

1/18/88 1163

## Ganciclovir for Invasive Cytomegalovirus Infection in Renal Allograft Recipients

R. Hrebinko, M.L. Jordan, J.S. Dummer, D.P. Hickey, R. Shapiro, C. Vivas, T.E. Starzl, R.L. Simmons, and T.R. Hakala

**C**YTOMEGALOVIRUS (CMV) is a major infectious complication of renal transplantation associated with significant morbidity and mortality.<sup>1-3</sup> Ganciclovir inhibits herpesvirus DNA polymerase<sup>4</sup> and has shown antiviral effects in vivo in several reported clinical studies.<sup>5-8</sup> We report our experience with the use of ganciclovir in treating tissue-invasive CMV infection following cadaver renal transplantation. The results suggest that ganciclovir is well tolerated and effective in arresting the progress of invasive CMV to life-threatening disease with little drug-related morbidity.

### MATERIALS AND METHODS

Of 419 cadaveric renal allograft recipients transplanted at our institution between November 1987 and September 1989, 36 (8.6%) (25 men and 11 women) developed invasive CMV infection (Table 1). Average patient age was  $42.1 \pm 11.5$  years (range, 18 to 71 years). Infection occurred following the primary transplant in 28 patients, after the second transplant in five, and after the third

transplant in three. In 16 of the 36 cases (44%), an allograft from a CMV-seropositive (IgG titer  $>1:20$ ) donor was transplanted into a seronegative recipient. Nine cases (25%) were seropositive to seropositive, five (14%) were seronegative to seropositive, and four (11%) were seronegative to seronegative. Serology was not available on two grafts, both of which were transplanted into seronegative recipients. All patients received a standard immunosuppressive regimen consisting of cyclosporine, prednisone, and azathioprine. Eighty-one percent of the patients with invasive CMV infections had been treated for rejection (prior to developing invasive CMV infections) with either increased steroid therapy ( $n = 18, 50\%$ ), OKT3 ( $n = 2, 6\%$ ), or steroids and OKT3 ( $n = 9, 25\%$ ). An additional eight patients had received prophylactic OKT3. Therefore, 19 patients (53%) received an average 13.2-day course (range, 6 to 19 days) of OKT3 before contracting CMV. All patients had received either "low-dose" (200 mg twice a day,  $n = 28$ ) or "high-dose" (up to 3,200 mg/d based on renal function,  $n = 8$ ) prophylactic acyclovir.<sup>9</sup> Thirty-six patients with clinically suspected CMV infection (unexplained fever  $>38.3$  for  $>2$  days,  $n = 3$  [8%]; leukopenia [white blood cell count  $<4,000$  mL],  $n = 21$  [58%]; thrombocytopenia ( $<100,000$ ,  $n = 6$  [17%]; diffuse pulmonary infiltrates,  $n = 9$  [25%]) were found to have invasive CMV a mean of 60.6 days (range, 28 to 133) after transplantation. Before starting ganciclovir, all 36 patients had tissue-invasive CMV infection documented by gastric or duodenal mucosal biopsy ( $n = 26, 72\%$ ), bronchoalveolar lavage ( $n = 14, 39\%$ ), allograft biopsy or nephrectomy ( $n = 6, 11\%$ ), or liver biopsy ( $n = 1, 3\%$ ). The biopsies were considered positive for CMV based on viral culture or histology/immunomicroscopy. Eleven patients (31%) had multiple sites involved. At the time of diagnosis, 27 patients (75%) had mild, six (17%) had moderate, and three (8%) had severe infection according to Peterson et al's criteria.<sup>10</sup> Ganciclovir (Syntex) was given at 2.5 mg/kg IV twice a day for a minimum of 7 days (mean,  $12.2 \pm 3.5$  days) and was continued until the patient was afebrile for 5 consecutive days. Dosage was adjusted according to the calculated creatinine clearance.

### RESULTS

Ganciclovir was well tolerated by all 36 patients. Side effects were limited to reversible neutropenia (white blood cell count  $<4,000$ /mL,  $n = 7$ ), thrombocytopenia ( $<100,000$ /mL,  $n = 2$ ), and rash ( $n = 1$ ), none of which required discontinuation of the drug. Serum creatinine

**Table 1. Clinical Characteristics of 36 Cadaveric Renal Transplant Recipients Who Subsequently Developed Invasive CMV Disease**

	n (%)
Patient age (y)	
Mean	$42.1 \pm 11.5$
Range	18-71
Sex	
Male	25 (69)
Female	11 (31)
Panel-reactive antibodies	
$<4\%$	20 (56)
4-80%	9 (25)
$>80\%$	7 (19)
Donor age (y)	
Median	45
Range	2-67
Donor recipient pretransplant CMV serology	
Positive/negative	16 (44)
Positive/positive	9 (25)
Negative/positive	5 (14)
Negative/negative	4 (11)
Treated for acute cellular rejection pre-CMV	
Yes	29 (81)
No	7 (19)
Type of treatment for acute cellular rejection (n = 29)	
High-dose steroids	18 (50)
OKT3	2 (6)
Steroids and OKT3	9 (25)

From the Division of Urologic Surgery/Renal Transplantation, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Address reprint requests to Dr R. Hrebinko, Division of Urologic Surgery/Renal Transplantation, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

© 1991 by Appleton & Lange  
0041-1345/91/\$3.00/+0

(SCr) was unaltered by ganciclovir in those patients with functioning grafts (mean SCr,  $4.1 \pm 1.6$  mg/dL before and  $3.8 \pm 1.9$  after treatment). Clinical improvement occurred in all 36 patients following the initial course of treatment. Seven patients had persistent asymptomatic viruria and two had recurrent invasive disease (allograft in one, stomach in one) eradicated with a second course of ganciclovir 60 and 50 days, respectively, after the first course. There was no correlation between CMV severity and recipient age ( $>$  or  $<$ 45 years), time to CMV onset after transplant, prior rejection, OKT3 use, or use of low-dose versus high-dose prophylactic acyclovir ( $P > .1$ ). Seventeen of 27 (63%) grafts are still functioning (mean follow-up, 12.7 months) in those patients originally having mild disease, three of six grafts (50%) in those with moderate disease, and zero of three (0%) in those with severe disease ( $P < .02$ ).

There were 17 graft losses in this series. Four grafts were already lost at the onset of CMV infection, owing to primary graft nonfunction ( $n = 2$ ) and chronic rejection ( $n = 2$ ). The remaining 11 grafts were lost from 10 days to 16 months (median, 5 weeks) following invasive CMV. One patient underwent allograft nephrectomy after immunosuppression was withheld for transverse myelitis 2 months after treatment with ganciclovir. A second patient lost his graft to rejection while immunosuppression was withheld for acute pancreatitis (with a negative CMV workup) 2 months after treatment. Another patient had recurrent oxalosis and graft failure 1 year after ganciclovir. The remaining grafts were lost to rejection. Of those patients that developed CMV without prior rejection, six of seven (86%) still have functioning allografts, while only 13 of 29 (45%) are still functioning in patients treated for rejection before CMV infection occurred. At mean follow-up of 12.7 months, the 1-year actuarial patient survival is 100%. The 1-year actuarial graft survival is  $55\% \pm 8.3\%$ , with a mean SCr of 2.5 mg/dL (range, 1.2 to 4.6 mg/dL). The 1-year actuarial patient and graft survival rates for the entire group of cadaveric renal transplants ( $n = 419$ ) done at our institution during the same time period are  $94.9\% \pm 1.2\%$  and  $79.7\% \pm 2.1\%$ , respectively.

## DISCUSSION

Previous studies have recommended the use of ganciclovir only for life- or sight-threatening CMV infection.<sup>5-8</sup> In the current series, ganciclovir was started as soon as the diagnosis of tissue-invasive CMV was made. With this approach, 100% patient survival was achieved with only

two cases of recurrent CMV infection, both of which responded to a second course of ganciclovir. The graft survival of 55% reported here is similar to that reported previously in CMV-infected patients not treated with ganciclovir.<sup>1-3,10</sup> Eighty-one percent of the patients in our series experienced at least one rejection episode prior to CMV. Thus, this group was at high risk for graft loss even had they not acquired CMV. In addition, our patients all had histologically proven disease and might be best categorized separate from those patients included in other studies in which the diagnosis was largely based on seroconversion and peripheral cultures.<sup>1-3,10</sup>

During the course of this study, ganciclovir was considered experimental at our institution and was available only on a compassionate release basis to patients with biopsy-proven, invasive CMV infections. Because the drug appears to be effective with infrequent side effects, we now start ganciclovir if there is a high index of suspicion for CMV based on history, physical examination, and serology, and continue therapy based on positive cultures and/or tissue biopsy and clinical parameters. We continue to use an initial 7-day course of ganciclovir and extend the treatment for prolonged fever or persistent signs and symptoms of CMV infection. The limited toxicity and prompt eradication of symptomatic disease observed in this series indicate that ganciclovir is a safe and effective form of therapy in renal transplant recipients with tissue-invasive CMV infection.

## REFERENCES

1. Simmons RL, Matas AJ, Rattazzi LC, et al: *Surgery* 82:537, 1977
2. Fryd DS, Peterson PK, Ferguson RM, et al: *Transplantation* 30:436, 1980
3. Marker SC, Howard RJ, Simmons RL, et al: *Surgery* 89:660, 1981
4. Field AK, Davies ME, DeWitt C, et al: *Natl Acad Sci USA* 80:4139, 1983
5. Collaborative DHPG Treatment Study Group: *N Engl J Med* 314:301, 1986
6. Snyderman DR: *Rev Infect Dis* 10:S554, 1988 (suppl)
7. Paya CV, Hermans PE, Smith TF, et al: *Transplantation* 46:229, 1988
8. Harbison MA, DeGirolami PC, Jenkins RL, et al: *Transplantation* 46:82, 1988
9. Balfour HH, Chace BA, Stapleton JT, et al: *N Engl J Med* 320:1381, 1989
10. Peterson PK, Balfour HH, Marker SC, et al: *Medicine* 59:283, 1980