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Two grams daily of oral acyclovir reduces the incidence of cytomegalovirus disease in CMV-seropositive liver transplant recipients

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Abstract Our objective in this study was to determine the efficacy of 2 grams a day of oral acyclovir administered for 16 weeks after transplantation for the prevention of cytomegalovirus (CMV) infection and disease in CMV-seropositive liver transplant recipients. Seventy-three adult liver transplant recipients, seropositive for CMV, were randomized to receive either 2 grams a day of oral acyclovir for 16 weeks after transplantation or no prophylaxis. The incidence of CMV disease was significantly lower in the acyclovir group (5 %) than in the control group (27 %; $P < 0.05$). By log-rank analysis, the differences in the probability of presenting CMV disease over the first 16 weeks and over the 1st year were also significant ($P < 0.05$). We conclude that 2 grams a day of oral acyclovir provides effective prophylaxis against CMV disease in CMV-seropositive liver transplant recipients.

Key words Acyclovir, cytomegalovirus, liver transplantation · Liver transplantation, cytomegalovirus, acyclovir · Cytomegalovirus, liver transplantation, acyclovir

Introduction

The efficacy of 3.2 g of oral acyclovir in preventing cytomegalovirus (CMV) infection and disease in transplant patients remains to be clearly established [1, 4–6, 8, 10]. A study has shown that a lower daily dose (2 g) of oral acyclovir can reduce the incidence of CMV disease in heart transplant recipients [3], but to date there have been no studies that evaluate this approach in liver transplant recipients (LTR). In this randomized study, we evaluate the efficacy of 2 grams a day (2 g q.d.) of oral acyclovir administered for 16 weeks after transplantation for the prevention of CMV infection and disease in CMV-seropositive LTR.

Patients and methods

From June 1991 through November 1993, all CMV-seropositive adult recipients of an orthotopic liver transplant were enrolled in a randomized, controlled study. Only those patients scheduled to undergo a second liver transplantation were excluded ($n = 5$). The protocol study was reviewed by the Hospital Ethics Committee and all patients gave written consent prior to being enrolled. The patients were randomized into two groups, one receiving acyclovir and the other no prophylaxis (control). Each group was supposed to contain at least 34 patients. This figure was based on an anticipated CMV disease rate of 40 % for the control group and 15 % for the prophylaxis group at 16 weeks after the procedure. With this sample size there was an 80 % chance of detecting a difference in the rate of CMV disease between the two groups at a 5 % significance level. Seventy-three consecutive adult patients were recruit-

ed for the study. The prophylaxis group received 400 mg of oral acyclovir five times daily, beginning as soon as the patients were able to tolerate oral intake (median time 7 days; range 3–30 days). Acyclovir administration was continued for 16 weeks.

The groups were compared with respect to age, sex, liver disease, hepatitis B and C virus pretransplantation infection, donor pretransplantation CMV serostatus, length of graft ischemia and transplant procedure, volume of operative blood, plasma and platelets used, steroids administered during the first 3 postoperative months, and the use of monoclonal antilymphocyte antibodies (OKT3) during the study period.

Immunosuppression consisted of a combination of prednisone and cyclosporin A. When graft rejection was documented by liver biopsy, a 3-day course of steroid boluses (500 mg) was given. In cases with poor response, a 10-day course of OKT3 was indicated. Surveillance blood cultures for CMV, using the shell vial and cell culture methods, were obtained weekly during the first 3 postoperative months, and monthly to the end of the study. CMV infection was defined as isolation of the virus in any body fluid or tissue sample culture. CMV disease included CMV syndrome and focal diseases such as hepatitis, pneumonitis, or gastrointestinal disease. CMV syndrome was defined as persistent fever, with or without leukopenia and thrombocytopenia in a patient with blood cultures positive for CMV, in the absence of other causes. CMV focal disease was diagnosed with the isolation of CMV from any tissue or body fluid plus compatible histological findings. The patients were followed-up for the development of CMV infection or disease for 12 months post-transplantation.

The comparability of the groups was assessed by the Fisher's exact test, the χ^2 test, or the Mann-Whitney U-test, where appropriate. The rates of CMV infection and CMV disease at 16 weeks after the procedure were compared using a two-tailed Fisher's exact test or the χ^2 test. Kaplan-Meier survival curves at 16 weeks and at 1 year post-transplantation were generated for the prophylactic and control groups to assess whether there were differences in time before the development of CMV infection or CMV disease. The curves were compared using log-rank analysis. Significance was defined as a P level below 0.05. All patients were included in an efficacy analysis (intent-to-treat analysis).

Table 1 Characteristics of patients included in the study

Characteristic	Acyclovir	Control
Patients	37	36
Median age (range)	57 (34–66)	54 (20–65)
Male/Female	25/12	23/13
Underlying disease		
Alcoholic liver disease	13 (35)	13 (36)
Cryptogenetic cirrhosis	1 (2)	1 (2)
HCV infection[a, b*]	26 (70)	17 (47)
Chronic HBsAg hepatitis	2 (5)	1 (2)
Hepatocellular carcinoma	2 (5)	1 (2)
Caroli's disease		2 (5)
Hemochromatosis		2 (5)
Primary biliary cirrhosis		2 (5)
CMV matching		
Donor +/recipient +	32 (86)	32 (88)
Donor –/recipient +	5 (13)	4 (11)
Intraoperative parameters (range)		
Time of ischemia	480 (170–800)	508 (240–1040)
Length of procedure	450 (300–780)	457 (315–720)
Blood units transfused	7 (0–51)	6 (0–38)
Platelets units transfused	10 (0–40)	10 (0–48)
Plasma units transfused	11 (3–54)	10 (3–38)
Immunosuppressive agents		
Total dose of corticosteroids in the first 3 months (g) and range	4.5 (0–10.3)	3.8 (1.6–14.9)
Use of OKT3	7 (19)	6 (16)
Operative complications		
Biliary	1 (2.7)	2 (5.5)
Vascular	3 (8.1)	2 (5.5)
Gastrointestinal bleeding	2 (5.4)	3 (8.3)

[a] Seven and three patients, respectively, with concomitant alcoholic liver disease and HCV infection
[b] Number (%), unless indicated
* $P < 0.05$

Results

Seventy-three patients were enrolled in the study. Thirty-seven patients were randomized to receive acyclovir and 36 to receive no prophylaxis. The median duration of acyclovir prophylaxis was 120 (11–120) days. Seven patients did not complete the prophylaxis regimen: four withdrew of their own accord, two presented mental disorders, and one died within the 1st month after transplantation.

The groups were similar with respect to all of the parameters studied, except for a higher incidence of hepatitis C virus infection in the acyclovir group (70 % versus 47 %; $P < 0.05$), as may be seen in Table 1. The incidence of HSV, fungal, and bacterial infections is shown in Table 2. Table 3 shows the incidence of CMV infection and disease at 120 days post-transplantation according to the serological status of the donors. Only 5 % (2/37) of patients given acyclovir presented CMV disease during the 120 days after transplantation, as compared to 27 % (10/36) of the control group ($P = 0.009$). The Kaplan-Meier estimates of the probability of presenting CMV disease by 16 weeks was 5.7 % in the prophylaxis group and 28.7 % in the control group ($P = 0.01$; Fig. 1). The episodes of CMV disease were identified as CMV hepatitis in seven cases (two in the acyclovir group), CMV syndrome in three, and CMV pneumonia in two.

Table 2 Infectious diseases after liver transplantation

Type of infection	Acyclovir	Control	P
HSV infection	7 (18.9)	16 (44.4)	0.018
Bacterial infection	9 (24.3)	13 (36.1)	NS
Invasive fungal infection	4 (10.8)	3 (8.3)	NS

Number (%), unless indicated

During long-term follow-up from day 120 to 1 year after transplantation, two additional acyclovir patients and one additional control patient developed CMV disease: esophagitis and disseminated CMV disease (diagnosed at necropsy) in the patients on prophylaxis, and CMV syndrome in the control group patient. Despite

Table 3 Incidence of CMV infection and disease at 16 weeks after transplantation according to donor *(D)* and recipient *(R)* serological status before transplantation

	CMV Infection						CMV Disease					
	Acyclovir		Control		RR 95 % CI	*P*	Acyclovir		Control		RR 95 % CI	*P*
	n	%	*n*	%			*n*	%	*n*	%		
D+ R+	5/32	(15)	11/32	(34)			2/32	(6)	8/32	(25)		
D− R+	1/5	(20)	3/4	(75)			0/5		2/4	(50)		
D+/− R+	6/37	(16)	14/36	(39)	0.42 (0.18–0.97)	0.03	2/37	(5)	10/36	(27)	0.19 (0.05–0.83)	0.009

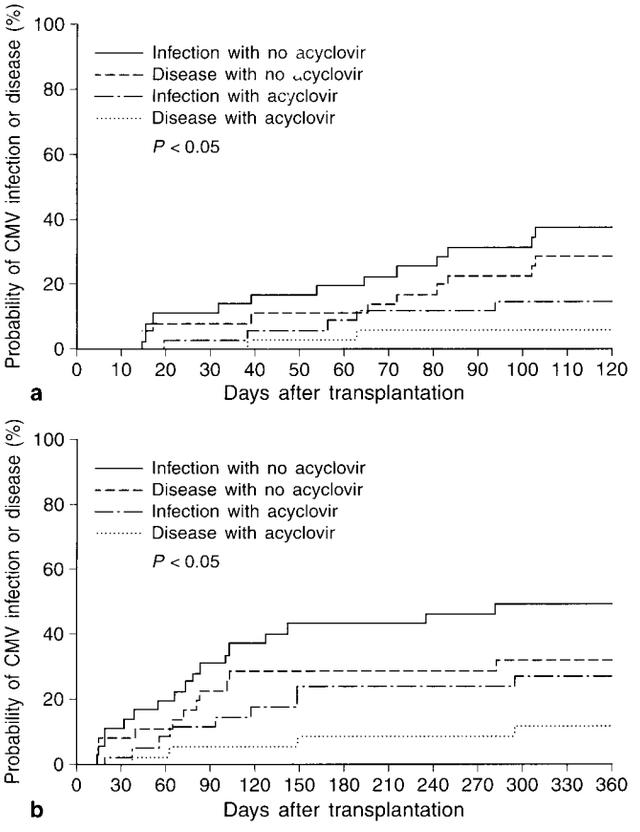

Fig. 1 a, b Kaplan-Meier log-rank estimates of the probability of CMV infection or disease **a** during the first 16 weeks or **b** 12 months after transplantation among acyclovir and control patients

these late cases, the risk of developing CMV disease was still much lower in the group with acyclovir prophylaxis (Fig. 1).

No abnormal increases in creatinine were observed in the treated group. One patient presented psychosis and another hallucinations. Acyclovir was withdrawn in these two cases; it was not possible to confirm that these manifestations were secondary to acyclovir.

Fifteen patients had died by the end of the follow-up period, seven in the acyclovir group and eight in the control group.

Discussion

Cytomegalovirus infection remains a significant cause of morbidity in the transplant setting [2]. In solid transplant recipients, it can produce disease and indirect effects, such as superinfections due to other microorganisms (fungi, *P. carinii*), as well as the induction of graft rejection [7]. The incidence of CMV infection and disease in LTR ranges from 23 % to 100 % and from 18 % to 70 %, respectively [4–9]. Since Balfour et al. [1] reported the efficacy of oral acyclovir in preventing CMV disease in renal transplant recipients, this prophylactic approach has been evaluated in other organ transplant patients, including liver recipients [3–4, 6, 8–9]. The majority of these studies have used a daily oral dose of 3.2 g [4, 6, 8]. Recently, the effectiveness of a dose of 2 g q. d. to prevent CMV infection and disease after heart transplantation has been evaluated [3]; however, no data in the liver transplant setting has been reported with this dose.

Although acyclovir meets many of the criteria of an ideal prophylactic drug, its efficacy in the liver transplant setting has yet to be clearly established. The present study evaluates the efficacy of 2 g q. d. of oral acyclovir to prevent CMV infection and disease in LTR as compared to a control group with no prophylaxis. Because of ethical considerations, we did not conduct a blinded study; it is absolutely necessary to know all of the variables in the event of complications in these patients, especially during the crucial immediate post-transplantation period. Our results demonstrate a significant reduction in the risk of developing CMV disease. Other authors have described similar results in the liver transplant setting, but with different acyclovir dosages or prophylactic strategies [8–10]. Saliba et al. [8] reported that oral acyclovir was effective in preventing CMV infection in CMV-seropositive LTR using a higher dose (3.2 g q. d.) of the drug. Stratta et al. [9] described similar results in a randomized trial using 2 g q. d. of oral acyclovir administered together with CMV immune globulin. In the population of CMV-seropositive transplant recipients in their study, Winston et al. [10] found a rate of CMV disease similar to ours using the 3.2 g q. d. oral acyclovir regimen.

Other authors have presented contrasting results [4, 5]. Martin et al. [4] and Paya et al. [6] suggest that acy-

clovir is ineffective for preventing CMV disease in studies that evaluated regimens of i.v. ganciclovir followed by acyclovir versus acyclovir alone in LTR. These results actually show that ganciclovir is very effective in preventing CMV infection in LTR. A comparison of their overall conclusions with our data is difficult because the studies were done with populations that included different CMV donor-recipient matching, while all of our recipients were CMV-seropositive. However, the incidence of CMV disease in the CMV-seropositive LTRs receiving acyclovir was similar to that found in our study. We must emphasize that the patients in the study had a low-to-intermediate risk of developing CMV infection or disease. Because all of the recipients were seropositive, we excluded retransplant patients and the rate of OKT3 use was low.

The real advantage of this approach is that an acceptably low rate of CMV disease may be reached in CMV-seropositive LTR using an easily administered oral drug. To further reduce this incidence, prolonged i.v. or oral ganciclovir is required. Moreover, a regimen of 2 grams daily would be safer than other approaches with higher doses or with ganciclovir. We observed a low rate of side effects; two patients presented mental disorders and no patients developed renal function impairment. In terms of costs, we did not perform an expense analysis, but reducing the dose of the drug makes it less expensive than other standarized regimens [1, 4–6, 8, 10] or than universal prophylaxis with ganciclovir or immune globulin.

In conclusion, our results show that in the CMV-seropositive LTR population, with its lower risk of developing post-transplantation CMV disease, 2 g q.d. of oral acyclovir provides effective prophylaxis. With the advantages of oral therapy, it could be considered a viable alternative to ganciclovir.

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