Transplant Int (1992) 5 [Suppl 1]: S30–S31

TRANSPLANT
International

Prophylaxis of CMV disease by ganciclovir (DHPG) in seronegative recipients of renal allograft from seropositive donors

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Abstract. In an open-label randomized study of prophylactic treatment by ganciclovir, 23 seronegative recipients of kidney allograft from seropositive donors were randomized to receive from day 14 to day 28 after transplantation either no treatment (n = 11) or ganciclovir, 5 mg/kg twice daily (n = 12). Both groups were similar in age, immunosuppressive therapy, number of acute rejections and in steroid bolus. Seroconversion occurred in ten patients of the control group (91 %) and in ten of the ganciclovir group (84 %). CMV disease occurred in ten patients of the control group (91 %) and in eight patients of the ganciclovir group (66 %), three of whom had asymptomatic viraemia. The delay between transplantation and onset of CMV disease was significantly increased by ganciclovir prophylaxis (78.5 ± 7.7 vs 46.5 ± 7.5 days, $P < 0.05$). We conclude that in renal transplant recipients at risk of CMV disease, ganciclovir prophylaxis delays the onset of the disease and seems to decrease its incidence and its severity.

Key words: Cytomegalovirus – Ganciclovir – Prophylaxis – Renal Transplantation.

Cytomegalovirus infection is the most frequent infectious complication observed in renal transplant recipients and may cause disease in up to 30 % of patients [8]. A high mortality rate has been reported in patients with CMV pneumonitis [9]. Therefore various methods to prevent CMV infection or disease have been proposed, for example selection of kidney graft from seronegative donors to seronegative recipients [2], prophylactic passive immunization by CMV-immune globulins [6] or prophylactic treatment by oral acyclovir [1]. Although compliance was difficult to obtain, high doses of oral acyclovir have been shown to prevent significantly CMV disease in renal transplant recipients [1]. The most evident effect was obtained in seronegative recipients of kidney from seropositive donors. Ganciclovir, an acyclic guanine analogue, is much more effective in vitro on the inhibition of CMV replication than acyclovir [7], and we [4] and others [3] have shown that ganciclovir is an effective treatment for CMV disease in transplanted patients. Therefore we decided to test the efficacy of prophylactic ganciclovir in renal transplant recipients at particular risk of CMV disease, i.e. seronegative recipients of kidney grafts from seropositive donors.

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Patients and methods

Patients and study design

From January 1990 to August 1991, 210 renal transplantations were performed in our two centres (Hôpital Tenon, Paris and Hôpital Henri Mondor, Créteil, France). A total of 23 patients who were seronegative and who had received a kidney from a seropositive donor were included in the study after they had given informed consent. On day 14 after transplantation, patients were randomized to receive either no treatment or ganciclovir, 5 mg/kg twice daily for 14 days. Doses were adapted to the renal function according to the instructions of the manufacturer. As shown in Table 1, the patients in the control group (n = 11) and the ganciclovir group (n = 12) were similar in mean age, immunosuppressive therapy, steroid pulses, number of rejection episodes, and tune between transplantation and the first rejection crisis. The male/female ratio was opposite in the two groups.

Patients of the control group and ganciclovir group were monitored once a week until the third month post-transplantation for clinical signs, viraemia, viruria, and serological status (ELISA or Latex agglutination). According to the clinical status, bronchioloalveolar lavage and/or gastrointestinal biopsies were performed. CMV antigens were detected by indirect immunofluorescence, and light microscopy was used for determination of the cytopathic effect. CMF infection was detected by serological methods. CMV disease was diagnosed on the association of clinical signs and virus isolation.

Results

As determined by serology, ten patients of the control group (91 %) and ten of the ganciclovir group (84 %) had CMV primary infection after transplantation. However,

Table 1. Patient population

	Control group	Ganciclovir group
Number	11	12
Sex (M/F)	2/9	11/1
Age	39.2 ± 4.4	46.2 ± 4.0
Sequential treatment	11	12
Steroid pulses	3.5 ± 0.9	3.0 ± 1.2
Rejection episodes	1.2 ± 0.3	1.1 ± 0.4
Time to first rejection (days)	20.8 ± 6.3	32.6 ± 11.3

symptomatic CMV disease was observed in the ten patients of the control group but in eight patients of the treated group (91 % versus 66 %, NS). The delay between transplantation and the occurrence of CMV disease was significantly longer in the treated group than in the control group (78.5 ± 7.7 versus 46.5 ± 7.5 days, $P < 0.05$). The severity of the CMV disease was also reduced by ganciclovir prophylaxis, since three patients of this group had asymptomatic disease with positive viraemia, compared with only one patient of the control group. The clinical symptoms were similar in both groups: generalized signs with asthenia, fever, leukopenia, thrombocytopenia (seven cases in the control group and five in the ganciclovir group), pneumonitis (one case in both groups) and gastrointestinal disease (three and one case, respectively); viraemia occurred in six cases in the control group and seven cases in the treated group; CMV was detected by bronchioloalveolar lavage in both groups (three and six cases, respectively). The ten patients of the control group and the eight patients of the prophylactic group who had CMV disease received a therapeutic course of ganciclovir for 14 days and all the patients recovered. No side-effects were observed during prophylaxis or curative treatments by ganciclovir.

Only one graft was lost after an irreversible vascular acute rejection in a patient of the control group. The mean plasma creatinine levels of the patients with a functioning graft was 148 ± 15 and 137 ± 19 µmol/l in the control and the treated group, respectively, after 2 to 23 months of follow-up. The patient survival levels of the rate is 100 % in both groups.

Discussion

Our study demonstrates that prophylactic administration of ganciclovir for 14 days during the 3rd and 4th week after transplantation slightly decreases the incidence of CMV disease in seronegative patients who received a kidney allograft from a seropositive donor. It significantly increases the delay between transplantation and the beginning of CMV disease and seems to decrease the severity of the disease.

Recently it has been shown in allogenic bone marrow recipients that asymptomatic CMV infection of the lung is a major risk factor for subsequent CMV interstitial pneumonia [5], and that prophylactic ganciclovir is effective in preventing the development of CMV interstitial pneumonia in patients with asymptomatic infection. However, these authors reported that a unique 14-day course of ganciclovir was not effective, and that maintenance therapy (5 mg/kg each day intravenously for 5 days per week) until day 120 was required. Although the number of patients included in our study was low, it seems that prophylactic administration of ganciclovir can decrease the incidence and the severity of CMV disease in renal transplant recipients. It significantly delays the onset of the disease. It is likely that a lower rate of CMV disease would have been observed if combined with maintenance therapy. Maintenance therapy, however, will not be easy to administer until oral forms of ganciclovir become available. At the present time, the mortality from CMV disease in renal transplant recipients, at least in our centres, has disappeared since the systematic screening for CMV infection and the use of ganciclovir in earlier stages of CMV disease. Conversely, the morbidity from CMV disease is increasing, since immunosuppressive treatments are more powerful. One hopes that, in the near future, patients with a high risk of CMV disease will be able to receive prophylactic treatment with oral forms of ganciclovir or its derivatives.

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