ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1995, p. 1643–1645 Vol. 39, No. 7
0066-4804/95/$04.00+0

Prospective Randomized Trial of Efficacy of Ganciclovir versus That of Anti-Cytomegalovirus (CMV) Immunoglobulin To Prevent CMV Disease in CMV-Seropositive Heart Transplant Recipients Treated with OKT3

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Received 9 January 1995/Returned for modification 20 February 1995/Accepted 24 April 1995

We compared the efficacy of ganciclovir versus that of cytomegalovirus (CMV) immunoglobulin for the prevention of CMV disease in 31 CMV-seropositive heart transplant recipients who had received early immunoprophylaxis with OKT3 monoclonal antibodies. The incidence of CMV disease and visceral involvement was much higher in the CMV immunoglobulin group than in the ganciclovir group (40 versus 6%, respectively; $P = 0.03$). No adverse effects were found in the CMV immunoglobulin group, but 19% of the patients in the ganciclovir group developed mild leukopenia or a mild increase in their serum creatinine levels.

Cytomegalovirus (CMV) is a major pathogen in cardiac transplant recipients. There has been considerable interest in developing methods that will minimize the risk of CMV infection in these patients. Recently, Merigan et al. (8) demonstrated that prophylactic administration of ganciclovir for 28 days after heart transplantation in CMV-seropositive patients reduced the incidence of CMV-induced illness. However, prophylaxis may not be necessary in all of these patients, but it is necessary for those at high risk for the development of CMV disease. Patients receiving OKT3 monoclonal antibodies represent such a group (5). We have recently demonstrated that a short course of ganciclovir appears to be useful in reducing the incidence of CMV disease when OKT3 is used for the treatment of steroid-resistant rejection in liver transplant recipients (7), but it is not known whether anti-CMV prophylaxis is also useful when OKT3 is used early after transplantation as an inductive prophylaxis against rejection. On the other hand, although the effect of either conventional or CMV hyperimmune globulin in solid organ transplantation has been quite variable (1a–4), it could be also useful in this situation. Consequently, we performed a prospective randomized trial to compare the efficacy of a short course (14 days) of ganciclovir versus that of CMV immunoglobulin in CMV-seropositive heart transplant patients who received OKT3 as induction immunosuppressive therapy.

(This study was presented in part at the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, Calif., 11 to 14 October 1992 [1].)

All CMV-seropositive patients older than 18 years who received a heart transplant in the Hospital Doce de Octubre, in Madrid, Spain, from January 1991 to December 1992 were eligible for participation in the trial. Patients were excluded from the study if they had received any other antiviral drugs within the 7 days before enrollment; had leukocyte counts of less than 1,500/mm^3, platelet counts of less than 50,000/mm^3, or a creatinine concentration in serum greater than 2.5 mg/dl; or died during the first week after the transplantation. All of them received cyclosporine, corticosteroids, azathioprine, and OKT3 monoclonal antibodies (Ortho Diagnostic Systems, Inc., Raritan, N.J.) at a dose of 5 mg daily intravenously for 14 days as induction immunosuppressive therapy. The Committee on the Use of Human Subjects in Research approved the study design.

Samples of blood (mixed leukocyte fraction) and urine and throat swabs were collected for viral culture at days 0, 15, 30, 60, 90, 180, and 360 and when clinically indicated. All specimens were processed for CMV detection by both conventional culture and the rapid shell vial assay on MRC-5 cell monolayers by accepted protocols (6, 9). The CMV serologic status of both donors and recipients (before transplantation) was assessed by latex test (CMV Scan latex agglutination test; Becton Dickinson, Cockeysville, Md.) and enzyme-linked immunosorbent assay (CMV immunoglobulin G Immunoassay; Diamedix Corp., Miami, Fla.) procedures. Routine blood determinations and leukocyte counts were performed twice weekly during the period of administration for CMV prophylaxis and monthly thereafter. Patients were clinically monitored weekly during the first admission and then monthly until 6 months. In addition, patients were evaluated twice weekly during any subsequent hospital admission.

The patients were randomly assigned to receive ganciclovir or CMV immunoglobulin. CMV immunoglobulin (Cytotect; BioTest Pharma, Frankfurt, Germany) was administered intravenously at a dosage of 100 mg/kg of body weight per day within 24 h of the transplantation and at weeks 2, 4, 6, 8, and 10 after transplantation. Ganciclovir (Syntex, Palo Alto, Calif.) was administered intravenously at a dosage of 5 mg/kg of body weight every 12 h daily for 14 days. The dose of ganciclovir was adjusted according to the patient's renal function, and the drug was started within 48 h of the transplantation in all patients.

The primary end points of the study were the development of CMV disease, visceral involvement, or death. Active CMV infection and disease were defined as described previously (7). Statistical analysis was performed by previously reported methods (7).

Thirty-five CMV-seropositive adult patients met the criteria for inclusion in the study. Four of them (two from each group)

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TABLE 1. General characteristics of the patients in both study groups

Characteristic	CMV immunoglobulin	Ganciclovir
No. of patients	15	16
Mean age (yr [range])	51.5 (30–64)	50 (27–62)
No. of males/no. of females	15/0	15/1
Donor serology (no. [%])		
CMV seropositive	7 (47)	11 (69)
CMV seronegative	8 (53)	5 (31)
Antirejection treatment (no. [%])		
Steroid bolus[a]	9 (60)	9 (56)
New course of OKT3	0	1 (6)
No. (%) with more than two episodes of severe rejection	8 (53)	8 (50)
No. with retransplantation	0	0
No. who completed the protocol[b]	13	15

[a] The steroid bolus consisted of >3 g of methylprednisolone.
[b] Three patients died during the first 6 months after transplantation.

were later excluded from the trial because they died during the first week following the transplant because of primary failure of the graft. Finally, 31 patients were analyzed in the study (16 in the ganciclovir group and 15 in the CMV immunoglobulin group). The general characteristics of the patients are given in Table 1. Both groups were similar with regard to age, sex, incidence of CMV seropositivity in donors, and grade of immunosuppression. All patients completed the established prophylactic protocol. Thirteen patients in the CMV immunoglobulin group and 15 patients in the ganciclovir group completed a full 6-month period of follow-up. The remaining three patients died within 6 months after transplantation (the causes of death were acute rejection, lymphoma, and disseminated aspergillosis).

The incidence of CMV infection within 180 days after transplantation was similar in both groups (Table 2), but the onset of CMV excretion was significantly delayed in patients receiving ganciclovir (mean, 73 days versus 36 days in the CMV immunoglobulin group). However, six people in the CMV immunoglobulin group but only one person in the ganciclovir group developed illness caused by CMV within 180 days after transplantation (Table 2), and only the patients (4 of 15 patients) allocated to the CMV immunoglobulin group developed visceral CMV involvement. Although all of these patients developed symptoms sufficiently severe to require rehospitalization, ganciclovir treatment, and invasive diagnostic procedures, no deaths were attributed to CMV.

The mean time to the development of disease in the CMV immunoglobulin group was 60 days (Fig. 1), while the only case of CMV disease in the ganciclovir group appeared 90 days after transplantation. The incidence of opportunistic infections was similar in both groups (Table 2). No adverse effects were found in the CMV immunoglobulin group, and only a mild increase in the creatinine level in serum (two patients) and a low-grade leukopenia (one patient) were observed in the ganciclovir group. A dose reduction was sufficient to control toxicity in the three patients. There was no difference between the two study groups with regard to the number of severe acute rejection episodes or death from causes other than CMV disease.

TABLE 2. Efficacy and safety of both groups of CMV prophylaxis within 180 days after transplantation

Characteristic	CMV immunoglobulin (n = 15)	Ganciclovir (n = 16)	P value
CMV infection (no. [%])	14 (93)	13 (81)	NS[a]
Isolation of CMV from (no. [%]):			
Blood	7 (47)	6 (37)	NS
Urine	11 (73)	13 (81)	NS
Throat	5 (33)	4 (25)	NS
First isolation of CMV (days)			
Mean	36	73[b]	<0.05[c]
Range	15–60	15–90	
CMV disease (no. [%])	6 (40)	1 (6)	0.03[d]
Viral syndrome	1	1	
Hepatitis	2	0	
Pneumonia	1	0	
GI gastrointestinal tract	1	0	
Disseminated disease	1	2	NS
Opportunistic infections (no. [%])			
Disseminated aspergillosis	1	1	
Milliary tuberculosis	0	1	
Pneumocystis carinii pneumonia	1	0	
Adverse events (no. [%])	0	3 (19)[e]	NS
Death (no. [%])	2 (13)	1 (6)	NS
Rejection	1	0	
Lymphoma	1	0	
Opportunistic infection	0	1	

[a] NS, not significant.
[b] Excluding two patients who were shedding CMV in their urine at the time of transplantation.
[c] Wilcoxon rank sum test.
[d] Fisher's exact test.
[e] Ganciclovir was associated with a mild and reversible increase in the creatinine level in serum (>1.5 mg/dl) in two patients and discrete leukopenia (2,000 leukocytes) in the other patients.

The incidence of CMV shedding in urine at day 30 was significantly lower in the ganciclovir group (12%) than in the

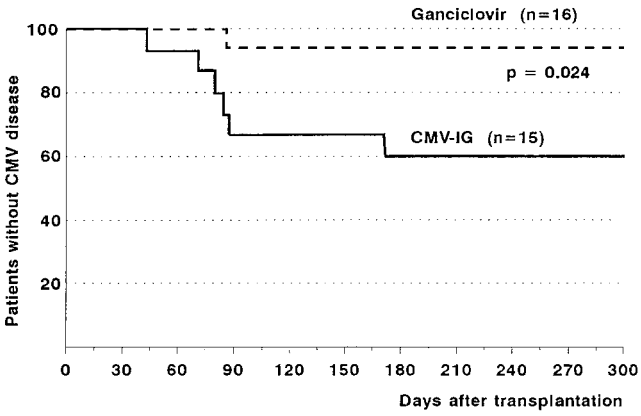

FIG. 1. Incidence of CMV disease in the two study groups estimated by the Kaplan-Meier method. IG, immunoglobulin.

CMV immunoglobulin group (67%) ($P < 0.01$), even though two patients in the ganciclovir group were already shedding CMV in their urine before the transplantation. The excretion of CMV was similar in both groups at day 60 (44 versus 80%), day 90 (69 versus 60%), and thereafter.

The most important conclusion that can be derived from our results is that a short course of ganciclovir (14 days) appears to be safe and useful in reducing the incidence and severity of the symptoms caused by CMV infection in CMV-seropositive heart transplant recipients who had received OKT3 monoclonal antibodies in the early posttransplantation period. In comparison with the more prolonged use of ganciclovir (28 days) suggested by Merigan et al. (8), this shorter course could allow reductions in cost and, potentially, could reduce the incidence of side effects. However, a direct comparison between the two regimens has been not done.

It has been suggested that CMV immunoglobulin reduces the incidence of CMV disease in CMV-seropositive liver transplant recipients, but the use of OKT3 sharply reduced the beneficial effect of CMV immunoglobulin (10). This could explain the poor results found in our patients receiving CMV immunoglobulin. The incidence of CMV disease in this group was similar (40%) to that found in the group of patients in the study by Merigan et al. (8) who received placebo (46%). Nonetheless, we cannot exclude some beneficial effect of CMV immunoglobulin, because none of the patients receiving this therapy died as a consequence of CMV disease.

Our study indicates that ganciclovir is well tolerated in heart transplant recipients. Ganciclovir was associated with only mild and reversible increases in the creatinine level in serum and low-grade leukopenia. Otherwise, the few observed adverse effects could also have been related to the many other drugs simultaneously administered to the patients.

Although the importance of effective prophylaxis for CMV disease in organ transplant recipients is clear, controversy exists about the most appropriate strategy in the subset of patients at highest risk, like those who receive OKT3 therapy. Our data suggest that ganciclovir is useful and that a short course of this drug could be effective in this setting.

We thank Federico Pulido for help in the statistical analysis and Gemma Rodríguez, Columbiana Prieto, and Carmen de Miguel for laboratory assistance.

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