Pharmacologic Basis for High-Dose Oral Acyclovir Prophylaxis of Cytomegalovirus Disease in Renal Allograft Recipients

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The incidence of cytomegalovirus disease, the most important infectious complication of renal transplantation, was reduced in renal allotransplant recipients by a regimen of prophylactic high-dose oral acyclovir. To analyze the pharmacologic aspects of our prophylactic approach, we evaluated safety, pharmacodynamics, and in vitro susceptibility data. One hundred four recipients of cadaveric renal allotransplants received either oral acyclovir (n = 53) in doses of up to 3,200 mg/day or a placebo (n = 51) for 12 weeks posttransplant. Leukocyte count and serum creatinine were selected as markers of laboratory safety and were evaluated pretransplant, at study midpoint (creatinine only), and at study completion. Concentrations of acyclovir in plasma were determined to verify the ability of the dosing strategy to achieve predicted values. Viral resistance was assessed by calculation of in vitro 50% inhibitory concentrations (IC50s) of acyclovir for the cytomegalovirus strains collected from the subjects. Our results showed no difference in leukocyte count or serum creatinine between the acyclovir and placebo recipients. Plasma acyclovir concentrations were maintained within the expected limits and did not differ between patients who developed cytomegalovirus disease and those who did not. The mean acyclovir IC50 for cytomegalovirus isolates were 42.6 μmol/liter in the acyclovir recipients and 48 μmol/liter in the placebo recipients. We conclude that the clinical benefit of high-dose oral acyclovir therapy occurred despite plasma drug concentrations below the mean IC50 for the patient viral isolates. Furthermore, the use of the regimen did not produce leukopenia, adversely affect renal function, or alter the susceptibility of cytomegalovirus strains to acyclovir. This approach and dose adjustment scheme may be appropriate for other immunocompromised patients at risk for cytomegalovirus infection and disease.

Cytomegalovirus is the single most important cause of infectious disease after renal transplantation (10, 14). Because cytomegalovirus disease occurs almost exclusively during the first 3 months after renal transplantation (16) and treatment has been difficult (1), we developed a prophylactic approach using the antiviral drug acyclovir. We demonstrated that high-dose oral acyclovir, given according to a scheme that adjusted for estimated creatinine clearance, reduced the incidence and severity of cytomegalovirus disease in recipients of cadaveric renal allografts (2). In addition to efficacy, comprehensive analyses of safety, pharmacodynamics, and in vitro susceptibilities of cytomegalovirus strains collected from the subjects were needed to evaluate the risk/benefit ratio of this prophylactic approach more thoroughly. These issues are addressed in the present report.

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MATERIALS AND METHODS

Study design. Recipients of cadaveric renal allotransplants who were at least 10 years old were eligible to participate. Patients were randomized to receive either acyclovir or a placebo after giving informed consent. Patients and clinicians remained blinded throughout the study period. Acyclovir was provided as 800-mg tablets; placebo tablets were identical in appearance and taste. All patients received a single tablet just prior to transplantation and again 24 h later. The subsequent dosing schedules for the remainder of the 12-week dosing period were based upon creatinine clearance (CLcr) estimated by the method of Jelliffe and Jelliffe for unstable serum creatinine (11). Patients with an estimated CLcr of <10 ml/min/1.73 m2 (<0.167 ml/s) received 800 mg daily; those with an estimated CLcr of between 10 and 25 ml/min/1.73 m2 (0.167 and 0.417 ml/s) received 800 mg three times daily; and those with an estimated CLcr of >25 ml/min/1.73 m2 (>0.417 ml/s) received 800 mg four times daily. Patients undergoing hemodialysis received 800 mg twice daily. All patients were cared for according to standard protocols at The University of Minnesota Hospital and Clinic and received our standard immunosuppressive regimen, which included quadruple therapy with antilymphoblast globulin, cyclosporine, prednisone, and azathioprine (9). Study participants received daily clinical and laboratory evaluations during the first week posttransplant and twice weekly thereafter until discharge. Thereafter, patients were seen in the outpatient clinic at 3 months and 1 year posttransplant.

Clinical laboratory evaluation of drug safety. Serum creatinine levels and peripheral leukocyte (WBC) counts were the primary laboratory parameters evaluated for safety. Values selected for analysis were serum creatinine levels measured at the beginning (pretransplant), midpoint, and end of the study and WBC counts obtained at the beginning (pretransplant) and end of the study for both acyclovir and placebo recipients. Changes in WBC counts from pretransplant to study completion were evaluated for differences between the
Acyclovir and placebo recipients with Student's t test for independent means. Serum creatinine measurements at the three time points were evaluated for differences between groups with analysis of variance (ANOVA) for repeated measures. If an initial test to detect any relationship between time and group suggested a significant time-group interaction, the statistical approach of Looney and Stanley was used (13). With that procedure, differences between the acyclovir and placebo groups with respect to serum creatinine levels were evaluated with an independent t test. Each observation period was considered separately, and a Bonferroni adjustment to the alpha level was made to maintain an error rate of 0.05. The change in serum creatinine levels over time was evaluated for significance with ANOVA for repeated measures and then with pairwise multiple comparisons that considered the two groups individually, with a Bonferroni adjustment to the alpha level to maintain an overall error rate of 0.05 across both sets of tests.

**Pharmacokinetic analysis.** Blood samples for the determination of plasma acyclovir concentrations were obtained on posttransplant day 5, 6, or 7 from all patients (Table 1). The sampling times were selected to reflect peak and trough concentrations; these days were chosen because our renal transplant patients usually are discharged shortly thereafter. Laboratory personnel were unblinded after the patients had completed the 12-week administration period of acyclovir or placebo, so that only those samples obtained from acyclovir recipients were analyzed for acyclovir concentrations. Plasma acyclovir concentrations were determined by a radioimmunoassay (17). The radioimmunoassay was considered acceptable if values for the plasma controls were within 10% of the stated value and the correlation coefficient from the weighted regression of the standard line was ≥0.995. The usable range of this radioimmunoassay for acyclovir was 1.25 to 115.3 μmol/liter when a 1:100 dilution of the unknown is used. The coefficients of variation for this range were between 6 and 10% both within and between assays.

Measured acyclovir concentrations were evaluated by visual inspection and tabulated for the maximum and minimum concentrations in plasma for each patient. For comparison, acyclovir recipients were divided into two groups: those who developed cytomegalovirus infection and/or disease and those who did not. A t test for independent means was used to determine whether any statistical difference existed between these two groups with respect to their plasma acyclovir concentrations. Additionally, the measured plasma acyclovir concentrations were evaluated by computer simulation of each patient’s concentrations in plasma and comparison of predicted versus measured observations. A one-compartment oral absorption pharmacokinetic model with elimination defined as a function of ClCR was used for the plasma drug concentration simulations (4). This model accommodates the nonuniform dosing schedules of the parameters and their changing ClCR. The nominal parameters used for the simulations were as follows: volume of distribution, 69 liters/1.73 m²; first-order elimination rate constant, (0.0025 × ClCR) + 0.021 h⁻¹; first-order absorption rate constant, 1.3 h⁻¹; and bioavailability, 0.20 (8).

Patients included in the initial evaluation of these model parameters were not included in the current data set. The ability of the pharmacokinetic model to predict plasma acyclovir concentrations was assessed by measures of precision and bias (19).

**Virologic evaluation.** Urine, throat swabs, and blood samples were collected for culturing from patients prior to transplantation, at discharge from the hospital, and at any subsequent clinic visits or hospitalizations during the first year after transplantation. Cytomegalovirus isolates from these specimens were frozen at −70°C until tested for acyclovir susceptibilities. The isolates selected for susceptibility testing were those collected during active cytomegalovirus disease or those obtained near the end of the 12-week period of oral dosing for patients who shed cytomegalovirus but did not have any symptoms. The in vitro concentration of acyclovir required for 50% inhibition of viral isolates (IC50) was determined by a novel and rapid method of DNA hybridization. In brief, confluent human foreskin fibroblast cell monolayers in 24-well plates were inoculated with dilutions of cytomegalovirus isolates grown in human foreskin fibroblast cell monolayers. The viral inoculum was generally used when the cytopathic effect was noted in at least 66 to 75% of the cell monolayer. The plates were centrifuged for 30 min at 550 × g, the inoculum was removed, and the plates were refed with minimum essential medium containing 10% fetal bovine serum and various concentrations of acyclovir. All dilutions were made in triplicate. After incubation at 37°C for 4 to 14 days, the DNA was extracted; cytomegalovirus DNA was detected and quantitated with a 125I-labeled probe for the BamHI fragment V region of the cytomegalovirus genome (Diagnostic Hybrids, Inc., Athens, Ohio). The IC50 was determined directly from the nonlinear curve obtained by plotting mean hybridization values (counts per minute) versus drug concentrations. Replicate experiments performed on six separate occasions with the Towne and AD 169 laboratory strains of cytomegalovirus revealed that the coefficients of variation for the susceptibility assay were 32% for Towne and 65% for AD 169.

To analyze the potential effect of exposure to acyclovir on the development of cytomegalovirus infection or disease and the possible emergence of resistant viral strains, we divided the patients into four groups according to whether they received acyclovir or a placebo and whether they had cytomegalovirus infection or disease. The IC50s obtained for the acyclovir and placebo subjects were tested for differences between groups with Student’s t test for independent means.

**RESULTS**

One hundred eighteen patients were enrolled in the study. However, 14 patients (6 in the acyclovir group and 8 in the placebo group) were excluded from final analysis because of the following reasons: failure to receive a kidney or early loss of the allograft unrelated to cytomegalovirus (5 patients), refusal to take study medication (4 patients), lack of follow-up data (2 patients), inadvertent acyclovir administration (1 patient), death from myocardial infarction (1 patient), and leukopenia (1 patient). Of the 104 evaluable patients, 53

<table>
<thead>
<tr>
<th>CLCR (mL/min/1.73 m²)</th>
<th>Dosing schedule (administration time, h)*</th>
<th>Sample collection (h postdose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25</td>
<td>QID (9, 13, 17, 21)</td>
<td>0, 2, 4</td>
</tr>
<tr>
<td>10-25</td>
<td>TID (9, 15, 21)</td>
<td>0, 2, 4, 6</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>BID (9, 21)</td>
<td>0, 2, 6, 8</td>
</tr>
<tr>
<td>&lt;10</td>
<td>QD (21)</td>
<td>0, 2, 6, 12</td>
</tr>
</tbody>
</table>

* QID, Four times per day; TID, three times per day; BID, two times per day; QD, one time per day.
received acyclovir and 51 received the placebo. These patients ranged in age from 15 to 68 years; median ages were 43 and 42 years in the acyclovir and placebo groups, respectively. The average weights were 70.0 kg for the acyclovir recipients and 66.8 kg for the placebo recipients.

A detailed analysis of clinical efficacy has been published previously (2). In brief, acyclovir significantly reduced the incidence of cytomegalovirus infection and disease after transplantation and significantly lengthened the time to the occurrence of these events. Four (7.5%) of 53 acyclovir recipients had cytomegalovirus disease, as did 15 (29%) of 51 placebo recipients (P = 0.002; two-tailed Fisher’s exact test). The greatest prophylactic benefit of acyclovir occurred in the subset of patients who were seronegative for cytomegalovirus before receiving a kidney from a seropositive donor. Among those patients, one of six in the acyclovir group compared with seven of seven in the placebo group developed cytomegalovirus disease. On the basis of the two-tailed Fisher’s exact test, acyclovir significantly reduced the incidence of the following signs and symptoms of cytomegalovirus disease: fever (P = 0.009), malaise (P = 0.009), pneumonia (P = 0.017), and viremia (P = 0.002).

Serum creatinine and WBC count data for both acyclovir and placebo recipients are given in Table 2. There was no difference between the acyclovir and placebo groups with respect to WBC counts either pretransplant or at study completion (P > 0.05; independent t test). The mean WBC counts declined for both groups from the pretransplant value to that at study completion, but this difference was not statistically significant (P > 0.05; paired t test), and the amount of the decline did not differ between groups (P > 0.05; independent t test).

The evaluation of the three mean serum creatinine measurements (pretransplant, study midpoint, and study completion) revealed a significant interaction between time and group (P < 0.008; ANOVA). The subsequent approach to the evaluation of creatinine data considered the acyclovir and placebo groups separately with respect to the changes in creatinine levels over time. Each observation period (pretransplant, study midpoint, and study completion) was considered individually for the comparison of creatinine levels between groups. Within both groups, creatinine levels at study midpoint and study completion were significantly lower than those pretransplant (P < 0.008; repeated-measures ANOVA followed by multiple comparisons with a Bonferroni adjustment). There was no difference between creatinine measurements at study midpoint and study completion within the acyclovir group (P > 0.008). However, these measurements were significantly different within the placebo group (P < 0.008). When each observation period was considered separately, there was no difference between the acyclovir and placebo recipients with respect to the creatinine measurements (P > 0.017; independent t test with the Bonferroni adjustment) at any of the three times.

As would be expected from the serum creatinine data, there were equal proportions of patients in the various dosing regimens at the time of study completion. In the acyclovir group, 43 (81%) patients received drug four times per day, 5 received drug three times per day, 4 received drug two times per day, and 1 received drug one time per day. Among placebo recipients, the corresponding values were 41 (80%), 6, 3, and 1.

**Pharmacokinetic analysis.** Overall plasma acyclovir concentrations ranged from 2 to 40 μmol/liter in the 185 plasma samples obtained from the 53 acyclovir recipients. The average maximum and minimum plasma acyclovir concentrations among all recipients were 13 and 7.4 μmol/liter, respectively (Tables 2 and 3). There was no difference in maximum and minimum concentrations between the acyclovir recipients who developed cytomegalovirus infection and/or disease and those who did not (P > 0.05; independent t test).

The relationship between the measured acyclovir concentrations and those predicted by the pharmacokinetic model was strong (Fig. 1). The line of best fit by least-squares

### Table 2. Laboratory safety in relation to acyclovir concentrations

<table>
<thead>
<tr>
<th>Patients and status (n)</th>
<th>Mean values for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC (10⁶ cells/liter)</td>
</tr>
<tr>
<td></td>
<td>Start</td>
</tr>
<tr>
<td>Acyclovir (53) (total)</td>
<td>8.2[a]</td>
</tr>
<tr>
<td>Cytomegalovirus infection and disease (19)</td>
<td>8.43</td>
</tr>
<tr>
<td>No cytomegalovirus infection or disease (34)</td>
<td>8.07</td>
</tr>
<tr>
<td>Placebo (53) (total)</td>
<td>7.9</td>
</tr>
<tr>
<td>Cytomegalovirus infection and disease (31)</td>
<td>8.10</td>
</tr>
<tr>
<td>No cytomegalovirus infection or disease (20)</td>
<td>7.57</td>
</tr>
</tbody>
</table>

*a Not significantly different from placebo recipients (P > 0.05; independent t test).

*b Not significantly different from placebo recipients (P > 0.017; ANOVA with multiple pairwise comparisons and a Bonferroni adjustment).

*c Significantly different from pretransplant value (P < 0.008; ANOVA with multiple comparisons and a Bonferroni adjustment).

*d Not significantly different from no cytomegalovirus infection or disease (P > 0.05; independent t test).

*e Significantly different from midpoint value (P < 0.008; ANOVA with multiple pairwise comparisons and a Bonferroni adjustment).

f NA, Not applicable.

### Table 3. Predicted and measured plasma acyclovir concentrations at days 5 to 7 posttransplantation

<table>
<thead>
<tr>
<th>Dosage regimen[a] (no. of patients)</th>
<th>Predicted (range)</th>
<th>Measured (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
<td>Minimum</td>
</tr>
<tr>
<td>QD (4)</td>
<td>15-23</td>
<td>7-15</td>
</tr>
<tr>
<td>BID (7)</td>
<td>17-25</td>
<td>9-17</td>
</tr>
<tr>
<td>TID (6)</td>
<td>14-22</td>
<td>7-15</td>
</tr>
<tr>
<td>QID (36)</td>
<td>8-16</td>
<td>2-10</td>
</tr>
</tbody>
</table>

*a Each dose was 800 mg. See Table 1, footnote a, for definitions.
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The regression was $y = -1.19 + 1.99x$, with a coefficient of determination of 0.88. Both the slope of the regression line and the intercept were significantly different from 0 ($P < 0.001$). The slope was also significantly different from 1 ($P < 0.001$). As assessed by measures of predictive performance, the overall precision (or root mean squared error) of the model predictions was 2.52 μmol/liter (95% confidence limits, 2.19 to 2.81 μmol/liter). The overall mean error or bias of the simulated values was 0.087 μmol/liter (95% confidence limits, −0.28 to 0.45 μmol/liter). Table 4 provides the precision and bias of the model predictions stratified on the basis of time of sample collection.

Virologic evaluation. Of the 50 viral isolates originally collected from the patients, 27 could be recovered from liquid nitrogen storage for in vitro susceptibility testing (Table 5). These isolates were obtained a mean time of 126 days posttransplant (standard deviation, 127 days). The mean IC$_{50}$ for cytomegalovirus isolates from 10 (55%) of 19 acyclovir recipients who shed virus after transplantation was 42.6 μmol/liter. This value was 48 μmol/liter for cytomegalovirus isolates from 17 (55%) of 31 placebo recipients who shed virus after transplantation. There was no difference in the IC$_{50}$ between the acyclovir and placebo recipients ($P > 0.05$; independent t test). IC$_{50}$ for 4 (15%) of the 27 isolates were <13 μmol/liter.

DISCUSSION

The present study further strengthens the rationale of using high-dose oral acyclovir to prevent cytomegalovirus disease after cadaveric renal transplantation. In addition to clinical efficacy (2), we showed that high-dose oral acyclovir did not produce leukopenia, adversely affect renal function, or alter the IC$_{50}$ for the viral isolates collected from the patients. Pharmacokinetic data also indicated that clinical benefit was obtained with average peak (13 μmol/liter) and trough (7 μmol/liter) concentrations well below the mean IC$_{50}$ for the cytomegalovirus isolates (47 μmol/liter) collected from the patients. For only 4 of the 27 isolates tested were the IC$_{50}$ below the peak plasma acyclovir concentra-

\begin{table}[ht]
\centering
\begin{tabular}{|c|c|c|}
\hline
Sample collection (h postdose) & Precision & Bias \\
\hline
0–2.49 & 3.38 (2.56–4.03) & 2.12 (1.33, 2.90) \\
2.5–4.49 & 2.02 (1.55–2.41) & −0.28 (−0.88, 0.32) \\
4.5–6.49 & 2.16 (1.47–2.68) & −0.62 (−1.41, 0.16) \\
6.5–10.49 & 2.27 (1.63–2.77) & −0.72 (−1.41, −0.03) \\
≥10.5 & 2.17 (0.57–3.01) & −1.08 (−1.98, −0.18) \\
All samples & 2.52 (2.19–2.81) & 0.087 (−0.28, 0.45) \\
\hline
\end{tabular}
\caption{Model performance}
\end{table}

\begin{itemize}
\item Values are reported as micromoles of acyclovir per liter (95% confidence limits).
\end{itemize}

This paradoxical observation invites further study of the mechanism of action of acyclovir against cytomegalovirus. We need to explain why the drug prevents cytomegalovirus disease but is of little value for its treatment. The data in this paper also call into question the applicability of present in vitro susceptibility testing methods to the design, conduct, and interpretation of clinical trials. Specifically, a comparison of the IC$_{50}$ and the measured concentrations in plasma could have led to the erroneous conclusion that this regimen would have been without clinical benefit.

There are several possible explanations for the results observed. Firstly, concentrations in plasma do not accurately reflect intracellular levels of acyclovir or its active metabolite, acyclovir triphosphate. Intracellular levels may be much higher than concomitantly measured concentrations in plasma. In addition, acyclovir triphosphate is a more potent inhibitor of cytomegalovirus DNA polymerase than is ganciclovir triphosphate (3). During the initial stages of viral replication, the intracellular load of replicating virus is low. Intracellular concentrations of acyclovir triphosphate may be sufficient to slow viral replication, thus forestalling disease expression and allowing the host to recover from the combined events of surgery and high-dose immunosuppressive therapy. Secondly, the in vitro system is a crude and inaccurate reflection of in vivo pharmacodynamics. Most in vitro susceptibility methods rely on the replication of cytomegalovirus in fibroblast cells. Cytomegalovirus replicates in vivo in leukocytes, epithelial cells, and endothelial cells, rather than fibroblasts. The metabolism of the drug in tissue culture fibroblasts is likely to be different from that in other types of cells. Finally, the in vitro system tests the effect of a drug on actively replicating virus. Different IC$_{50}$ might be obtained if a cell culture system that would examine the effect of a drug on the reactivation of latent virus could be developed.

High-dose oral acyclovir did not produce leukopenia in our study. This finding, in conjunction with those of other reports (5, 12, 15), provides convincing evidence that oral acyclovir has negligible myelosuppressive effects at concentrations used clinically.

Serum creatinine values decreased significantly over the study period among the acyclovir and placebo recipient groups. Acyclovir did not delay this decrease. Indeed, the acyclovir recipients reached their apparent posttransplant baseline creatinine concentration faster than did the placebo recipients. There was no difference ($P > 0.008$) between the study midpoint and study completion serum creatinine values in the acyclovir recipients, although the study completion value was significantly lower ($P < 0.008$) than the study midpoint value in the placebo recipients. This finding may have been related to an effect of cytomegalovirus infection.
or disease. The average serum creatinine value in the placebo recipients with cytomegalovirus infection or disease was 257 μmol/liter; this value was 180 μmol/liter in those without cytomegalovirus infection or disease. More importantly than this difference within the placebo group, however, was the lack of a significant difference for the pretransplant, study midpoint, or study completion measurements when the serum creatinine levels of the acyclovir recipients were compared with those of the placebo recipients. Thus, acyclovir did not have an adverse effect upon kidney function, as reflected by the serum creatinine levels in these renal allograft recipients.

Acyclovir is primarily excreted by the kidneys in an unchanged state and is poorly soluble in bladder urine (12). Intravenous administration of acyclovir has been associated with a reversible elevation in serum creatinine that most likely results from the crystallization of the drug in the renal collecting tubules leading to obstructive nephropathy (18). An elevation in serum creatinine can also occur with high doses of oral acyclovir, as we observed in one patient in our open-label pharmacokinetic study (8). It has been suggested that acyclovir may also have a synergistic nephrotoxic effect with agents such as cyclosporine (20). Our renal function data mitigate against this hypothesis because cyclosporine was a routine component of the immunosuppressive regimen for these renal allograft recipients.

The dose adjustment scheme developed for this trial allowed us to maintain plasma acyclovir concentrations within the range predicted by our pharmacokinetic model. Because the dosing strategy performed so well, the failure of acyclovir to prevent cytomegalovirus infection or disease in some subjects cannot be explained on the basis of different plasma drug concentrations. The fact that acyclovir had no adverse effect on renal function in this trial may also be an attribute of our dose adjustment scheme. The comparison of measured with model-predicted concentrations in plasma by the technique of predictive performance indicated that the model overpredicts near the time of peak concentration and underpredicts near the time of trough concentration; the degree of bias, however, should not represent a clinical concern. The overall precision and the precision for the respective sampling times were quite similar. The predictability of our model suggests that it provides an accurate characterization of the disposition of oral acyclovir in these patients. Furthermore, given that acyclovir elimination was defined as a function of CL\textsubscript{CR}, the relationship developed between pharmacokinetic parameters and patient characteristics is able to accommodate the wide fluctuations that develop in drug clearance as allograft function improves and stabilizes. The high degree of predictability of our model suggests that it may be useful in designing dosing strategies for other patient populations and in conducting concentration-controlled clinical trials. More accurate control of concentrations in plasma could likely be obtained by refining the a priori population values used in this study and then using adaptive control algorithms and Bayesian parameter estimations.

The development of resistance to antiviral agents has become a clinical reality (6, 7). In vitro susceptibility data from this 12-week prophylactic trial of high-dose oral acyclovir suggest that such exposure did not alter the relative susceptibilities of the cytomegalovirus isolates to the drug. However, further surveillance for the emergence of drug-resistant isolates must continue.

In summary, we previously demonstrated the efficacy of high-dose oral acyclovir for the prevention of cytomegalovirus disease in renal allograft recipients. The present report documents that the clinical benefit occurred despite peak and trough concentrations in plasma lower than the mean IC\textsubscript{50} for the patients viral isolates. Therapy did not produce leukopenia or delay the decrease in serum creatinine that accompanies successful transplantation of an allograft. The dose adjustment scheme developed for this trial contributed to the safe administration of drug to these patients. Finally, 12 weeks of high-dose oral acyclovir did not appear to alter the IC\textsubscript{50}s for the cytomegalovirus isolates collected from the patients.

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