1729

Acyclovir/Cytomegalovirus Immune Globulin Combination Therapy for CMV Prophylaxis in High-Risk Renal Allograft Recipients

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CYTOMEGALOVIRUS (CMV) remains a common complication after renal transplantation. As previously reported, CMV has a significant impact not only on the clinical outcome after transplantation but also on its cost; for patients with CMV, cost is increased 2.9-fold as a result of extended hospitalization.[1]

The risk of developing CMV disease after renal transplantation is highest in seronegative patients who receive grafts from seropositive donors (R-D+). In this population, the incidence of CMV-associated morbidity approaches 60%.

Numerous strategies have been employed to prevent CMV disease after transplantation, including the exclusion of antibody-positive donors for antibody-negative recipients,[2] active immunization with CMV-attenuated vaccines,[3] passive immunization with CMV immunoglobulin (CMV-Ig),[4] and antiviral chemotherapy including high-dose acyclovir (ACV),[5] gancyclovir,[6] and interferon.[7] Although each agent has achieved some success, none has successfully eliminated the virus.

MATERIALS AND METHODS

Of 792 patients receiving renal allograft transplants at the University of Pittsburgh Medical Center (UPMC) between June 1, 1989, and May 1, 1993, 116 (14.6%) R-D+ patients were retrospectively evaluated. In this 47-month period, two different protocols for prophylaxis against CMV were followed; during the first 17 months, 43 patients received high-dose ACV alone (group 1); during the following 30 months, 73 patients received high-dose ACV in combination with CMV-Ig (group 2). Acyclovir dosage was calculated following the guidelines suggested by Balfour et al[5] and adjusted if required by the clinical situation. The CMV-Ig combination was administered according to the dosage and schedule suggested by Snydman.[4]

Clinical characteristics of the patients are summarized in Table 1. Both groups were comparable for age, sex, graft source (living, related/cadaver), number of retransplantations, number of highly sensitized recipients, and adult vs pediatric recipients.

In group 1, the initial immunosuppressive protocol included FK 506 and Prednisone (Pred) in 20 patients, cyclosporine (CyA), Pred and Imuran in 16 patients, and CyA and Pred in 7 patients.

In group 2, all 73 patients received FK 506 and Pred immunosuppression; 28 patients also received Imuran (Table 1).

Mean follow-up was 28 months (range, 20 to 38 months) for group 1, and 13.8 months (range 2.1 to 31 months) for group 2. The following laboratory tests were performed before transplantation, daily while the patient was in the hospital, and at least weekly for the first 6 months posttransplantation: CBC with differential, electrolytes, BUN, creatinine, glucose, liver-function profile, cholesterol, calcium, phosphorus, uric acid, and magnesium.

Table 1. Clinical Characteristics and Immunosuppression in the Study Groups

	Regimen	
	Acyclovir Alone	Acyclovir + Globulin
Number of Patients	43	73
Sex		
Male	25 (58%)	53 (73%)
Female	18 (42%)	20 (27%)
Mean age (years)	36 (range 4–62)	38 (range 1–67)
Donor		
Living	3 (7%)	7 (10%)
Cadaveric	40 (93%)	66 (90%)
Retransplantation	12 (28%)	16 (22%)
PRA >40%	7 (16%)	10 (14%)
Adult/pediatric recipients	41/2	68/5
Mean follow-up (months)	28 (range 20–38)	13.8 (range 2.1–31)
FK 506, Prednisone	20 (47%)	45 (62%)
FK 506, Prednisone, Imuran	—	28 (38%)
Cyclosporine, Prednisone	7 (16%)	—
Cyclosporine, Imuran, Prednisone	16 (37%)	

Before transplantation, CMV titers were measured in all recipients and kidney donors; herpes simplex and Epstein-Barr virus titers were also measured. Specimens of urine, buffy coat, and throat swabs were collected at weekly intervals until discharge, at regular outpatient appointments, and during any subsequent hospital admission to rule out CMV. Specimens from other sites (ie, gastrointestinal biopsies, renal biopsies, bronchoalveolar lavage) were also processed when invasive CMV disease was investigated. Samples were tested for CMV by conventional cell-culture methods and by shell vial assay for early CMV antigen detection. In addition, quantitation of CMV IgG and IgM was also performed with an automated immunofluorescent test.

Asymptomatic CMV infection (ACI) was defined as antibody seroconversion not attributable to globulin infusion, and/or viral shedding, and/or positive early antigen detection or positive cul-

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Table 2. CMV Disease: Manifestations and Sites

	Regimen	
	Acyclovir Alone	Acyclovir + Globulin
Clinical manifestations	Number of Patients (%)	Number of Patients (%)
Viral syndrome	1 (5)	2 (12)
Localized disease	15 (75)	15 (88)
Disseminated disease	4 (20)	0 (0)
Sites of invasive CMV		
Gastric/duodenal mucosa	14 (70)	15 (88)
Urine	—	2 (12)
Bronchi/lungs	5 (25)	—
Retina	1 (5)	—

ture, without symptoms. Symptomatic CMV disease (SCD) was classified as viral syndrome, localized CMV disease, or disseminated CMV disease.[8] Viral syndrome was considered as the association of laboratory documentation of CMV infection and fever >38°C for 2 or more days with either atypical lymphocytosis >3%, white cell count <4000/mm.^{3} or platelet count <100,000/mm.^{3} Localized CMV disease was defined as the invasion of a single organ determined histopathologically and/or by culture of virus from tissue. Disseminated CMV was considered to be a tissue involvement of two or more noncontiguous sites.

Disease severity was based on six features defined previously by Simmons:[9] (1) prolonged fever (temperature >38.3°C for more than 7 days); (2) diffuse pulmonary infiltrate; (3) gastrointestinal bleeding; (4) pancreatitis; (5) transplant nephrectomy; (6) development of another systemic infection. Patients with severe CMV disease had at least three of these six features; patients with moderate disease had two of these features; mild disease was defined by the presence of not more than one of these features.

Proportions were analyzed using chi-square or Fisher's Exact Test when appropriate. A significant difference was defined as $P < .05$.

RESULTS

The overall rates of ACI and SCD were 5% and 32%, respectively. The incidence of SCD differed significantly between group 1 (47%) and group 2 (23%) ($P = .01$). The median day for SCD diagnosis was 67 days (range, 25 to 178 days) in group 1 and 87 days (range, 14 to 365 days) in group 2. The rate of ACI did not differ significantly between group 1 (1%) and group 2 (7%) ($P = .41$).

In both groups, localized CMV disease was the most frequent clinical manifestation (Table 2) and was most frequently documented in the gastrointestinal tract. However, CMV pneumonia was observed only in group 1.

In group 1, moderate to severe disease was observed in 75% of the patients, including two lethal cases. In group 2, the degree of the disease was always mild; no deaths were attributable to CMV.

The overall rate of rejection episodes was higher in group 1 (56%) than in group 2 (34%) ($P = .038$). There was also a difference in administration of OKT3 to treat steroid-resistant acute cellular rejection (ACR). In group 1, 8 of 43 patients (19%) received OKT3; 3 of 73 patients (4%) were given OKT3 in group 2 ($P = .025$). However, rejection did not seem to affect the development of CMV in either group; in group 1, 10 of 24 patients (42%) previously treated for rejection developed SCD vs 10 of 19 patients (52%) never treated for rejection ($P = .5$); in group 2, SCD was diagnosed in 8 of 25 patients (32%) treated for rejection and in 9 of 48 patients (19%) never treated ($P = .3$).

Overall one-year patient and graft survival rates were 93% and 70% in group 1, and 93% and 87% in group 2.

No difference was observed in the incidence of SCD in group 1 for the patients receiving CyA (10 of 23 patients, 43%), compared with the patients receiving FK 506 (10 of 20 patients, 50%; $P = .9$).

DISCUSSION

The availability of gancyclovir to treat CMV has been a critically important development in transplantation. It has transformed CMV from a feared, potentially lethal disease, into a largely manageable problem. Preventing CMV, however, is still preferable because it reduces morbidity and cost. The prophylaxis literature thus far looked at single agents, high-dose acyclovir,[5] CMV hyperimmuneglobulin,[4] and gancyclovir.[6] Although there are reports suggesting that these single agents can be effective, there are also disappointing studies. It seems logical to try a combination of agents to optimize prophylaxis and reduce the rate of CMV in the high-risk group as much as possible. The combination of high-dose ACV and CMV-Ig is the first step in this direction. In our experience, this combination was more effective than high-dose ACV alone, reducing the rate of CMV disease in this series from 47% to 23%. In addition, the severity of illness seemed to be attenuated in the combination therapy group.

At the present time, we are conducting a prospective, randomized trial comparing the combination of high-dose ACV and CMV-Ig with a 2-week course of prophylactic gancyclovir followed by high-dose ACV. Other potential options might include using all three agents, ie, gancyclovir, CMV-Ig, and high-dose ACV. In addition, monoclonal antibodies to CMV are being evaluated. Further investigation will be required to establish the best prophylactic regimen for CMV; this study suggests that the combination of high-dose ACV and CMV-Ig may be useful.

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