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


**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 previously reported. CMV has a significant impact not only on the clinical outcome after transplantation but also on its 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, active immunization with CMV-attenuated vaccines, passive immunization with CMV immunoglobulin (CMV-Ig), and antiviral chemotherapy including high-dose acyclovir (ACV), gancyclovir, and interferon. 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. and adjusted if required by the clinical situation. The CMV-Ig combination was administered according to the dosage and schedule suggested by Snyderman.

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.

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 (i.e., 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-

**Table 1. Clinical Characteristics and Immunosuppression in the Study Groups**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acyclovir Alone</th>
<th>Acyclovir + Globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>43</td>
<td>73</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (58%)</td>
<td>53 (73%)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (42%)</td>
<td>20 (27%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>36 (range 4-62)</td>
<td>38 (range 1-67)</td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td>3 (7%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Cadaveric</td>
<td>40 (63%)</td>
<td>66 (90%)</td>
</tr>
<tr>
<td>Retransplantation</td>
<td>12 (28%)</td>
<td>16 (22%)</td>
</tr>
<tr>
<td>PRA &gt;40%</td>
<td>7 (16%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Adult/pediatric recipients</td>
<td>41/2</td>
<td>68/5</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>28 (range 20-38)</td>
<td>13.8 (range 2.1-31)</td>
</tr>
<tr>
<td>FK 506, Prednisone</td>
<td>20 (47%)</td>
<td>45 (62%)</td>
</tr>
<tr>
<td>FK 506, Prednisone, Imuran</td>
<td></td>
<td>28 (38%)</td>
</tr>
<tr>
<td>Cyclosporine, Prednisone</td>
<td>7 (16%)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, Imuran, Prednisone</td>
<td>16 (37%)</td>
<td></td>
</tr>
</tbody>
</table>

From the University of Pittsburgh (M.L.J., M.M., J.M., J.M.), University of Pittsburgh Medical Center, Pittsburgh, Penn.

© 1995 by Appleton & Lange
0041-1345/95/$3.00/0
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, CMV hyperimmunoglobulin, and gancyclovir. 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.

REFERENCES


