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M. Halme
I. Lautenschlager
L. Halme
P. Tukiainen
S. Mattila

Ganciclovir prophylaxis after lung and heart–lung transplantation

M. Halme (✉) · P. Tukiainen
Division of Pulmonary Medicine and Clinical Physiology,
Department of Medicine,
Helsinki University Central Hospital,
Haartmaninkatu 4, FIN-00290 Helsinki,
Finland
Fax +358 9 471 2691

I. Lautenschlager
Department of Virology,
Helsinki University Central Hospital,
Helsinki, Finland

L. Halme · S. Mattila
Department of Surgery, Helsinki
University Central Hospital, Helsinki
Finland

Abstract Cytomegalovirus (CMV) infection causes both acute and chronic allograft damage. The aim of this study was to analyze the utility of ganciclovir in preventing CMV infection in pulmonary allografts. Thirty five consecutive lung (LTX) and heart–lung (HLTX) transplant patients were studied from 1990 to 1996. CMV prophylaxis was started in January 1995. Recipients with CMV-positive serology received ganciclovir on postoperative days (POD) 7–28. Acyclovir was given on POD 29–90. Recipients with CMV-negative serology received ganciclovir on POD 7–90 if the serology of the donor was positive. CMV was demonstrated by rapid cell vial culture and/or detecting CMV-specific antigens in bronchoalveolar lavage (BAL) samples. The time point of the first BAL fluid specimen exhibiting CMV was estimated using the Life Table method. BAL samples of all the recipients without ganciclovir treatment became positive for CMV, whereas two of the 11 patients with ganciclovir administration remained negative. Ganciclovir significantly ($P < 0.05$) delayed but did not absolutely prevent CMV infection after LTX and HLTX.

Key words Ganciclovir · Prophylaxis · CMV infection · Lung transplantation

Introduction

Cytomegalovirus (CMV) has been the single most frequent pulmonary pathogen after lung transplantation (LTX), the highest incidence occurring 2–4 months posttransplant. The virus is a well-established cause of both acute and chronic pulmonary allograft damage [2], the prevalence of CMV pneumonia varying between 28 and 59% [3, 6]. A mortality rate as high as 56% has been reported among LTX patients with CMV pneumonia [2]. In addition, CMV infection and pneumonia have been coupled to the development of brochiolitis obliterans syndrome [4, 8].

The appearance of CMV infection is strongly influenced by the seropositivity of donor and recipient. It is well known that either donor or recipient seropositivity increases the risk of the recipient developing viral infection, with the positive donor/negative recipient (D+/R−) group at most risk of severe disease [6, 7]. In Finland, the prevalence of CMV seropositivity among adults is about 80%, which implies a constant hazard during organ transplantation but, on the other hand, CMV-negative recipients are rare.

Ganciclovir is a potent specific antiviral drug, capable of inhibiting the replication of CMV, and is the drug of choice for treatment of CMV disease. Recently, because CMV disease is a serious risk factor for death following LTX, ganciclovir has also been used in the prevention of CMV disease, either alone or combined with high-dose acyclovir. Both universal prophylaxis of recipients at risk for infection and preemptive treatment of recipients of infection to abort the development of disease have been used. Although most centers have preventive protocols, there is no consensus concerning the most effective approach [12]. In Finland, a CMV prophylaxis protocol of either ganciclovir alone or in com-

Table 1 Patient characteristics of 27 lung *(LTX)* and 8 heart–lung *(HLTX)* recipients (*CMV* cytomegalovirus)

Characteristic	Cytomegalovirus (CMV) prophylaxis	
	Yes	No
Number of patients	11	24
Male/female	8/3	14/10
Age, mean (range)	45 years (17–61)	41 years (23–60)
LTX	5	22
HLTX	6	2
Diagnosis		
Pulmonary hypertension	5	9
Obstructive lung disease	5	8
Interstitial lung disease	1	7
CMV serological status of recipient (R) and donor (D)		
R+/D+	8	16
R+/D−	2	5
R−/D+	1	2
R−/D−	0	1

Table 2 Cytomegalovirus *(CMV)* prophylaxis depending on CMV serology of recipient *(R)* and donor *(D)* (*POD* postoperative day, *iv* intravenously)

R/D	POD	Ganciclovir	Acyclovir
+/±	7–22	5 mg/kg iv twice daily	
	22–28	5 mg/kg iv once daily 5 days/week	
	29–90	–	800 mg 4 times/day
−/+	7–28	5 mg/kg iv twice daily	
	29–90	5 mg/kg iv once daily 5 days/week	
−/−		No prophylaxis, CMV-seronegative blood products	

bination with acyclovir for LTX and heart-lung transplantation (HLTX) recipients was started in January 1995. The purpose of this study was to analyze the efficacy of this protocol in preventing CMV infection in pulmonary allografts.

Materials and methods

Thirty five consecutive transplant patients (27 LTX and 8 HLTX) surviving ≥ 1 month postoperatively were studied between February 1990 and February 1996. All patients received cyclosporine, azathioprine, and methylprednisolone as immunosuppressive treatment. The patient characteristics are given in Table 1.

Before 1995 no strategies to prevent CMV infection were used. However, one HLTX patient received the treatment in December 1994 (before the protocol was officially started) due to his CMV status (R−/D+). From January 1995, CMV prophylaxis was given to all LTX and HLTX recipients according to the protocol shown in Table 2. After ganciclovir treatment, high-dose acyclovir was given orally to R+/D± recipients through postoperative days (POD) 29–90, whereas R−/D+ patients continued with intravenous ganciclovir. Eleven recipients (5 LTX, 6 HLTX) received the ganciclovir (± acyclovir) treatment, while 24 controls (22 LTX, 2 HLTX) received no prophylaxis (Table 1).

Bronchoalveolar lavage (BAL) was performed in all patients both routinely 1, 2, 3, 4 weeks and 3, 6, and 12 months postoperatively and as required till the end of the follow-up (February 1997). CMV was demonstrated in BAL specimens by rapid cell vial culture and/or detecting CMV-specific antigen-positive cells of alveolar origin [9, 10]. The time point of the first BAL fluid specimen exhibiting CMV was estimated using the Life Table method.

When CMV was identified in a BAL specimen, the recipient was diagnosed as having CMV infection. The definition of CMV disease required the finding of CMV infection combined with clinical symptoms.

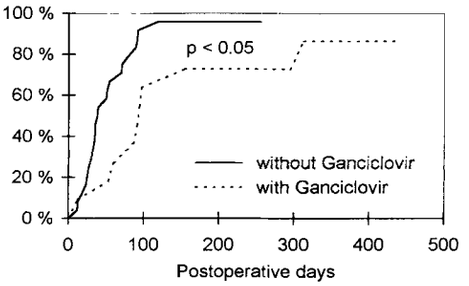

Fig. 1 The curves for the estimated turning point of the first bronchoalveolar lavage fluid specimen exhibiting cytomegalovirus

Results

Among the group receiving CMV prophylaxis, eight patients were R+/D+, two were R+/D−, and one was R−/D+. In the group with no prophylaxis, the numbers were 16, 5, and 2, respectively. One of these patients was R−/D− (Table 1).

All recipients without prophylaxis developed CMV infection (detected from BAL specimens), whereas BAL specimens from two patients in the prophylaxis group remained CMV negative till the end of the follow-up. The curves for the estimated turning point (POD) for CMV positivity in the BAL specimens for recipients with and without prophylaxis are shown in Fig. 1. Recipients with ganciclovir (± acyclovir) prophylaxis developed the CMV infection significantly later than the group of recipients without prophylaxis ($P < 0.05$).

After detecting CMV in BAL specimens, 4 (36%) of 11 recipients with prophylaxis compared to 16 (67%) of 24 recipients in the group without prophylaxis developed CMV disease. There was one death related to CMV disease in each treatment group. Both of these recipients were R−/D+.

Discussion

In this study, our prophylaxis protocol, which consisted of intravenous ganciclovir alone or combined with high-dose oral acyclovir from 1 week to 3 months postoperatively, significantly delayed the appearance of CMV in BAL samples. In two recipients, BAL specimens remained CMV free through the follow-up time, whereas all patients without prophylaxis showed CMV in BAL samples. CMV-related deaths were associated with CMV status rather than with the treatment given. Prophylaxis could thus not prevent the development of CMV infection in the majority of patients but the significant delay achieved by the ganciclovir protocol protected these patients during the first postoperative months when high levels of immunosuppression are necessary.

In an early study no benefit could be demonstrated by using short courses of ganciclovir prophylaxis for LTX recipients [1]. Thereafter, protocols with longer courses, lasting at least until POD 28, were started. Our prophylaxis resembles these regimens and our result is also in accordance with previous reports. In addition to demonstrating a delay in developing CMV disease after ganciclovir prophylaxis among LTX recipients, a significant survival benefit has also been detected [2, 11].

Duncan et al. [5] have compared the effect of high-dose acyclovir with continued intravenous ganciclovir in LTX recipients. After high-dose intravenous ganciclovir until POD 28, the patients were stratified on the basis of serological status to receive either intravenous ganciclovir 5 times a week (R−) or high-dose oral acyclovir (R+) until POD 90. Prolonged ganciclovir treatment was found more effective in decreasing early incidences of CMV. No episodes of CMV infection were found during the ganciclovir treatment. In our study, only one R−/D+ recipient received prolonged intravenous ganciclovir treatment. Despite this prophylaxis, the patient developed CMV infection during the ganciclovir treatment and died 6 months postoperatively because of CMV disease.

Our data confirm the result of previous reports by demonstrating a benefit for CMV-seropositive recipients receiving ganciclovir prophylaxis until POD 28. The protective role of high-dose acyclovir after intravenous ganciclovir treatment in our study is not clear. In the future, orally given ganciclovir may replace oral acyclovir in the prophylaxis of CMV. Therefore, placebo-controlled trials are needed to determine the optimal use of these drugs in the prevention of CMV infection.

In our study, the distribution of recipient/donor CMV seropositivity was fairly well balanced between the treatment groups, which strengthens the value of our results. Although they are rare cases, in a population with a high seroprevalence of CMV, the management of R−/D+ recipients is difficult. CMV serological matching remains today the most effective method of protecting CMV-negative LTX recipients from fatal CMV infections.

In conclusion, although ganciclovir prophylaxis did not prevent the development of CMV infection, it delayed it and thus protected the recipients from CMV infections during the first postoperative months.

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