Fletcher C, Chinnock BJ, Balfour HH (1987) Ganciclovir treatment of cytomegalovirus disease in transplant recipients and other immunocompromised hosts. JAMA 257:3082–3087
4. Cantarovich M, Hiesse Ch, Lantz O, Fassi-Fihri S, Charpentier B, Fries D (1988) Treatment of cytomegalovirus infection in renal transplant recipients with 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Transplantation 45: 1139–1141
5. Rubin RH, Tolkoff-Rubin NE, Olivier D, Rota TR, Hamilton J, Betts RF, Pass RF, Hillis W, Szmuness W, Farrell ML, Hirsch MS (1985) Multicenter seroepidemiologic study of the impact of cytomegalovirus infection on renal transplantation. Transplantation 40:243–249
6. Constanzo-Nordin MR, Swinnen LJ, Fisher SG, O'Sullivan EJ, Pifarre R, Heroux AL, Mullen GM, Johnson MR (1992) Cytomegalovirus infections in heart transplant recipients: relationship to immunosuppression. J Heart Lung Transplant 11:837–846
7. Hibberd PL, Tolkoff-Rubin NE, Cosimi B, Schooley RT, Isaacson D, Doran M, Delvecchio A, Delmonico FL, Auchincloss H, Rubin RH (1992) Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. Transplantation 53:68–72
8. Cooper DKC, Novitzky D, Schlegel V, Muchmorte JS, Cucchiara A, Zuhdi N (1991) Successful management of symptomatic cytomegalovirus disease with Ganciclovir after heart transplantation. J Heart Lung Transplant 10: 656–663
9. Rubin RH (1993) Infectious disease complications of renal transplantation. Kidney Int 44:221–236
10. Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE (1989) Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. JAMA 261:3561–3566
11. Loebe M, Schuller S, Zais O, Warnecke H, Fleck E, Hetzer R (1990) Role of cytomegalovirus infection in the development of coronary artery disease in the transplanted heart. J Heart Transplant 9:707–711

12. Normann S, Salomon D, Leelachaikul P, Leelachaikul P, Khan SR, Staples ED, Alexancer JA, Mayfield WR, Knauf DG, Sadler LA, Selman S (1991) J Heart Lung Transplant 10:674–687
13. Duncan S, Cook D (1991) Survival of Ganciclovir-treated heart transplant recipients with cytomegalovirus pneumonitis. Transplantation 52:910–913
14. Ho M (1991) Cytomegalovirus infection and indirect sequelae in the immunocompromised transplant patient. Transplant Proc 23:2–7
15. Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, Resta S, Dunn D, Gamberg P, Ratkovec M, Richenbacher WE, Millar RC, DuMond C, DeAmond B, Sullivan V, Cheney P, Buhles W, Stinson E (1992) A controlled trial of Ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med 326:1182–1186
16. Snydman DR (1991) Prevention of cytomegalovirus disease with intravenous immune globulin. Transplant Proc 23:20–25
17. Laske A, Gallino A, Mohacsi P, Bauer EP, Carrel T, von Segesser LK, Turina MI (1991) Prophylactic treatment with Ganciclovir for cytomegalovirus infection in heart transplantation. Transplant Proc 23:1170–1173