

## VALACYCLOVIR FOR THE PREVENTION OF CYTOMEGALOVIRUS DISEASE AFTER RENAL TRANSPLANTATION

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### ABSTRACT

**Background** Cytomegalovirus (CMV) disease is a major complication of organ transplantation. We hypothesized that prophylactic treatment with valacyclovir would reduce the risk of CMV disease.

**Methods** A total of 208 CMV-negative recipients of a kidney from a seropositive donor and 408 CMV-positive recipients were randomly assigned to receive either 2 g of valacyclovir or placebo orally four times daily for 90 days after transplantation, with the dose adjusted according to renal function. The primary end point was laboratory-confirmed CMV disease in the first six months after transplantation.

**Results** Treatment with valacyclovir reduced the incidence or delayed the onset of CMV disease in both the seronegative patients ( $P < 0.001$ ) and the seropositive patients ( $P = 0.03$ ). Among the seronegative patients, the incidence of CMV disease 90 days after transplantation was 45 percent among placebo recipients and 3 percent among valacyclovir recipients. Among the seropositive patients, the respective values were 6 percent and 0 percent. At six months, the incidence of CMV disease was 45 percent among seronegative recipients of placebo and 16 percent among seronegative recipients of valacyclovir; it was 6 percent among seropositive placebo recipients and 1 percent among seropositive valacyclovir recipients. At six months, the rate of biopsy-confirmed acute graft rejection in the seronegative group was 52 percent among placebo recipients and 26 percent among valacyclovir recipients ( $P = 0.001$ ). Treatment with valacyclovir also decreased the rates of CMV viremia and viruria, herpes simplex virus disease, and the use of inpatient medical resources. Hallucinations and confusion were more common with valacyclovir treatment, but these events were not severe or treatment limiting. The rates of other adverse events were similar among the groups.

**Conclusions** Prophylactic treatment with valacyclovir is a safe and effective way to prevent CMV disease after renal transplantation. (N Engl J Med 1999; 340:1462-70.)

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**C**YTOMEGALOVIRUS (CMV) is the leading cause of infectious complications after organ transplantation and has been implicated as a cause of graft rejection. In renal transplantation, the risk of CMV disease is highest in the second month after transplantation and is largely determined by the serologic status of the donor and

the recipient for CMV.<sup>1,2</sup> Recipients who are CMV-negative and who receive a transplant from a CMV-positive donor are at highest risk for disease (40 to 73 percent), CMV-positive recipients are at moderate risk (6 to 38 percent), and CMV-negative recipients who receive a transplant from a CMV-negative donor are at the lowest risk (<1 percent).<sup>1-13</sup> The heavy use of immunosuppressants also increases the risk.<sup>1,14-16</sup>

Manifestations of CMV disease range from a mild viral syndrome to severe end-organ involvement (e.g., pneumonitis, hepatitis, and gastrointestinal disease).<sup>1,9,10</sup> Indirect evidence identifies CMV as a risk factor for acute graft rejection,<sup>1,11,12</sup> which is correlated with poor long-term graft survival.<sup>13-15</sup> Through its effects on the immune system, CMV also increases the risk of fungal and other superinfections in transplant recipients.<sup>1,2,16</sup> Historically, the mortality rate from untreated organ-invasive CMV disease was 65 percent.<sup>17</sup> The availability of effective therapy<sup>18-20</sup> has reduced this figure significantly among renal-transplant recipients,<sup>8,21</sup> but the increased morbidity and overall costs of transplantation associated with CMV persist.<sup>10,22</sup> High-dose oral acyclovir is well tolerated, but prophylactic use of acyclovir has not gained wide acceptance<sup>9</sup> despite the fact that it reduces the risk of CMV disease among recipients of renal<sup>23-25</sup> and other solid-organ<sup>26-28</sup> transplants. The limited efficacy of acyclovir may be a result of its low oral bioavailability and the low in vitro sensitivity of CMV to the drug.<sup>29,30</sup> Valacyclovir, a prodrug, has a higher level of bioavailability,<sup>31</sup> thus providing potentially effective oral prophylaxis. We conducted a randomized, double-blind, placebo-controlled study to test whether

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valacyclovir is safe and efficacious as prophylaxis against CMV disease in recipients of renal allografts from cadaveric donors.

## METHODS

### Study Design

The study was placebo-controlled, since there was no accepted, standard regimen of prophylaxis at the inception of the study. The institutional review boards or ethics committees at 27 centers in the United States and Europe approved the study, which followed Good Clinical Practices guidelines. Patients who had received a renal transplant from a cadaveric donor and who were at least 13 years of age were eligible for enrollment once they or, in the case of children, their parents or guardians had provided written informed consent. CMV-negative patients who received a transplant from a CMV-negative donor, those with active herpesvirus infection, and those who received other antiviral agents within two weeks before transplantation were excluded.

Patients were randomly assigned in a 1:1 ratio according to study site to receive either 2 g of valacyclovir (Valtrex or Zelitrex, Glaxo Wellcome) four times per day or matching placebo. The dose was adjusted on the basis of renal function: patients whose creatinine clearance exceeded 75 ml per minute received the 8-g dose, those with a creatinine clearance of 51 to 75 ml per minute received 6 g per day (1.5 g four times daily), those with a creatinine clearance of 26 to 50 ml per minute received 4.5 g per day (1.5 g three times daily), those with a creatinine clearance of 10 to 25 ml per minute received 3 g per day (1.5 g twice daily), and those who had a creatinine clearance of less than 10 ml per minute or who were on dialysis received 1.5 g per day.

The CMV status of the patients was determined by enzyme immunoassay or radioimmunoassay. Prophylaxis was initiated within 72 hours after transplantation and continued for 90 days. The efficacy of treatment was assessed for six months, and the safety of treatment and survival of patients and allografts were assessed for one year. Anti-CMV therapy could be initiated at any time during the prophylactic period according to the standard practice of the participating institutions.

The primary end point was the occurrence of CMV disease, as defined below. Active CMV infection was detected by conventional or shell-vial surveillance cultures of blood and urine obtained from all patients at entry into the study, weekly during hospitalization for transplantation and all subsequent hospitalizations, every other week through month 3, and then monthly for the next three months. Viremia was not confirmed by nonculture methods (e.g., antigen detection or polymerase-chain-reaction testing).

Secondary end points were rejection, function (a graft was considered functional if the creatinine clearance was at least 10 ml per minute or there was no need for dialysis), and survival of the graft; the occurrence of herpes simplex disease, varicella-zoster disease, or other infections with any non-herpesvirus; survival; and medical-resource use. Safety was monitored by hematologic and chemical evaluations and urinalysis, and adverse events were reported. The results of surveillance cultures were revealed only if deemed essential to patient care.

### Definition of CMV Disease

Presumptive CMV disease was defined so as to allow the diagnosis to be consistent at all study sites. CMV disease was presumed to be present if a patient had had a fever for at least three consecutive days plus one or more of the following, with other causes ruled out: leukopenia, thrombocytopenia, pneumonitis, gastrointestinal disease, hepatitis, ophthalmologically detected retinitis, or other clinically significant manifestations such as nephritis or constitutional symptoms (e.g., myalgia). Alternatively, CMV disease was presumed to be present in the event of any illness that was responsive solely to treatment with ganciclovir or foscarnet.

Cases of CMV disease were confirmed on the basis of laboratory analysis of specimens obtained within seven days after the diagno-

sis. All reported episodes of CMV disease were evaluated in a blinded fashion by an end-points committee chaired by an independent expert, and only episodes ratified by this panel were analyzed.

### Statistical Analysis

We estimated that 172 seronegative patients and 320 seropositive patients would be needed to provide the study with a power of 80 percent to detect a reduction in the incidence of CMV disease from 40 percent to 20 percent in the seronegative group and from 8 percent to 1 percent in the seropositive group at the 0.05 level with a two-tailed test. All variables except medical-resource use were analyzed according to the intention-to-treat principle (i.e., all patients who underwent randomization were included). All events were calculated from the date of randomization to the time of an event or to the end of follow-up for patients who did not reach an end point, and differences between treatments were determined by Cox proportional-hazards regression analysis,<sup>32</sup> after adjustment for country as a background covariate. The rates of the most frequent adverse events were compared between treatment groups by Fisher's exact test. Patients who discontinued treatment prematurely were still included in the analysis of the primary end point (efficacy). Data on all patients who did not reach an end point were censored at the end of follow-up. Hazard ratios (relative risks) and 95 percent confidence intervals were calculated as measures of differences between treatments. Kaplan-Meier estimates of incidence were calculated. Mean use of medical resources was compared with the use of Student's *t*-test. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. There were no interim analyses of efficacy.

## RESULTS

From July 7, 1992, to December 11, 1996, 208 patients were assigned to the seronegative group (seropositive donor, seronegative recipient) and 408 patients to the seropositive group (seronegative or seropositive donor, seropositive recipient). The seronegative group included five inadvertently randomized patients who were CMV-negative and who had received a transplant from a CMV-negative donor; all five were included in the intention-to-treat analyses. There was a median of 5.5 seronegative patients per site (range, 1 to 23) and a median of 20 seropositive patients per site (range, 2 to 42). The characteristics of the treatment groups were well balanced at base line (except in terms of sex in the seronegative group assigned to receive valacyclovir) (Table 1).

Seronegative patients received a mean of 5.3 g of valacyclovir per day or 4.7 g of placebo per day, and seropositive patients received a mean of 4.7 g of valacyclovir per day or 4.8 g of placebo per day. Compliance with the treatment regimen was similar in the groups: among seronegative patients, it was 89 percent in the valacyclovir group and 88 percent in the placebo group, and among seropositive patients, it was 84 percent and 87 percent, respectively. Among the seronegative patients, fewer patients in the valacyclovir group than in the placebo group prematurely discontinued treatment or did not complete follow-up (16 percent vs. 29 percent). The proportions of seronegative patients who withdrew because of an adverse event were similar (7 percent vs. 8 percent). Among the seropositive patients, the proportions who prematurely discontinued treatment or did not com-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	SERONEGATIVE GROUP		SEROPOSITIVE GROUP	
	VALACYCLOVIR (N=102)	PLACEBO (N=106)	VALACYCLOVIR (N=204)	PLACEBO (N=204)
Age — yr	43.6±13.1	40.3±14.2	45.1±13.0	45.6±13.5
Sex — %				
Male	75	59	60	61
Female	25	41	40	39
Race — %				
Black	8	10	16	20
White	91	90	68	66
Other	0†	0	16	14
Indication for transplantation — no. (%)				
Chronic glomerulonephritis	29 (28)	26 (25)	48 (24)	42 (21)
Diabetic nephrosclerosis	11 (11)	11 (10)	20 (10)	24 (12)
Hypertensive nephrosclerosis	9 (9)	7 (7)	30 (15)	33 (16)
Polycystic kidney disease	7 (7)	9 (8)	27 (13)	24 (12)
Pylonephritis	7 (7)	11 (10)	7 (3)	13 (6)
Rejection of previous graft	8 (8)	4 (4)	11 (5)	9 (4)
Other‡	31 (30)	38 (36)	61 (30)	59 (29)
No. of HLA-antigen mismatches	2.7±1.4	3.1±1.4	3.2±1.4	3.2±1.4
Previous renal transplantation — no. (%)	11 (11)	12 (11)	40 (20)	39 (19)
Induction therapy				
Monoclonal antibodies§	11 (11)	11 (10)	41 (20)	39 (19)
Polyclonal antibodies¶	42 (41)	48 (45)	78 (38)	83 (41)
Primary immunosuppression — no. (%)				
Induction therapy plus cyclosporine-based triple-drug regimen	45 (44)	53 (50)	107 (52)**	106 (52)
Cyclosporine-based triple-drug regimen	40 (39)	36 (34)	70 (34)	67 (33)
Induction therapy plus two-drug regimen	3 (3)	3 (3)	6 (3)	7 (3)
Two-drug regimen	9 (9)	10 (9)	19 (9)	22 (11)
Mycophenolate mofetil plus one of the above regimens	4 (4)	3 (3)	0	0
Unknown††	1 (1)	1 (1)	2 (1)	2 (1)

\*Plus-minus values are means ±SD.

†The race of one patient was not recorded.

‡Other indications included tubulointerstitial nephrosclerosis, vascular or atheroembolic disease, and idiopathic disease.

§Muromonab-CD3 was given.

¶Antilymphocyte globulin or antithymocyte globulin was given.

||This group included five patients who received tacrolimus.

\*\*This group included one patient who received tacrolimus.

††Patients in this category were withdrawn from the study one or two days after randomization, and their immunosuppressant regimen was not recorded.

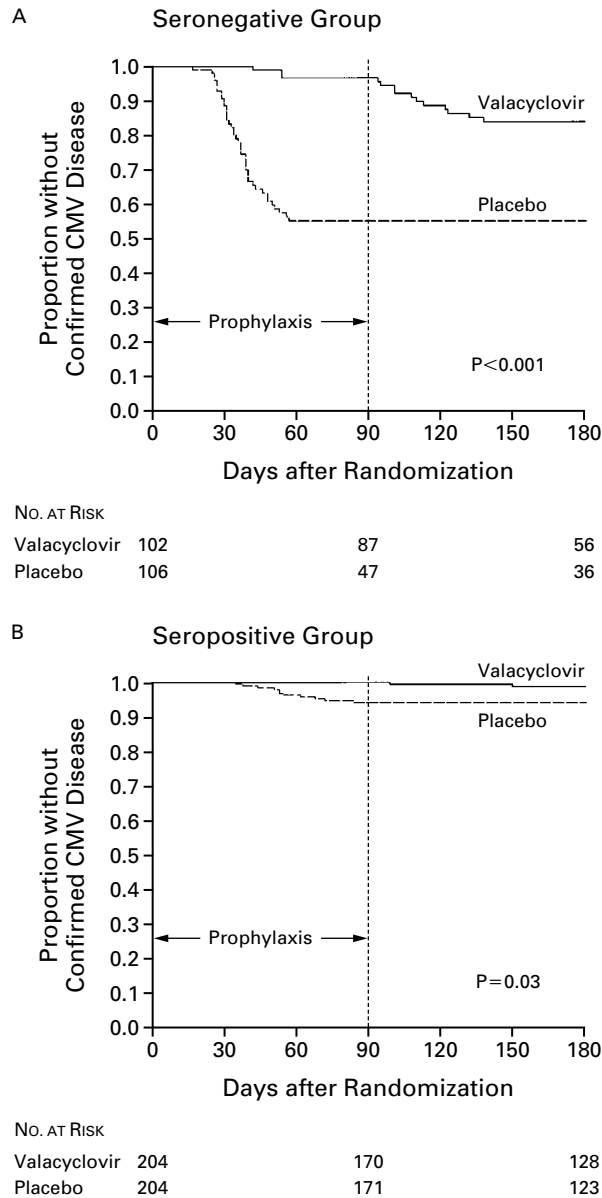
plete follow-up were similar in the valacyclovir group and the placebo group (19 percent vs. 17 percent), with 5 percent and 3 percent, respectively, withdrawing because of an adverse event.

### CMV Disease

Valacyclovir significantly reduced the incidence of, or increased the time to, laboratory-confirmed CMV disease. Figure 1 shows the proportions of patients who were free of confirmed CMV disease at 90 and 180 days. During the 90-day period of prophylaxis, the incidence of disease among the seronegative patients was 45 percent in the placebo group and 3 percent in the valacyclovir group; the respective values for the seropositive patients were 6 percent and 0 percent. The incidence of disease at six months among

the seronegative patients was 16 percent for valacyclovir recipients and 45 percent for placebo recipients. Among the seropositive patients, the incidence of disease at six months was 1 percent for valacyclovir recipients and 6 percent for placebo recipients. Thus, during the six-month study, the risk of CMV disease was 78 percent lower among seronegative patients who received valacyclovir (hazard ratio, 0.22; 95 percent confidence interval, 0.12 to 0.40;  $P < 0.001$ ) and 82 percent lower among seropositive patients who received the drug (hazard ratio, 0.18; 95 percent confidence interval, 0.04 to 0.83;  $P = 0.03$ ).

In the seronegative group, the incidence of CMV end-organ disease at six months was 25 percent among placebo recipients and 4 percent among valacyclovir recipients (hazard ratio, 0.15; 95 percent confidence



**Figure 1.** Kaplan–Meier Estimates of the Proportions of Patients without Laboratory-Confirmed CMV Disease in the Seronegative Group (Panel A) and the Seropositive Group (Panel B).

interval, 0.04 to 0.30;  $P < 0.001$ ). End-organ disease was reported in 4 seronegative recipients of valacyclovir (2 had pneumonitis, 1 had gastroenteritis, and 1 had hepatitis) and 27 seronegative recipients of placebo (7 had pneumonitis, 6 had gastroenteritis, 19 had hepatitis, 6 had nephropathy, and 2 had other manifestations); some patients had more than one manifestation). Recurrent disease was seen in two seronegative recipients of valacyclovir and in five seronegative placebo recipients. No seropositive recipient of valacyclovir had end-organ disease, as compared

with four seropositive recipients of placebo. No seropositive patient had more than one episode of CMV disease. One death (that of a seronegative patient who was receiving placebo) was attributed to CMV disease.

In both groups overall compliance with the protocol was greater among patients who received valacyclovir (75 percent in the seronegative group and 81 percent in the seropositive group) than among those who received placebo (60 percent and 70 percent, respectively). The results of an efficacy analysis that excluded all noncompliant patients did not differ significantly from the results of the intention-to-treat analysis.

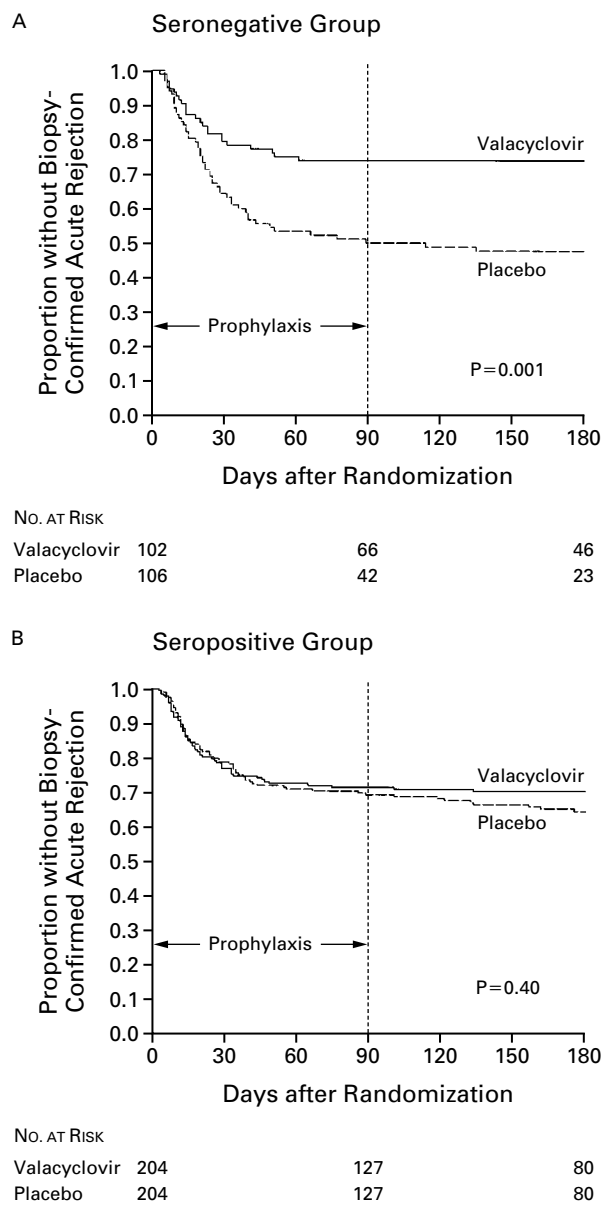
Analysis of the patients in whom prophylaxis failed did not indicate that these patients received increased levels of immunosuppression. Most of these patients had other causes of fever (e.g., sepsis, urinary tract infection, and wound infection).

#### Active CMV Infection

Valacyclovir significantly reduced the incidence of active CMV infection. In the seronegative group, the incidence of CMV viremia at six months was 20 percent among valacyclovir recipients and 45 percent among placebo recipients. In the seropositive group, the corresponding values were 14 percent and 35 percent. The six-month incidence of CMV viruria was 44 percent among seronegative recipients of valacyclovir and 56 percent among seronegative recipients of placebo. In the seropositive group, the corresponding values were 33 percent and 60 percent. Thus, the risk of viruria was 51 percent lower among seronegative patients who received valacyclovir (hazard ratio, 0.49; 95 percent confidence interval, 0.32 to 0.76;  $P = 0.001$ ) and 68 percent lower among seropositive patients who received the drug (hazard ratio, 0.32; 95 percent confidence interval, 0.24 to 0.44;  $P < 0.001$ ).

#### Graft Rejection

The risk of acute graft rejection was significantly reduced among seronegative recipients of valacyclovir (Fig. 2). The rate of biopsy-confirmed acute rejection at six months was 26 percent among seronegative valacyclovir recipients and 52 percent among seronegative placebo recipients (Table 2 and Fig. 2). The corresponding values for clinical acute rejection were 39 percent and 61 percent. Thus, at six months in the seronegative group, the rate of biopsy-confirmed cases was 57 percent lower (hazard ratio, 0.43; 95 percent confidence interval, 0.27 to 0.70;  $P = 0.001$ ) and the rate of clinical acute rejection was 45 percent lower (hazard ratio, 0.55; 95 percent confidence interval, 0.37 to 0.83;  $P = 0.004$ ) among those who received valacyclovir. In the seropositive group, there was no statistically significant difference in the incidence of biopsy-confirmed acute rejection (30 per-



**Figure 2.** Kaplan–Meier Estimates of the Proportions of Patients without Biopsy-Confirmed Acute Graft Rejection in the Seronegative Group (Panel A) and the Seropositive Group (Panel B).

cent among valacyclovir recipients and 36 percent among placebo recipients,  $P=0.40$ ). A trend toward a lower risk of clinical rejection was observed in this group (37 percent among valacyclovir recipients and 48 percent among placebo recipients; hazard ratio, 0.75; 95 percent confidence interval, 0.55 to 1.03;  $P=0.07$ ). Fewer seronegative recipients of valacyclovir than of placebo required antilymphocyte-antibody therapy. This difference was not seen in the seropositive group (Table 2).

There was no significant difference in the rate of chronic graft rejection in the first six months or in one-year graft survival. Similar proportions of patients had functional grafts immediately after transplantation (range, 71 to 76 percent) and at the time of the last full assessment (range, 87 to 90 percent; median time after transplantation, 180 to 183 days). Serum creatinine values were similar in the seronegative and seropositive groups at base line and one, two, and three months after transplantation.

**Other Herpesvirus Diseases**

Valacyclovir significantly reduced the risk of clinical herpes simplex virus disease in seronegative patients (hazard ratio, 0.33; 95 percent confidence interval, 0.15 to 0.74;  $P<0.01$ ) and seropositive patients (hazard ratio, 0.16; 95 percent confidence interval, 0.09 to 0.30;  $P<0.001$ ). In the seronegative group, the incidence at six months was 9 percent among valacyclovir recipients and 24 percent among placebo recipients. In the seropositive group, the corresponding values were 8 percent and 34 percent. Varicella-zoster virus disease developed in two seronegative recipients of placebo (2 percent) and nine seropositive recipients (4 percent), whereas it did not develop in any recipients of valacyclovir.

**Other Infections**

The risk of non-herpesvirus infections was significantly reduced in seronegative recipients of valacyclovir (hazard ratio, 0.51; 95 percent confidence interval, 0.35 to 0.74;  $P=0.001$ ). The incidence of infection at six months was 53 percent among valacyclovir recipients and 71 percent among controls. In the seronegative group, recipients of valacyclovir had a lower rate of candida infections (10 percent vs. 22 percent,  $P=0.04$ ) and staphylococcus infections (12 percent vs. 21 percent,  $P=0.07$ ) than the placebo recipients. There was no significant difference between groups in the incidence of infection in the seropositive group.

**Survival**

Twenty-two deaths occurred during the 12-month follow-up. In the seronegative group, the 12-month survival rate was 95 percent among valacyclovir recipients and 96 percent among placebo recipients. In the seropositive group, the respective rates were 99 percent and 95 percent. There were no major differences in the causes of death; the majority involved cardiovascular disorders or infectious complications. No deaths were attributed to treatment.

**Use of Medical Resources**

Seronegative patients who received valacyclovir had significantly fewer admissions to the hospital than seronegative patients who received placebo (2.0 vs. 2.3,  $P=0.04$ ), fewer days of hospitalization (26.9

**TABLE 2.** INCIDENCE OF ACUTE GRAFT REJECTION AND ANTILYMPHOCYTE-ANTIBODY THERAPY AT SIX MONTHS.

CHARACTERISTIC	SERONEGATIVE GROUP			SEROPOSITIVE GROUP		
	VALACYCLOVIR (N=102)	PLACEBO (N=106)	P VALUE*	VALACYCLOVIR (N=204)	PLACEBO (N=204)	P VALUE*
Acute rejection — no. (%)†						
Biopsy-confirmed	27 (26)	55 (52)	0.001	61 (30)	73 (36)	0.40
Clinical	40 (39)	65 (61)	0.004	75 (37)	98 (48)	0.07
Days to onset of biopsy-confirmed acute rejection — range	3–240	5–182		3–183	3–237	
Treatment with antilymphocyte antibodies — no. (%)‡	15 (15)	29 (27)		42 (21)	45 (22)	
Monoclonal antibodies§	5 (5)	17 (16)		21 (10)	28 (14)	
Polyclonal antibodies¶	11 (11)	14 (13)		24 (12)	20 (10)	

\*P values were calculated by Cox proportional-hazards model according to the intention-to-treat principle.

†Kaplan–Meier estimates are given. Clinical acute graft rejection was defined on the basis of clinical and biochemical signs and symptoms suggestive of acute graft rejection.

‡Antilymphocyte-antibody therapy was defined as treatment started more than seven days after randomization. Some patients received more than one type of preparation.

§Muromonab-CD3 was given.

¶Antilymphocyte globulin or antithymocyte globulin was given.

vs. 32.4,  $P=0.04$ ), fewer special laboratory procedures performed ( $P=0.007$ ) and fewer routine laboratory procedures performed ( $P<0.01$ ), and fewer days of ganciclovir treatment ( $P<0.01$ ). Seropositive patients who received valacyclovir had significantly fewer admissions to the hospital than seropositive patients who received placebo (1.8 vs. 2.1,  $P=0.01$ ) and fewer days of ganciclovir treatment ( $P=0.02$ ). The use of resources in the outpatient setting was similar among the seronegative and seropositive patients and according to treatment.

**Safety**

The overall rates of adverse events in the first six months after transplantation were similar in the two groups. The rates of adverse events according to body system were also similar with the exception of those pertaining to the central nervous system (31 percent among seronegative valacyclovir recipients and 23 percent among seronegative placebo recipients; respective values in the seropositive group, 31 percent and 20 percent). The only events that occurred more frequently among valacyclovir recipients than among placebo recipients were hallucinations ( $P=0.03$  in the seronegative group and  $P<0.001$  in the seropositive group) and confusion ( $P=0.02$  in the seropositive group) (Table 3). The majority of the central nervous system events among valacyclovir recipients, which also included abnormalities in thinking, agitation, and depression (rate,  $\leq 4$  percent for all three), were mild, were not treatment limiting, and were reversible with adjustments in the study medication. Thrombotic microangiopathy was reported in one seropositive val-

**TABLE 3.** MOST FREQUENT ADVERSE EVENTS.\*

EVENT	SERONEGATIVE GROUP		SEROPOSITIVE GROUP	
	VALACYCLOVIR (N=102)	PLACEBO (N=106)	VALACYCLOVIR (N=204)	PLACEBO (N=204)
	number of patients (percent)			
Hypertension	16 (16)	16 (15)	18 (9)	9 (4)
Anemia	14 (14)	16 (15)	22 (11)	21 (10)
Leukopenia	14 (14)	11 (10)	12 (6)	14 (7)
Fever	13 (13)	14 (13)	12 (6)	19 (9)
Abdominal pain	13 (13)	13 (12)	13 (6)	21 (10)
Diarrhea	12 (12)	16 (15)	15 (7)	20 (10)
Headache	8 (8)	14 (13)	21 (10)	19 (9)
Nausea	9 (9)	6 (6)	16 (8)	16 (8)
Peripheral edema	10 (10)	12 (11)	13 (6)	17 (8)
Vomiting	7 (7)	9 (8)	18 (9)	14 (7)
Dyspnea	9 (9)	7 (7)	13 (6)	7 (3)
Hallucination	5 (5)	0†	21 (10)	3 (1)‡
Confusion	6 (6)	2 (2)	16 (8)	5 (2)§
Constipation	6 (6)	4 (4)	15 (7)	12 (6)
Pain	4 (4)	11 (10)	18 (9)	10 (5)
Insomnia	7 (7)	4 (4)	10 (5)	6 (3)
Edema	10 (10)	6 (6)	3 (1)	8 (4)
Hypophosphatemia	7 (7)	5 (5)	3 (1)	5 (2)

\*The 12 commonest events in the seronegative group, the seropositive group, and each valacyclovir group are included. P values were calculated by Fisher's exact test.

† $P=0.03$  for the comparison with the seronegative valacyclovir group.

‡ $P<0.001$  for the comparison with the seropositive valacyclovir group.

§ $P=0.02$  for the comparison with the seropositive valacyclovir group.

acyclovir recipient and in one seronegative and one seropositive placebo patient, and it was not attributable to treatment. There were no clinically important differences with regard to the distribution or change from base line of any laboratory measurements, including serum creatinine.

### DISCUSSION

We found that prophylactic treatment with valacyclovir reduced the risk of CMV disease and graft rejection after cadaveric renal transplantation, with minimal adverse effects. CMV disease occurred during the prophylactic period in only 3 percent of seronegative valacyclovir recipients and in no seropositive recipients. The incidence of end-organ disease was also lower, suggesting that prophylactic valacyclovir prevented viral dissemination or ameliorated the disease. Such a mechanism is consistent with the finding of low rates of CMV viremia and viruria among valacyclovir recipients.

Another important finding was the reduction in the risk of acute graft rejection. The prevention of acute rejection is considered essential to the long-term success of renal transplantation. CMV infection is a risk factor for acute rejection, although the role of CMV prophylaxis remains controversial. The finding that CMV prophylaxis with valacyclovir also reduces the risk of acute rejection suggests an important association between CMV infection and allograft rejection. The results of a recent meta-analysis<sup>28</sup> indicate that the use of other anti-CMV agents is not associated with a decrease in the risk of acute rejection. The reduction in the rate of acute rejection among valacyclovir recipients in our study may ultimately be associated with prolonged graft survival.

In view of the observed antirejection effect of valacyclovir, its future use in combination with new immunosuppressants (e.g., mycophenolate mofetil and tacrolimus) bears consideration. In our study, fewer than 5 percent of patients received mycophenolate mofetil or tacrolimus, both of which reduce the rate of acute rejection to levels below those achieved with the cyclosporine-based regimens used in 95 percent of patients.<sup>33,34</sup> Valacyclovir has no direct immunomodulatory properties, and the reduction in the risk of acute rejection may be attributable to its effect on CMV. On the basis of our results and evidence from a recent study that mycophenolate mofetil potentiates the antiherpetic effects of several compounds,<sup>35</sup> concomitant administration of valacyclovir with mycophenolate mofetil may result in a lower risk of rejection and CMV disease than is seen with either agent alone, compensating for the increased risk of CMV disease associated with treatment with mycophenolate mofetil.<sup>33</sup>

The reduction in the risk of herpes simplex virus disease among recipients of valacyclovir underscores the role of this drug as a broad-spectrum antiherpetic

agent. The risk of other infections was also reduced among valacyclovir recipients, possibly reflecting direct effects such as decreases in CMV-induced immunosuppression and damage to integumentary barriers.<sup>1,36</sup> The lower rates of use of antilymphocyte antibodies among valacyclovir recipients as a result of the decreased rate of acute rejection may have also decreased the rate of other infections.

Hallucinations were the only adverse events reported more frequently among valacyclovir recipients in both the seronegative and seropositive groups. Adverse events were generally mild, reversible, and not treatment limiting and have been reported previously after the intravenous administration of acyclovir.<sup>37</sup> Valacyclovir was not associated with nephrotoxicity, and laboratory monitoring did not reveal any adverse effects. The incidence of thrombotic microangiopathy among valacyclovir recipients (0.3 percent) was not increased above the background rate in this population.<sup>38,39</sup> Survival rates at one year were within the expected range.<sup>40</sup> These data indicate that the safety profile of valacyclovir was similar to that of placebo.

Our study population was representative of typical renal-transplant recipients. Therefore, we believe that our findings are widely applicable and suggest that all seronegative and seropositive patients can be considered for valacyclovir prophylaxis. Because the incidence of CMV disease is lower among seropositive patients than seronegative patients, it may be reasonable to target prophylaxis to subgroups of seropositive patients at higher risk — for example, seropositive patients who receive a second transplant from a seropositive donor and who receive high doses of immunosuppressants. Extension of treatment with valacyclovir beyond 90 days after transplantation may further reduce the risk of CMV disease, particularly among patients whose immunosuppressive regimen has not been fully tapered. Given that the prevalence, timing, and manifestations of CMV disease and the viral burdens involved are similar after other types of solid-organ transplantations (e.g., liver and heart<sup>1</sup>), valacyclovir prophylaxis may also be beneficial in these settings. The efficacy of valacyclovir provides an alternative choice for CMV prophylaxis, allowing ganciclovir — the current standard for the management of CMV disease — to be reserved for the treatment of CMV disease and thus potentially decreasing the likelihood of creating strains that are resistant to ganciclovir.

In summary, treatment with valacyclovir for 90 days after transplantation significantly reduced the risk and delayed the onset of CMV disease with minimal adverse effects. It also significantly reduced the risk of acute graft rejection among seronegative patients, with a trend toward such a reduction among seropositive patients. Valacyclovir significantly diminished the risk of herpes simplex virus disease and other infections. Valacyclovir has several advantages over conventional

strategies, including ease of administration and less use of inpatient medical resources.

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## APPENDIX

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## REFERENCES

- Rubin RH. Impact of cytomegalovirus infection on organ transplant recipients. *Rev Infect Dis* 1990;12:Suppl 7:S754-S766.
- Ho M. Cytomegalovirus infection and indirect sequelae in the immunocompromised transplant patient. *Transplant Proc* 1991;23:Suppl 1:2-7.
- Balfour HH Jr, Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. *N Engl J Med* 1989;320:1381-7.
- Kletzmayer J, Kotzmann H, Popow-Kraupp T, Kovarik J, Klausner R. Impact of high-dose oral acyclovir prophylaxis on cytomegalovirus (CMV) disease in CMV high-risk renal transplant recipients. *J Am Soc Nephrol* 1996;7:325-30.
- Fryd DS, Peterson PK, Ferguson RM, Simmons RL, Balfour HH Jr, Najarian JS. Cytomegalovirus as a risk factor in renal transplantation. *Transplantation* 1980;30:436-9.
- Hibberd PL, Tolckoff-Rubin NE, Cosimi AB, et al. Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. *Transplantation* 1992;53:68-72.
- Conti DJ, Freed BM, Singh TP, Gallichio M, Gruber SA, Lempert N. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplant recipients. *Arch Surg* 1995;130:1217-22.
- Marker SC, Howard RJ, Simmons RL, et al. Cytomegalovirus infection: a quantitative prospective study of three hundred twenty consecutive renal transplants. *Surgery* 1981;89:660-71.
- Winston DJ. Prevention of cytomegalovirus disease in transplant recipients. *Lancet* 1995;346:1380-1.
- Murray BM. Management of cytomegalovirus infection in solid-organ transplant recipients. *Immunol Invest* 1997;26:243-55.
- Pouteil-Noble C, Ecochard R, Landrivoon G, et al. Cytomegalovirus infection — an etiological factor for rejection? A prospective study in 242 renal transplant patients. *Transplantation* 1993;55:851-7.
- The TH, Grefte JM, van der Bij W, van Son WJ, van den Berg AP.

CMV infection after organ transplantation: immunopathological and clinical aspects. *Neth J Med* 1994;45:309-18.

- Gulanikar AC, MacDonald AS, Sungurtekin U, Belitsky P. The incidence and impact of early rejection episodes on graft outcome in recipients of first cadaver kidney transplants. *Transplantation* 1992;53:323-8.
- Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, Persson N-H. The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporine regimens. *Transplantation* 1993;56:307-15.
- Naimark DMJ, Cole E. Determinants of long-term renal allograft survival. *Transplant Rev* 1994;8:93.
- Chatterjee SN, Fiala M, Weiner J, Stewart JA, Stacey B, Warner N. Primary cytomegalovirus and opportunistic infections: incidence in renal transplant recipients. *JAMA* 1978;240:2446-9.
- Reusser P. Human cytomegalovirus infection and disease after bone marrow and solid organ transplantation. *Baillieres Clin Infect Dis* 1996;3:357-71.
- Jordan ML, Hrebinko RL, Dummer JS, et al. Therapeutic use of ganciclovir for invasive cytomegalovirus infection in cadaveric renal allograft recipients. *J Urol* 1992;148:1388-92.
- Nicholson ML, Veitch PS, Donnelly PK, Flower AJE, Bell PRF. Treatment of renal transplant-associated cytomegalovirus infection with ganciclovir. *Transplant Proc* 1990;22:1811-2.
- Dunn DL, Mayoral JL, Gillingham KJ, et al. Treatment of invasive cytomegalovirus disease in solid organ transplant patients with ganciclovir. *Transplantation* 1991;51:98-106.
- Metselaar HJ, Weimar W. Cytomegalovirus infection and renal transplantation. *J Antimicrob Chemother* 1989;23:Suppl E:37-47.
- McCarthy JM, Karim MA, Krueger H, Keown PA. The cost impact of cytomegalovirus disease in renal transplant recipients. *Transplantation* 1993;55:1277-82.
- Vasquez EM, Sanchez J, Pollak R, Vrahnos D, Fabrega AJ, Maddux MS. High-dose oral acyclovir prophylaxis for primary cytomegalovirus infection in seronegative renal allograft recipients. *Transplantation* 1993;55:448-50.
- Dunn DL, Gillingham KJ, Kramer MA, et al. A prospective randomized study of acyclovir versus ganciclovir plus human immune globulin prophylaxis of cytomegalovirus infection after solid organ transplantation. *Transplantation* 1994;57:876-84.
- Chitwood KK, Heim-Buthey KL, Ney AL, et al. Questionable benefit of prophylactic acyclovir in renal transplant recipients at high risk for cytomegalovirus disease. *Clin Transplant* 1993;7:320-4.
- Saliba F, Eyraud D, Samuel D, et al. Randomized controlled trial of acyclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients. *Transplant Proc* 1993;25:1444-5.
- Gavalda J, de Otero J, Murio E, et al. Two grams daily of oral acyclovir reduces the incidence of cytomegalovirus disease in CMV-seropositive liver transplant recipients. *Transplant Int* 1997;10:462-5.
- Couchoud C, Cucherat M, Haugh M, Pouteil-Noble C. Cytomegalovirus prophylaxis with antiviral agents in solid organ transplantation: a meta-analysis. *Transplantation* 1998;65:641-7.
- Fletcher CV, Englund JA, Edelman CK, Gross CR, Dunn DL, Balfour HH Jr. Pharmacologic basis for high-dose oral acyclovir prophylaxis of cytomegalovirus disease in renal allograft recipients. *Antimicrob Agents Chemother* 1991;35:938-43.
- Cole NL, Balfour HH Jr. In vitro susceptibility of cytomegalovirus isolates from immunocompromised patients to acyclovir and ganciclovir. *Diagn Microbiol Infect Dis* 1987;6:255-61.
- Weller S, Blum MR, Doucette M, et al. Pharmacokinetics of the acyclovir pro-drug valacyclovir after escalating single- and multiple-dose administration to normal volunteers. *Clin Pharmacol Ther* 1993;54:595-605.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 1995;60:225-32.
- Mayer AD, Dmitrewski J, Squifflet J-P, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. *Transplantation* 1997;64:436-43.
- Neyts J, Andrei G, De Clercq E. The novel immunosuppressive agent mycophenolate mofetil markedly potentiates the antiherpesvirus activities of acyclovir, ganciclovir, and penciclovir *in vitro* and *in vivo*. *Antimicrob Agents Chemother* 1998;42:216-22.
- Wagner JA, Ross H, Hunt S, et al. Prophylactic ganciclovir treatment reduces fungal as well as cytomegalovirus infections after heart transplantation. *Transplantation* 1995;60:1473-7.
- Morris DJ. Adverse effects and drug interactions of clinical importance with antiviral drugs. *Drug Saf* 1994;10:281-91.

- 38.** Candinas D, Keusch G, Schlumpf R, Burger HR, Gmür J, Largiadèr F. Hämolytisch-urämisches Syndrom nach Nierentransplantation: prognostische faktoren. *Schweiz Med Wochenschr* 1994;124:1789-99.
- 39.** Schwarz A, Krause PH, Offermann G, Keller F. Recurrent and de

novo renal disease after kidney transplantation with or without cyclosporin A. *Am J Kidney Dis* 1991;17:524-31.

**40.** Ramos EL, Tilney NL, Ravenscraft MD. Clinical aspects of renal transplantation. In: Brenner BM, Rector FC Jr, eds. *The kidney*. 4th ed. Philadelphia: W.B. Saunders, 1991:2361-407.