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Treatment of cytomegalovirus pneumonitis with ganciclovir in renal transplantation

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Abstract. Ganciclovir, also called DHPG, was administered intravenously to eight renal transplant recipients with life-threatening cytomegalovirus (CMV) pneumonitis. One patient died of pulmonary failure; a favorable clinical response was observed in the seven others. In one patient, CMV pneumonitis recurred but responded well to a second course of the drug. At no time was the immunosuppressive regimen completely stopped in the seven surviving patients. Six of them maintained a good renal function 1-11 months after treatment with ganciclovir. No toxic effect was detected during therapy. We conclude that ganciclovir appears to be a promising and effective treatment for CMV pneumonitis after renal transplantation.

Key words: Cytomegalovirus - Pneumonitis - Ganciclovir - Renal transplantation.

Cytomegalovirus (CMV) infection remains the most common viral infection in renal transplant recipients, and pneumonitis is the most severe consequence of CMV infection. Peterson et al. [7] reported a 48% mortality rate among patients with CMV pneumonitis; the pneumonitis was nearly always fatal among those patients requiring assisted ventilation.

Antiviral therapies, such as vidarabine and acyclovir, have proved to be poorly effective against CMV [6, 10]. Ganciclovir, an analogue of guanine and structurally very close to acyclovir, has been shown to be much more effective than acyclovir in inhibiting CMV replication in vitro [9]. Clinical experience with ganciclovir is still limited, yet preliminary results are encouraging. The Collaborative DHPG Treatment Study Group reported a clinical response rate of 40% in their seven cases of CMV pneumonitis in immunocompromised patients [1].

In April 1986, ganciclovir became available at our institution and was administered to our patients with CMV pneumonitis. Because this is a life-threatening complication, we felt justified not including a control group. Here we report our experiences with the first eight patients treated.

Patients and methods

Between April 1986 and January 1988, 181 patients underwent renal transplantation at the University of Louvain. During the same period of time, 8 patients (4.4%) developed CMV pneumonitis and received ganciclovir.

Immunosuppressive regimen

All patients received a prophylactic quadruple drug immunosuppressive regimen combining:

1. Methylprednisolone 15 mg/kg IV on the day of transplantation and then prednisolone begun at 0.5 mg/kg per day and tapered to 0.15 mg/kg per day by 9 months post-transplantation.

2. Azathioprine 1 mg/kg per day orally.

3. Cyclosporin A (CsA) orally, started either a few hours after transplantation in patients with a urinary output higher than 200 ml per hour or on the day when serum creatinine was below 2 mg/dl in patients with a post-transplant diuresis less than 200 ml per hour. The daily dosage of CsA was then progressively increased up to a maximum of 10 mg/kg per day. Thereafter, the CsA dosage was adjusted to keep serum creatinine close to normal range (0.8-1.3 mg/dl) and trough CsA serum level below 100 ng/ml (TDX, Abbott, Irving, Tex.).

4. Antilymphocyte globulins (Pressimum, Behring, Marburg, FRG) given before transplantation at a dosage of 50 mg/kg per day for 3 days and 25 mg/kg per day for 11 additional days.

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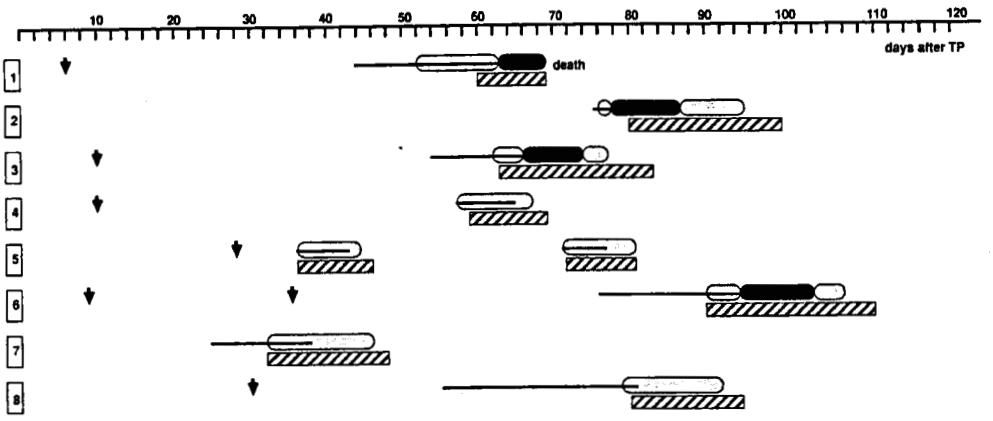

Fig. 1. Course of CMV pneumonitis in 8 renal graft recipients treated with ganciclovir. ↓ Rejection episode, — fever, O pneumonitis, ● pneumonitis requiring pulmonary assistance, ▨ ganciclovir

Table 1. Eight patients (6 men, 2 women) 15-52 years of age (mean 37 years)

Original nephropathy	
CGN	2
CIN	2
Alport	1
Fabry	1
Diabetes	1
Unknown	1
Graft source	
Living donor	2
Cadaver donor	6 (+pancreas in 1)
Acute rejection before CMV disease	
Episodes	0 (2 patients)
	1 (5 patients)
	2 (1 patient)

Rejection episodes were treated with IV methylprednisolone (4.5 grams given within 6 days) without increasing the daily dose of oral prednisolone. Steroid-resistant episodes were treated with a 10-day course of ALG (Pressimum, Behring, Marburg, FRG), RATG (Fresenius, Oberursel, FRG), or OKT_3 (Ortho-Cilag, N.J., USA).

Ganciclovir was supplied by Wellcome Research Laboratories (Erembodegem, Belgium) for patients 1-7 and by Syntex Research Laboratories (Brussels, Belgium) for patient 8. It was administered intravenously as a 1-h infusion at a dosage of 2.5 mg/kg every 8 h when the creatinine clearance was higher than 50 ml/min, and at a dosage of 1.5 mg/kg every 8 h when the creatinine clearance was below 50 ml/min. It was given for 10-20 days.

Diagnosis of CMV pneumonitis

The diagnosis of CMV pneumonitis was established using the following criteria:

1. Presence of fever and bilateral interstitial infiltrates on chest X-rays that could not be attributed to anything other than CMV

2. Presence of an active CMV infection that could be demonstrated either by appearance of CMV antibodies (seroconversion) and/or a fourfold increase in titers (by complement fixation and ELISA tests) or by one or more cultures of the bronchoalveolar fluid positive for CMV

Clinical response was judged as favorable when fever disappeared and chest radiograph was clear.

Virological studies

All patients were screened for CMV before transplantation (serology) and for the first 3 weeks after transplantation (serology and urine culture).

CMV was isolated on MRC 5 cells with seroneutralization of herpes simplex virus by human serum antibodies; CMV was detected by cytopathic effect (CPE) and, when needed, by immunofluorescence with monoclonal antibodies (Biosoft, Paris, France). Urine specimens were obtained twice weekly from all patients while they were hospitalized. Six of the eight patients underwent a bronchoalveolar lavage before starting ganciclovir.

CMV serology was performed using a quantitative enzyme-linked immunosorbent assay method for titration of IgG and IgM antibodies (Behring-Hoechst, Marburg, FRG) and a microtiter complement fixation test. Primary infection was diagnosed by seroconversion with high titers of IgM ($\geq$ 1/160). Reactivation diagnosis was based on an increase in IgG antibodies and complement fixation (fourfold or greater rise). During hospitalization for pneumonitis, serum was obtained at least twice weekly for determination of antibody titers.

Toxicity

Complete blood counts, hepatic transaminases, and serum electrolytes were measured three times per week during therapy.

Results

Patient characteristics are summarized in Table 1. One of the patients (case 6) was diabetic and received a combined renal-pancreatic graft. As shown in Fig. 1, six of the eight patients had experienced at least one rejection episode before appearance of CMV disease.

The CMV infection (Table 2) was primary in six patients who were seronegative at the time of transplantation and secondary (reactivation) in the other two. In patient 1, ganciclovir was started 5 days

Table 2. Virological study. ND, Not done; Neg, negative; BAL, bronchoalveolar lavage; Urine, days before (−) or after (+) the start of ganciclovir

Patient no.	Results of isolation		Serology		
	BAL	Urine	IgM (ELISA)	IgG (ELISA)	IgG (CF)
1	+	−35	1/20	1/20480	1/512
2	+	−24	1/640	1/1280	1/256
3	+[a]	+5	1/20	1/20	<1/4
4	+	−30[b]	1/20	1/20480	1/128
5	ND	Neg	1/160	1/1280	1/60
6	+	−51[b]	1/160	1/5120	1/128
7	+	Neg	1/160	1/20480	>1/1024
8	ND	Neg	1/640	1/5120	1/128

[a] Done on days 0, 7, and 10 after the start of ganciclovir. The first and second samples were positive; the last one was negative
[b] Became negative after 6 days of ganciclovir

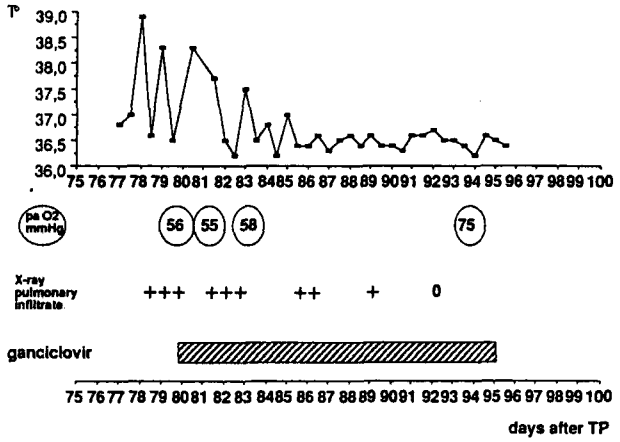

Fig. 2. Treatment of CMV pneumonitis with ganciclovir in a renal graft recipient

after the appearance of interstitial infiltrates on chest roentgenograms. Assisted ventilation was required 2 days later and immunosuppression was stopped. Clinical status worsened and retinitis (probably due to CMV) developed. The patient remained febrile and died from respiratory failure 8 days after starting ganciclovir. Persistence of pneumonitis was demonstrated by autopsy studies.

In the seven other patients, a favorable course was observed. In three of them, pneumonitis was severe enough to require assisted ventilation. Patient 2 was already being ventilated at the initiation of therapy. Patients 3 and 6 needed transient pulmonary assistance after starting ganciclovir; their respiratory condition subsequently improved and they recovered. In the seven patients, fever abated 2-12 (mean: 7.3) days and chest X-rays cleared 8-18 (mean: 12.5) days after starting ganciclovir. This is particularly well exemplified in patient 8 (Fig. 2). This patient had been febrile for 2 weeks when pneumonitis appeared. After the start of ganciclovir, his temperature dropped within 3 days and his chest X-ray cleared completely within 12 days. In one case (patient 5), CMV pneumonitis recurred 25 days after a 10-day course of ganciclovir but responded well to a second course of the drug. In none of the seven surviving patients was the immunosuppressive regimen stopped at the time of pneumonitis; it was just transiently reduced in four of them. In patients 2, 3, and 6, azathioprine was stopped while prednisolone and CsA were maintained; in patient 4, CsA was stopped while prednisolone and azathioprine were maintained. In six of the patients, graft function remained unchanged during and after therapy. One patient (case 7) experienced progressive chronic rejection.

Currently, 1-11 (mean: 8) months after pneumonitis, the seven patients are doing well. Pulmonary recovery was not complete in one patient (case 2), as witnessed by decreased CO-diffusing capacity and a chest X-ray film suggestive of secondary pulmonary fibrosis.

Virological study (Table 2)

Bronchoalveolar lavage (BAL) was performed on six patients and was found to be positive in all of them. In one of the patients (case 6), BAL was repeated on days 7 and 10 after the start of ganciclovir. The first and second samples were positive; the last one was negative.

Urine was positive in four patients (cases 1, 2, 4, and 6) before ganciclovir therapy, and it appeared positive during therapy in one other patient (case 3). It remained negative in the other three. In patients 4 and 6, urine isolation for CMV became negative after 6 days of therapy. In the three other patients, urine remained positive.

As mentioned earlier, CMV infection was primary in six patients and secondary in the other two. Seven of the eight patients had a positive IgG serology by CF and ELISA; titers obtained by CF varied from 1/64 to >1/1024. Serology remained negative in one case (patient 3) despite this patient's having suffered from a major pneumonitis.

Adverse reactions

There were no significant changes in blood cell count (patient 8 had neutropenia before the start of ganciclovir but spontaneously recovered under ther-

apy), serum transaminases, or serum electrolytes throughout the ganciclovir treatment in any patient.

Discussion

CMV pneumonitis remains a main cause of death in renal transplant recipients. Peterson et al. [7] reported a case fatality of 48% among patients with CMV pneumonitis; moreover, mortality rose to over 90% in patients requiring pulmonary assistance. In our center, of the 16 patients who developed CMV pneumonitis between 1981 and 1986, only 2 patients survived (one of whom required assisted ventilation). In the past, antiviral therapy (vidarabine, acyclovir) for CMV pneumonitis has proved to be disappointing [6, 10].

Recently, a randomized trial demonstrated that the prophylactic use of CMV immunoglobulins was able to decrease the incidence of CMV pneumonitis; however, the efficacy of those globulins in the treatment of established CMV infection remains to be shown [8]. Thus, treatment of CMV pneumonitis currently consists of reducing or stopping the immunosuppressive therapy. Unfortunately, this approach has been responsible for acute rejection episodes and graft losses.

Recently, three case report studies have demonstrated that ganciclovir appears to be effective in treating CMV pneumonitis after renal transplantation [2, 3, 5]. We report on eight other treated patients. Our preliminary experience has been with an open-label uncontrolled trial and, thus, we are unable to firmly establish the efficacy of ganciclovir. Nevertheless, there are several factors that seem to point in a positive direction. First, the favorable treatment outcome for seven of our eight patients contrasts with the nearly uniformly fatal outcome that was the rule before the administration of ganciclovir either to our patients with CMV pneumonitis at the stage of assisted ventilation or to the patients reported in the literature [7]. A second argument is found in the temporal relationship between the introduction of ganciclovir and the improvement of the disease. This is particularly striking in our last case. This patient had been febrile for 2 weeks when ganciclovir was started. Without receiving any antibiotic therapy, his temperature dropped as early as 3 days after starting ganciclovir and subsequently remained normal. At the same time, pneumonitis subsided, as evidenced by clinical and radiological improvement. A third argument is the cessation of productive CMV infection after the start of ganciclovir. Indeed, in two of our five patients with positive CMV-shedding in the urine, isolation became negative 6 and 10 days after the start of ganciclovir. Moreover, in another patient, we repeated bronchoalveolar lavage during ganciclovir therapy and were able to document clearance of the virus from the bronchoalveolar fluid 10 days after the onset of therapy. Taken together, our observations strongly suggest that ganciclovir is, indeed, effective in treating CMV pneumonitis in renal tranplant recipients.

It seems, however, that ganciclovir should be initiated early after the appearance of the pneumonitis in order to be effective. The delay in therapy may very well have been a critical factor contributing to the fatal outcome of case 1. It is also worth noting that the other patient who received delayed ganciclovir treatment had a chest X-ray film and a CO-diffusing capacity consistent with a secondary pulmonary fibrosis several months after the recovery of pneumonitis.

A 15- or 20-day course of ganciclovir may also be preferable to a 10-day course. Relapse did, indeed, occur in one of the two patients (cases 4 and 5) treated for only 10 days, but it did not occur in any of the five other patients treated for at least 15 days.

Two important factors may contribute to the different clinical responses in our study and in previously reported studies. The first factor is the occurrence of pulmonary opportunistic superinfections, which are a well-known complication of CMV pneumonitis [7]. In the cases reported by Erice et al. [3] and by Hecht et al. [5] among renal transplant recipients, the patients who died had experienced pulmonary superinfection with *Pseudomonas aeruginosa* and *Candida albicans*. In our experience, superinfections never occurred, perhaps because the four patients with the most serious cases of pneumonitis, who required assisted ventilation, were treated in intensive care units with massive antibiotherapy including trimethoprimsulfamethoxazole, erythromycin, cephalosporins, and amphotericin B. Further clinical studies should indicate whether or not antibiotics need to be administered prophylactically during ganciclovir therapy.

The second major difference between our trial and other reports [2, 5] involves the patient's immunosuppression. Indeed, there are three reasons why we chose to reduce the immunosuppressive regimen as infrequently as possible. The first is that reduction of the immunosuppressive regimen may cause acute rejection episodes. Second, CMV disease is reported to be responsible for graft rejection [7]. Third, according to the hypothesis by Grundy et al. [4], restoration of the patient's immune capabilities may bring on CMV pneumonitis. The fact that all of

our patients in whom the immunosuppressive regimen had been maintained (or transiently reduced) recovered from CMV pneumonitis and maintained a good renal function is very encouraging. By contrast, in the study by Hecht et al. [5], of the four renal transplant recipients treated with ganciclovir for CMV pneumonitis and in whom the immunosuppressive regimen was stopped, two patients died and the two surviving patients lost their grafts. Finally, in our trial, no adverse effects - including the classically reported neutropenia [3, 5] - were recorded.

We conclude that ganciclovir appears to be effective in treating CMV pneumonitis after renal transplantation, and we recommend that treatment be initiated as soon as possible. We no longer wait for the appearance of pneumonitis before starting the treatment in the presence of CMV infection, especially when it is a primary infection. Our policy has evolved even further: we do not hesitate to give ganciclovir to a seronegative patient experiencing fever from an unexplained origin 1-3 months after transplantation before having virological and serological confirmation of CMV infection. A course of 15-20 days is probably safer than 10 days in order to avoid relapse. This therapy does not appear to be harmful at the dosage recommended by the manufacturer in patients with normal or near-normal renal function.

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