

# Incidence of Cytomegalovirus Disease in Renal Transplantation Without Antilymphocyte Induction: Is Prophylaxis Necessary?

S.R. Smith, D.W. Butterly, P.J. Conlon, R.C. Harland, and O.E. Emovon

CYTOMEGALOVIRUS (CMV) remains an important contributor to morbidity in renal transplant recipients and may also be associated with both acute rejection<sup>1</sup> and chronic allograft failure.<sup>2</sup> Available pharmacologic approaches to prevent CMV disease are expensive and not universally effective. It remains unclear which regimen for CMV prophylaxis is most effective and which patients should receive it. Our center has had a relatively low rate of tissue-invasive CMV disease, perhaps because antilymphocyte therapy for induction immunosuppression is not used except for patients receiving a simultaneous kidney and pancreas transplant. To guide the use of CMV prophylaxis, we sought to quantify the incidence of CMV infection and its effect on graft survival in our renal transplant recipients.

## METHODS

In the period 1990 to 1993, 266 patients received a kidney transplant at our center. Patients who also received a pancreas transplant ( $n = 44$ ) and patients who died or whose grafts failed within 1 month of transplantation ( $n = 13$ ) were excluded from the analysis, leaving 209 patients to form the basis for this study. Patients were treated with cyclosporine beginning on the day of transplantation (maintenance dose 3 to 6 mg/kg per day adjusted by blood levels to lower half of therapeutic range), azathioprine (maintenance dose 2 mg/kg per day with downward adjustment for leukopenia), and prednisone (maintenance dose 0.14 mg/kg per day). No patient received induction antilymphocyte therapy. Episodes of acute rejection were generally confirmed by biopsy and treated with 3 to 5 pulses of intravenous methylprednisolone (1 g until August 1991, 500 mg thereafter) and anti-CD3 antibody for 7 to 14 days (5 mg IV) if needed. Seven patients received CMV prophylaxis with oral acyclovir.

## Statistical Analysis

Values of continuous demographic and clinical variables are expressed as the mean  $\pm$  standard deviation. Patients who died with a functioning renal allograft were considered graft losses. Nonparametric estimates of graft and patient survival were obtained by the Kaplan-Meier method.<sup>3</sup> Univariable and multivariable proportional hazards survival analyses were performed using Cox models.<sup>4</sup> The proportional hazards assumption for categorical variables and the assumption of linearity for continuous variables was explicitly tested and confirmed.<sup>5</sup> The interaction of donor CMV status with recipient CMV status was included in the multivariable model to test the hypothesis that graft survival is different depending on the combination of donor and recipient CMV exposure. The analyses

Table 1. Baseline Characteristics

N	209
Age	40 $\pm$ 12
Race	White 61% Black 39%
Donor source	Cadaver 72% Living donor 28%
Number HLA mismatches	2.7 $\pm$ 1.5
Diabetes mellitus	15%
Retransplant	11%
Donor CMV positive	38%
Recipient CMV positive	65%

were performed using the SAS software package (SAS Institute, Cary, NC).

CMV infection was diagnosed when any of the following was found: (a) isolation of the virus from a cultured specimen; (b) presence of characteristic CMV cytopathologic effect or positive immunohistochemistry in a biopsy specimen or bronchoalveolar lavage fluid; (c) fourfold rise in anti-CMV IgG titer; (d) anti-CMV IgM seroconversion. Tissue-invasive CMV disease was defined as: (a) hepatitis, CMV infection plus persistently elevated transaminase levels; (b) pneumonitis, bronchoalveolar lavage or transbronchial biopsy positive for CMV cytopathologic effect or positive immunohistochemistry; (c) gastrointestinal ulceration, biopsy specimen positive for CMV cytopathologic effect or positive immunohistochemistry.

## RESULTS

Baseline characteristics of the 209 patients are shown in Table 1. The prevalence of CMV positivity was much higher in the recipients than the donors. Overall 27 patients (13%) developed CMV infection. Of those with positive donor (D+) serology, 22% developed CMV infection versus 9% with negative donor (D-) serology ( $P < .01$ ). Negative recipient (R-) serology was more tightly associated with CMV infection as 29% of the R- group developed CMV infection versus 7% in the R+ group ( $P < .001$ ). Of the 27 patients who manifested CMV infection, only eight experienced tissue invasive disease, including four with hepatitis, three with pneumonitis, and one with gastrointestinal ulcer-

From the Department of Medicine, Division of Nephrology, Department of Surgery, Duke University Medical Center, Durham, North Carolina.

Address reprint requests to Stephen R. Smith, MD, DUMC Box 3014, Durham, NC 27710.

Table 2. CMV Outcomes

	N	CMV Infection	CMV Hospital Days	4-Year Graft Survival
All*	209	27 (13%)	210 (mean 1.0)	74%
D+/R+	47	2 (4%)	28 (mean 0.6)	70%
D+/R-	28	14 (50%)	106 (mean 3.8)	70%
D-/R+	80	7 (9%)	54 (mean 0.7)	76%
D-/R-	26	2 (8%)	7 (mean 0.3)	71%

\*Includes 28 patients with unknown donor or recipient CMV status.

ation. The remainder had a combination of cytopenia with fever and positive serology. Table 2 shows the rate of CMV infection, the number of hospital days attributable to CMV disease, and the 4-year graft survival by donor and recipient serologic status. Four of the eight cases of tissue invasive disease and 50% of all CMV infection occurred in the donor positive/recipient negative group. In addition, more than half of all hospital days attributable to CMV infection were for patients in the D+/R- group, although they made up only 13% of the patients in the study. Only 3 of the 27 patients who had CMV infection had been previously treated for acute rejection, while 6 of 27 had an episode of acute rejection in the 6 months following CMV infection. Cadaveric versus living donor transplantation, Black race, and an increase in the number of mismatched HLA antigens were significant predictors of poorer graft survival. In the multivariable analysis, only race and the number of HLA mismatches were independently predictive. Neither donor nor recipient CMV status provided significant information regarding 4-year graft survival, nor did the interaction of donor and recipient CMV status. Put differently, the graft survival rates in Table 2 for the four different serologic groups are not significantly different. Figure 1 shows that graft survival curves for the D+/R- group versus all the

other patients are nearly identical. Graft survival at 4 years was numerically worse in the 27 patients who had CMV infection (63%) versus the patients who did not have CMV infection (76%), although this difference was not statistically significant.

## DISCUSSION

To be able to apply a rational and cost-effective strategy for the prevention of CMV disease, we must first understand the extent of the problem. The burden of CMV disease was low in these patients not given antilymphocyte induction therapy except in the D+/R- group. It thus may be difficult to justify the use of expensive and only partially effective preventive measures such as CMV immune globulin,<sup>6</sup> acyclovir,<sup>7</sup> or ganciclovir<sup>8</sup> in the non-high-risk groups. A perfectly effective prophylactic strategy given to the D+/R- group only (28 patients or 13% of the total group) would prevent 106 hospital days and outpatient intravenous ganciclovir treatment for 14 patients for 2 weeks after the hospital stay. The wholesale cost in our locale of this treatment is roughly \$90,000, while prophylaxis for 28 patients using a 7-day course of intravenous ganciclovir followed by 3 months of oral ganciclovir costs \$105,000. If oral ganciclovir is used for a period of time after intravenous therapy for CMV infection, the cost to benefit ratio of the prophylactic strategy becomes more favorable. In any event, these data suggest that the cost to benefit ratio of prophylactic therapy is reasonable in the D+/R- group, but not in the low-risk groups in which six times as many patients would need to receive prophylactic therapy to prevent 13 episodes of infection.

It is important to note that patients treated with induction antilymphocyte therapy and those treated with mycophenolate mofetil rather than azathioprine may have higher rates of CMV infection. These observations should not be generalized to that group. Additionally, the more sensitive CMV antigen testing has replaced detection of CMV antibodies since the patients in the present study were transplanted so that the infection rates noted in this study are lower than would be detected today.<sup>9</sup> This study did not have the power to detect even a moderate difference in long-term graft survival among the different serologic groups, but there was not a suggestion that the D+/R- group has worse graft survival. Those with CMV infection did tend to have a lower rate of graft survival, although this was not significant. A larger and longer-term prospective

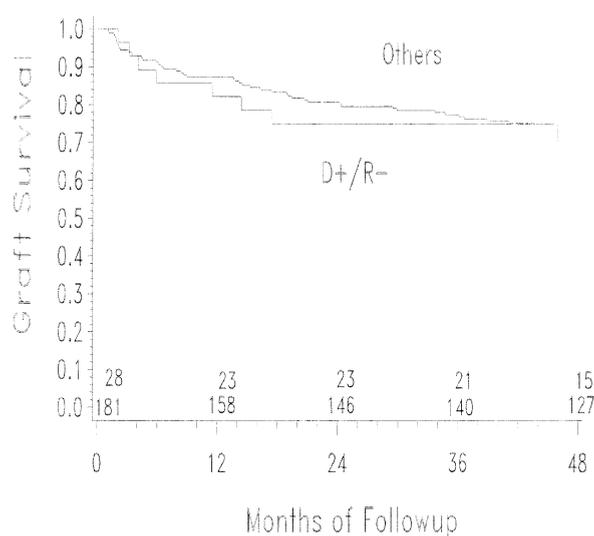


Fig 1. Kaplan Meier graft survival curves for the D+/R- group and for all other serologic groups combined. Number of patients being followed in each group is shown along the abscissa.

study would be required to determine whether CMV infection is indeed associated with a higher rate of chronic allograft failure.

In conclusion, the rate of CMV infection is low except in the D+/R- serologic group, and current regimens for chemoprophylaxis should not be routinely used in the non-high-risk groups. Prophylaxis of the D+/R- group is appropriate, although it would not be expected to result in major cost savings.

#### REFERENCES

1. Pouteil-Noble C, Ecochard R, Landrison G, et al: Transplantation 55:851, 1993
2. Rubin RH, Tolkoff-Rubin NE, Oliver D, et al: Transplantation 40:243, 1985
3. Kaplan EL, Meier P: J Am Stat Assoc 53:457, 1958
4. Cox DR: J Royal Statistical Soc B 34:187, 1972
5. Harrell FE, Lee KL, Pollock BG: J Nat Cancer Inst 80:1198, 1988
6. Snyderman DR, Werner BG, Heinze-Lacey B, et al: N Engl J Med 317:1049, 1987
7. Balfour HH, Chace BA, Stapleton JT, et al: N Engl J Med 320:1381, 1989
8. Hibberd PL, Tolkoff-Rubin NE, Conti D, et al: Ann Int Med 123:18, 1995
9. Murray BM, Amsterdam D, Gray V, et al: J Am Soc Nephrol 8:1448, 1997