MAJOR ARTICLE

A Randomized, Controlled Trial Comparing Ganciclovir to Ganciclovir Plus Foscarnet (Each at Half Dose) for Preemptive Therapy of Cytomegalovirus Infection in Transplant Recipients

Frank M. Mattes,[1] Emma G. Hainsworth,[1] Anna-Maria Geretti,[6] Gaia Nebbia,[6] Grant Prentice,[2] Michael Potter,[2] Andrew K. Burroughs,[3] Paul Sweny,[4] Aycan F. Hassan-Walker,[1] Sylvester Okwuadi,[1] Caroline Sabin,[5] Geraldine Amooty,[3] Vanessa S. Brown,[4] Sarah C. Grace,[2] Vincent C. Emery,[1] and Paul D. Griffiths[1]

Departments of [1]Virology, [2]Haematology, [3]Liver Transplantation, [4]Renal Transplantation, and [5]Primary Care and Population Sciences, Royal Free and University College Medical School and Royal Free Hampstead National Health Service Trust, and [6]Department of Virology and Public Health Laboratory, King's College Hospital (Dulwich), London, United Kingdom

Forty-eight patients who provided 2 consecutive blood samples that tested positive for cytomegalovirus DNA by polymerase chain reaction (PCR) were randomized to receive either full-dose ganciclovir (5 mg/kg intravenously [iv] twice daily) or half-dose ganciclovir (5 mg/kg iv once daily) plus half-dose foscarnet (90 mg/kg iv once daily) for 14 days. In the ganciclovir arm, 17 (71%) of 24 patients reached the primary end point of being CMV negative by PCR within 14 days of initiation of therapy, compared with 12 (50%) of 24 patients in the ganciclovir-plus-foscarnet arm ($P = .12$). Toxicity was greater in the combination-therapy arm. In patients who failed to reach the primary end point, baseline virus load was 0.77 $\log_{10}$ higher, the replication rate before therapy was faster (1.5 vs. 2.7 days), and the viral decay rate was slower (2.9 vs. 1.1 days) after therapy. Bivariable logistic regression models identified baseline virus load, bone-marrow transplantation, and doubling time and half-life of decay as the major factors affecting response to therapy within 14 days. This study did not support a synergistic effect of ganciclovir plus foscarnet in vivo.

Cytomegalovirus (CMV) is a common infectious agent that, unless the patient is immunocompromised, rarely causes symptoms. After transplantation of bone marrow or solid organs, CMV can cause fever, pneumonitis, hepatitis, enteritis, or retinitis, collectively termed "CMV disease." Natural-history studies show that CMV viremia precedes CMV disease and that the peak virus load correlates strongly with the development of CMV disease [1, 2]. In multivariable statistical models, peak virus load explains the previously identified risk factors of donor/recipient serostatus [1–3]. Management strategies for preventing CMV disease include giving antiviral prophylaxis to patients from the time of transplant onward [4] or using the results of virologic surveillance to identify asymptomatic patients with viremia and offering them antiviral therapy [5] before disease develops (preemptive therapy).

In our institution (Royal Free and University College Medical School, London, UK), bone marrow, liver, and renal transplant patients are tested twice weekly by use of polymerase chain reaction (PCR) [6]. Preemptive therapy with ganciclovir (5 mg/kg twice daily) is given intravenously (iv) for 14 days to patients with 2 consecutive positive results by PCR. Ganciclovir-induced neutropenia is treated by switching to foscarnet, a drug that is nephrotoxic and causes electrolyte imbalances [7]. Ganciclovir and foscarnet show in vitro synergistic activity against CMV [8], and a randomized trial of patients with AIDS showed significantly delayed progression of CMV retinitis in patients who received this combination [9]. We therefore hypothesized that a

Received 23 April 2003; accepted 1 November 2003; electronically published 1 April 2004.

Financial support: Wellcome Trust (program grant).

Reprints or correspondence: Prof. Paul D. Griffiths, Royal Free and University College Medical School, Royal Free Campus, Rowland Hill St., NW3 2PF London, UK (p.griffiths@rfc.ucl.ac.uk).

The Journal of Infectious Diseases 2004; 189:1355–61

0022-1899/2004/18908-0004$15.00

combination strategy consisting of half-dose ganciclovir and half-dose foscarnet (the regimen used for the maintenance phase of the trial in patients with AIDS [9]) may provide more-efficacious control of CMV viremia in the transplant setting, while reducing the risk of severe adverse effects when used for preemptive therapy. This article describes the results of a randomized, controlled trial designed to test this hypothesis and to investigate the virologic determinants of the outcome of therapy.

SUBJECTS AND METHODS

The general treatment of patients undergoing bone-marrow, liver, or renal transplantation at our institution is described in detail elsewhere [1–3]. Of note, no antiviral prophylaxis for CMV is given to recipients of solid organs, whereas all bone-marrow transplant recipients receive high-dose aciclovir, according to a previously published protocol [10].

Monitoring of CMV. Whole-blood samples were obtained twice weekly from all patients and were tested for CMV DNA by use of a PCR method described elsewhere [11]. The sensitivity of the assay is 200 genomes/mL of blood, a value that has been shown to identify patients at risk of future CMV disease [11]. All CMV-positive samples were quantified using a quantitative-competitive PCR described in detail elsewhere [12]. These quantitative values were not available to clinicians treating the patients enrolled in the present study.

Randomized trial design. Patients who provided 2 consecutive blood samples that tested positive for CMV by PCR for the first time after transplantation were invited to enter the randomized trial, which was approved by the local ethics committee (institutional review board of the Royal Free Hospital, London, UK). Patients were randomized to receive either full-dose ganciclovir (5 mg/kg twice daily) or half-dose ganciclovir (5 mg/kg once daily) plus half-dose foscarnet (90 mg/kg once daily) for 14 days. Doses were adjusted according to renal function. Patients received granulocyte colony-stimulating factor (G-CSF) at the discretion of the physician. Randomization was stratified by type of organ transplanted. The trial was administered by use of sealed envelopes containing the randomization code, which were opened after the patient had provided informed consent. Patients with impaired renal function (creatinine clearance, <30 mL/min), neutropenia ($<0.5 \times 10^9$ cells/L), or HIV infection were excluded from the study. Patients in either arm of the study who failed to clear their CMV viremia within 14 days of initiation of therapy could either be withdrawn from the study or be given a further course of therapy, at the discretion of the physician. The first patient was enrolled in December 1998, and the last was enrolled in February 2001. Patients who developed serious adverse events related to toxicity profiles of ganciclovir (neutropenia) or foscarnet (electrolyte disturbance or renal impairment) could be withdrawn from the study, be switched to the other arm, or be allowed to continue receiving the study drug, with a reduced dose.

Statistical analysis. The primary end point was the proportion of patients who became CMV negative by PCR within 14 days of initiation of therapy. Secondary end points addressed the safety and tolerability of combination therapy and changes in CMV load during therapy. All analyses were by intention to treat. Comparison of continuous variables, such as virus load, between groups was achieved by use of the 2-sided *t* test. The Mann-Whitney *U* test was used for the comparison of viral replication rates. The rate constant κ, for viral growth or decay, before or after therapy, was computed assuming exponential growth/decay, as described elsewhere [13]. Doubling times and half-life of decay were calculated by use of the following formulae: $t_d = \ln(2)/\rho$ and $t_{1/2} = -\ln(2)/\kappa$, respectively. Simple linear least-squares fit regression models were used to analyze the relationship between viral replication kinetics and virus load. Factors associated with the primary end point were modelled with a univariable and multivariable logistic regression model using intention-to-treat design. Kaplan-Meier plot and a log-rank test were used to test the hypothesis that both therapy arms were equally effective.

Important practical difficulties in the coadministration of these 2 compounds were anticipated. Specifically, foscarnet and ganciclovir are incompatible in the same dilution fluid, and the low solubility of foscarnet increased the fluid challenge the patients were subjected to. For these reasons, it was decided that only a substantial superiority of the combination would be clinically significant. On the basis of historical data, 50% of patients given ganciclovir monotherapy were expected to become CMV negative by PCR within 14 days of initiation of therapy. A study size of 48 patients (24 in each arm) had 90% power to detect a statistically significant ($P < .05$) increase in this rate, to 90%. Data were analyzed with the computer program R [14].

RESULTS

Baseline characteristics. Details of the patients randomized to each therapy arm are given in table 1. The patients were well matched for sex, age, and CMV donor/recipient serostatus. Virus loads at day 0 (baseline virus load) were similar in both therapy arms (4.28 $\log_{10}$ genomes/mL [ganciclovir] vs. 4.01 $\log_{10}$ genomes/mL [ganciclovir plus foscarnet]; $P = .73$, Mann-Whitney *U* test). There was no difference between the time that the second sample was positive for CMV by PCR and the time of initiation of therapy, when patients were stratified according to therapy allocation (median, 4 days for ganciclovir and 5 days for ganciclovir plus foscarnet; $P = .24$, Mann-Whitney *U* test) or transplant type (median, 4 days for bone marrow and 5 days for solid organ; $P = .19$, Mann-Whitney *U* test).

Table 1. Characteristics of patients, by therapy assignment.

Characteristic	Therapy allocation	
	GCV	GCV plus FOS
No. of patients randomized, by type of transplantation	24	24
Bone marrow	8	9
Liver	8	9
Renal	8	6
Age, median (range), years	50 (2–68)	45 (2–56)
Sex, M:F	15:9	14:10
CMV IgG D/R status[a] (bone marrow, liver, renal), no. of patients		
D^+/R^-	2 (1, 1 ,0)	3 (0, 3, 0)
D^-/R^+	4 (1, 2, 1)	6 (2, 1, 3)
D^+/ R^+	15 (6, 4, 5)	15 (7, 5, 3)
D^-/R^-	1 (0, 1, 0)	0 (0)
Baseline CMV load, median (range), $\log_{10}$ genomes/mL	4.3 (2.7–5.9)	4.0 (3.0–6.2)

NOTE. +, Seropositive; −, seronegative; CMV, cytomegalovirus; D, donor; FOS, foscarnet; GCV, ganciclovir; R, recipient.

[a] CMV IgG serostatus of donor is unknown for 2 patients (both renal transplant recipients).

Assessments of virological responses. The primary end point of being CMV negative (<200 genomes/mL) by PCR was reached by 17 (71%) of 24 patients randomized to receive ganciclovir and by 12 (50%) of 24 patients randomized to receive combination therapy ($P = .14$, χ^2 test). Among those who reached the primary end point, the median time until a blood sample was found to be negative for CMV was 6 days in the ganciclovir arm, compared with 5.5 days in the combination-therapy arm (median, 6 days vs. 11 days, when considering all patients, by use of a Kaplan-Meier approach; table 2). A Kaplan-Meier plot illustrating the proportions and times when patients became CMV negative within the first 14 days of therapy is shown in figure 1. Three patients in the ganciclovir-therapy arm and 1 patient in the combination-therapy arm had already become CMV negative by PCR at day 0. Two patients (both in the combination-therapy arm) had no CMV-negative results by PCR within 50 days. Antiviral therapy was stopped in 1 patient (ganciclovir arm) at day 12. Statistically, for the primary end point, there was no difference between the 2 therapy arms. ($P = .19$, log-rank test). With respect to drug toxicity, 7 patients experienced toxicity, all of whom were in the combination-therapy arm (7/24 in the combination-therapy arm vs. 0/24 in the ganciclovir arm; $P = .009$, Fisher's exact test; table 2). All cases of switching and dose reduction because of toxicity occurred in the solid-organ transplant group (4 liver and 2 renal transplant recipients), whereas 1 patient in the bone-marrow transplant group was withdrawn from the study (ganciclovir-plus-foscarnet arm) at day 12 because of failure to engraft the donated marrow. In 6 patients who continued in the study, toxicity was compatible with the toxicity profile of

Table 2. No. of patients reaching the primary and secondary end points of the study, by therapy assignment.

Characteristic end points	Therapy allocation		
	GCV	GCV plus FOS	*P*
Primary, CMV negative by PCR within 14 days of initiation of therapy	17 (71)	12 (50)	.12[a]
Secondary, patients stopping or reducing dose because of toxcicity within 14 days of initiation of therapy	0 (0)	7 (29)	.009[2]
Time to CMV-negative result by PCR, median, days			
Patients reaching primary end point	6	5.5	
All patients, Kaplan-Meier	6	11	
Patients developing a second episode of CMV viremia after successful therapy (within 365 days)			
Patients reaching primary end point	1	4	.35[b]
All patients	6	9	.53[b]

NOTE. Data are no. (%) of patients, unless otherwise noted. CMV, cytomegalovirus; FOS, foscarnet; GCV, ganciclovir; PCR, polymerase chain reaction.

[a] χ^2 test.

[b] Fisher's exact test.

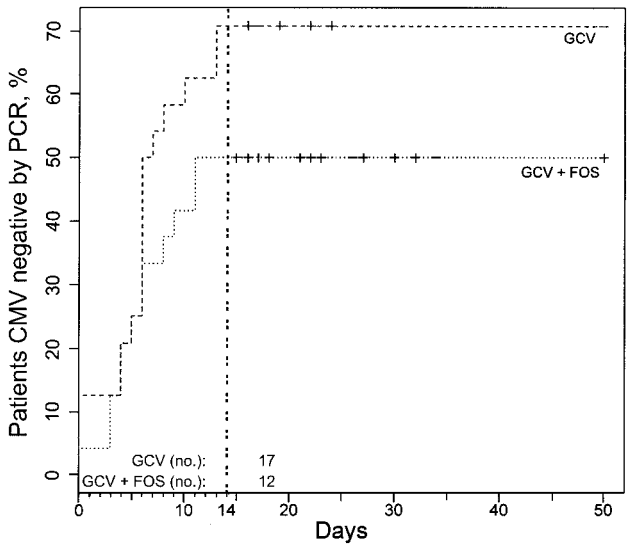

Figure 1. Kaplan-Meier analysis of time to reach the primary end point, for patients randomized to the ganciclovir (GCV) or GCV-plus-foscarnet (FOS) therapy arm. The vertical dashed line at day 14 indicates the primary end point of the study. Crosses after 14 days indicate when a patient who failed to reach the study end point became cytomegalovirus (CMV) negative.

foscarnet. Three of these patients switched to ganciclovir, and, for 3 patients, the dose was reduced (table 3).

Virologic predictors of the outcome of therapy. In 42 of the 48 patients, we were able to measure virologic parameters, such as virus load at initiation of therapy, viral growth before therapy, and viral decay rates during therapy. Patients who failed to reach the primary end point had a higher virus load at baseline (difference, 0.77 $\log_{10}$ genomes/mL; $P = .02$, t test; figure 2). Although there was no difference in the viral replication rate (day^{-1}, ρ for ganciclovir, 0.33 vs. ρ for ganciclovir plus foscarnet, 0.43; $P = .91$, Mann-Whitney U test) or viral decay rate (day^{-1}, κ for ganciclovir, -0.42 vs. κ for ganciclovir plus foscarnet, -0.28; $P = .26$, Mann-Whitney U test) in virus load, between the 2 therapy arms, the viral decay rate was significantly higher in patients who reached the primary end point than in those who failed to control replication to <200 genomes/mL at day 14 (day^{-1}, κ for no failure, -0.61 vs. κ for failure, -0.24, corresponding to half-life of decay of 1.1 days and 2.9 days, respectively; $P < .0002$; figure 3*A*). Similar results in viral decay rates were obtained when patients were analyzed according to transplant type (bone marrow vs. solid organ; data not shown). Analyses of the viral replication kinetics before therapy revealed that patients who failed to reach the primary end point had a significantly faster CMV growth rate (day^{-1}, κ for failure, 0.46 vs. κ for no failure, 0.26; $P < .002$; figure 3*B*). These growth rates correspond to viral doubling times of 1.51 days and 2.7 days, respectively.

The correlation between viral decay rates and baseline virus load, for patients who reached or failed to reach the primary end point, are shown in figure 4. There was a significant correlation between baseline CMV load and decay rate in each group (r^2 for failure, 0.6 vs. r^2 for no failure, 0.52; $P < .001$). In addition, when patients were stratified according to whether they had reached the primary end point, there was a strong correlation between the viral growth rate and the viral decay rate after therapy (r^2 for failure, 0.49 vs. r^2 for no failure, 0.73; $P = .001$; data not shown).

Quantifying the risks associated with poor antiviral response. Univariable linear regression models were used to identify factors associated with the primary end point (CMV negative by PCR within 14 days of initiation of therapy). In these models, higher virus load on the day of initiating antiviral therapy (odds ratio [OR], 2.39; 95% confidence interval [CI], 1.05–5.45), faster viral doubling time (t_d; OR, 2.95; 95% CI, 1.28–6.82) before therapy, and slower half-life of decay in virus load ($t_{1/2}$; OR, 3.01; 95% CI, 1.45–6.25) after therapy were all associated with failure to reach the primary end point. Age (≤40 vs. >40 years), sex, transplant type (bone marrow vs. solid organ), study drug (ganciclovir vs. combination), or delay of therapy did not appear to be associated with the primary end point (table 4). As a consequence of the strong correlation between virus load at initiation of therapy, replication rate before therapy, and viral decay rate after therapy, multivariable

Table 3. No. of patients with reported drug toxicities during the study period, clinical management parameters, and study outcome.

Transplant type	Randomized drug	Days after transplantation	Day of toxicity	Abnormal clinical parameter[a]	Attributable to study drug	Treatment	Study outcome
Bone marrow	Combination	73	12	Failure to engraft	No	Withdrawn	Failure
Liver	Combination	38	4	Creatinine, 129; magnesium, 0.38; calcium, 1.58	Yes	Switched to GCV	Failure
Liver	Combination	34	4	Creatinine, 130; magnesium, 0.51; calcium, 2.04	Yes	Switched to GCV	Failure
Liver	Combination	36	6	Creatinine, 162; magnesium, 0.52; calcium, 1.7	Yes	Switched to GCV	Failure
Liver	Combination	44	9	Creatinine, 167; magnesium, 0.57	Yes	Dose reduction	No failure
Renal	Combination	40	11	Creatinine, 154; magnesium, 0.64	Yes	Dose reduction	No failure
Renal	Combination	40	11	Creatinine, 182	Yes	Dose reduction	No failure

NOTE. GCV, ganciclovir.

[a] Normal range: creatinine, 0–97 μmol/L; calcium, 2.1–2.6 mmol/L; magnesium, 0.7–1.0 mmol/L.

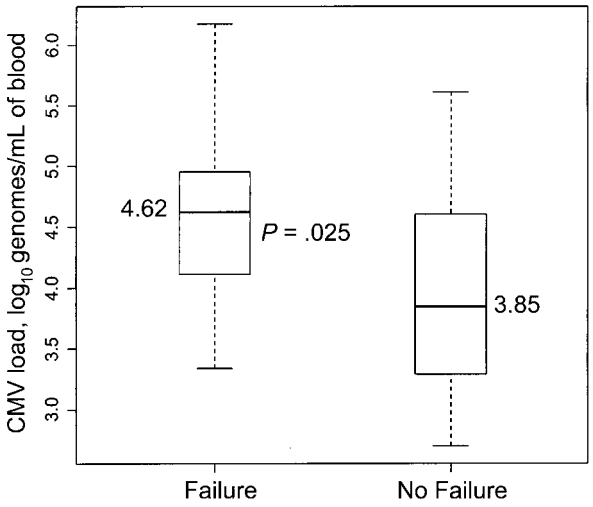

Figure 2. Box-plots illustrating the relationship between baseline virus loads for patients who reached the primary end point of becoming cytomegalovirus (CMV) negative within 14 days of initiation of therapy (no failure) and patients who failed to reach the primary end point (failure). Horizontal lines display the 10th, 25th, 50th *(thick line),* 75th, and 90th percentiles, with boxes encompassing 50% of values.

models including all these factors did not produce meaningful results. Consequently, we undertook a series of bivariable logistic regression models. The results of these models illustrate, that, in all cases, type of transplant (bone marrow) was associated with failing to become CMV DNA negative within 14 days of initiation of therapy (table 4). In addition, the measure of the viral replication (higher baseline virus load, faster doubling time, or slower viral half-life of decay) was independently associated with failure to reach the primary end point.

Subsequent episodes of CMV viremia. In 15 (31%) of 24 patients, we observed a second episode of CMV viremia within 1 year after they finished the first course of therapy. When analysis was performed according to the initial randomized drug, there was no significant difference in the number of patients who experienced a second episode of CMV viremia (ganciclovir = 6 and ganciclovir plus foscarnet = 9; $P = .5$, Fisher's exact test; table 2). However, patients who failed to reach the primary end point of the study were more likely to have a second episode of CMV viremia ($P = .01$, Fisher's exact test). In addition, among patients with a second episode of viremia, there was a trend for higher baseline virus load and faster replication rate before therapy (data not shown).

DISCUSSION

The main conclusion of this randomized, controlled clinical trial is that, for preemptive therapy in transplant recipients, the combination of half-dose ganciclovir and foscarnet therapy is not superior to ganciclovir monotherapy. The viral decay rate after therapy was very similar between patients randomized to receive ganciclovir and those randomized to receive the combination therapy. However, with respect to the primary end point of being CMV negative by PCR by day 14, there was a trend in favor of the ganciclovir arm. Thus, the lack of a significant benefit of the combination of ganciclovir and foscarnet

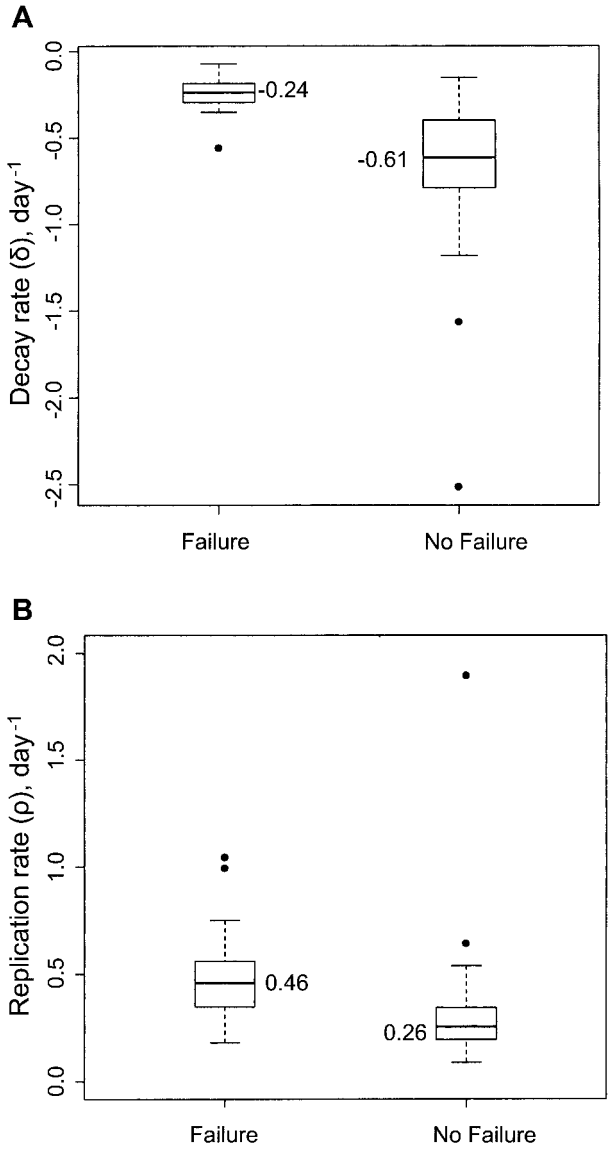

Figure 3. *A* and *B,* Box-plots showing the viral decay rate (δ) after initiating antiviral therapy *(A)* and the replication rate (ρ) before initiating antiviral therapy *(B),* for patients who reached the primary end point of becoming cytomegalovirus (CMV) negative within 14 days of initiation of therapy (no failure) and patients who failed to reach the primary end point (failure). Replication rate and decay rate were each statistically significantly different in patients who failed to reach the primary end point, compared with patients who did not fail to reach the primary end point. Horizontal lines display the 10th, 25th, 50th *(thick line),* 75th, and 90th percentiles, with boxes encompassing 50% of values. Dots represent values outside the 90% limits.

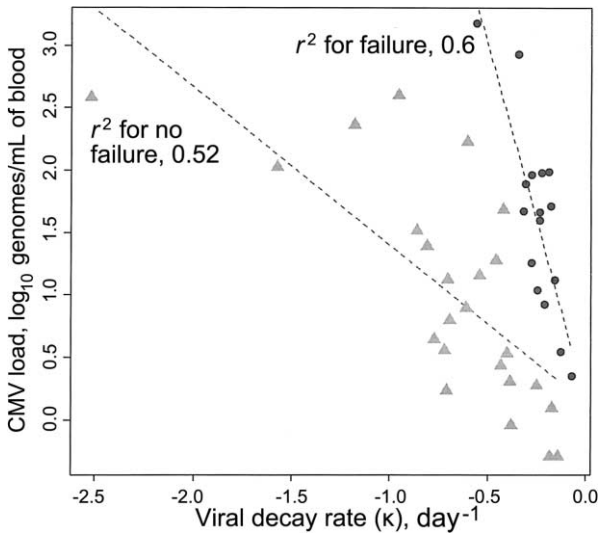

Figure 4. Scatter-diagram showing the correlation between viral decay rate (κ) and baseline cytomegalovirus (CMV) load. Data are stratified according the study end point. A correlation line was fitted for each strata (●, failure; ▲, no failure), and the goodness of fit is expressed as an r^2 value.

could not be explained by inadequate study power. Since patients were well matched at baseline for all known prognostic variables, including donor/recipient serostatus and baseline virus load, this outcome was surprising. The hypothesis that the combination therapy might be superior to ganciclovir monotherapy was based on 2 previously published observations: (1) ganciclovir plus foscarnet is synergistic in vitro [8] and (2) the combination (using the same doses as used here) proved to be superior in controlling CMV retinitis in patients with AIDS [9]. However, we now know that extrapolation of data from in vitro studies with anti-CMV compounds can be misleading, since aciclovir, which has a poor efficacy in vitro, has been shown to be efficacious in vivo within a series of randomized, controlled clinical trials [15, 16]. Furthermore, the results of the randomized, controlled trial of ganciclovir and foscarnet in patients with AIDS retinitis, which showed a clear superiority of the combination therapy, were obtained in a group of patients who had experienced high-level CMV replication and had been pretreated with ganciclovir. We have previously shown that the rapid dynamics of CMV, coupled with prolonged persistence of low levels of ganciclovir, can result in a rapid flux of wild-type and drug-resistant virus populations and that in vitro culture of viruses in the absence of ganciclovir can result in an underappreciation of the quantity of resistant viruses present in the clinical inoculum [13, 17]. Thus, a high incidence of unrecognized resistance to ganciclovir could explain the observed differences between the trials, with the ganciclovir-plus-foscarnet arm showing improved virologic and clinical benefit in patients with AIDS retinitis, because of the ability to control low-level ganciclovir-resistant strains of viruses with mutations in the UL97 gene. Alternatively, foscarnet may have had a modest effect on HIV replication; therefore, in retrospect, the AIDS trial may represent an early example of combination antiretroviral therapy, rather than synergistic anti-CMV activity of both drugs.

In the present study, the availability of data on virus loads enabled us to investigate virological parameters associated with therapy failure. Patients who failed to control replication to low levels (<200 genomes/mL) within 14 days of initiation of therapy had a significantly higher baseline virus load, a much faster viral growth rate before therapy (average $t_{1/2}$, 1.5 days), and a much slower viral decay rate after therapy (average $t_{1/2}$, 2.9 days), compared with patients who reached the primary end point. These observations on the importance of viral growth rate and decay after therapy, in patients with poor response to antiviral therapy, have important practical implications, and further studies are required to determine the role of host parameters in facilitating the removal of CMV-infected cells after initiating therapy.

It is known that a subset of patients treated via preemptive therapy will experience a recurrence of viremia. In the present study, this constituted 31% of the cohort. Patients who failed to reach the primary end point of the study were more likely to have a second episode of CMV viremia within the first year

Table 4. Univariable and multivariable analysis of risk factors associated with the primary end point of becoming cytomegalovirus (CMV) DNA negative by polymerase chain reaction by day 14.

Model, risk factors	OR (95% CI)	*P*
Univariable models		
Transplant group, bone marrow vs. solid organ	2.36 (0.70–7.94)	.17
CMV load[a], per $\log_{10}$ increase	2.39 (1.05–5.44)	.038
Age, ⩽40 vs. >40	1.19 (0.37–3.86)	.77
Study drug, GCV vs. GCV plus FOS	0.41 (0.13–1.35)	.144
Sex, male vs. female	0.59 (0.18–1.91)	.37
Doubling time, per day decrease	2.95 (1.28–6.82)	.01
Half-life of decay, per day increase	3.01 (1.45–6.25)	.003
Multivariable model 1		
Transplant group, bone marrow vs. solid organ	3.94 (0.92–16.92)	.064
CMV load[a], per $\log_{10}$ increase	2.96 (1.01–6.15)	.048
Multivariable model 2		
Transplant group, bone marrow vs. solid organ	3.79 (0.78–18.24)	.09
Doubling time, per day decrease	3.02 (1.28–7.14)	.018
Multivariable model 3		
Transplant group, bone marrow vs. solid organ	7.46 (1.19–46.71)	.031
Half-life of decay, per day increase	3.7 (1.55–8.84)	.003

NOTE. CI, confidence interval; FOS, foscarnet; GCV, ganciclovir; OR, odds ratio.

[a] Virus load measured at day of initiation of therapy.

($P = .013$, Fisher's exact test; data not shown). In addition, patients who had a second episode of viremia had a higher virus load at baseline, a higher replication rate before antiviral therapy, and a slower viral decay rate after initiating antiviral therapy (data not shown). This latter observation is similar to those of Humar et al. [18], who showed that solid-organ transplant recipients who had second episodes of viremia had a $t_{1/2}$ of 8.8 days after iv ganciclovir therapy, compared with a $t_{1/2}$ of 3.17 days for patients with a single episode of CMV viremia.

In conclusion, this trial has shown that, at the doses used, combination antiviral therapy with ganciclovir plus foscarnet for CMV viremia does not appear to control viral replication better than does ganciclovir monotherapy. Other investigators have reported uncontrolled studies of full-dose therapy with ganciclovir plus foscarnet [19] or increasing doses of foscarnet plus constant ganciclovir, at the doses used here [20]. Future randomized trials could consider using 1 of these regimens as a way of obtaining better control of CMV replication after transplantation.

References

1. Cope AV, Sabin C, Burroughs A, Rolles K, Griffiths PD, Emery VC. Interrelationships among quantity of human cytomegalovirus (HCMV) DNA in blood, donor-recipient serostatus, and administration of methylprednisolone as risk factors for HCMV disease following liver transplantation. J Infect Dis **1997**; 176:1484–90.
2. Cope AV, Sweny P, Sabin C, Rees L, Griffiths PD, Emery VC. Quantity of cytomegalovirus viruria is a major risk factor for cytomegalovirus disease after renal transplantation. J Med Virol **1997**; 52:200–5.
3. Gor D, Sabin C, Prentice HG, et al. Longitudinal fluctuations in cytomegalovirus load in bone marrow transplant patients: relationship between peak virus load, donor/recipient serostatus, acute GVHD and CMV disease. Bone Marrow Transplant **1998**; 21:597–605.
4. Hart GD, Paya CV. Prophylaxis for CMV should now replace preemptive therapy in solid organ transplantation. Rev Med Virol **2001**; 11:73–81.
5. Emery VC. Prophylaxis for CMV should not now replace pre-emptive therapy in solid organ transplantation. Rev Med Virol **2001**; 11:83–6.
6. Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD. Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation. Lancet **2000**; 355:2032–6.
7. Jacobson MA. Treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. N Engl J Med **1997**; 337: 105–14.
8. Manischewitz JF, Quinnan GV Jr, Lane HC, Wittek AE. Synergistic effect of ganciclovir and foscarnet on cytomegalovirus replication in vitro. Antimicrob Agents Chemother **1990**; 34:373–5.
9. Combination foscarnet and ganciclovir therapy vs. monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The Cytomegalovirus Retreatment Trial. The Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. Arch Ophthalmol **1996**; 114:23–33.
10. Prentice HG, Gluckman E, Powles RL, et al. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. Lancet **1994**; 343:749–53.
11. Kidd IM, Fox JC, Pillay D, Charman H, Griffiths PD, Emery VC. Provision of prognostic information in immunocompromised patients by routine application of the polymerase chain reaction for cytomegalovirus. Transplantation **1993**; 56:867–71.
12. Kidd IM, Clark DA, Emery VC. A non-radioisotopic quantitative competitive polymerase chain reaction method: application in measurement of human herpesvirus 7 load. J Virol Methods **2000**; 87:177–81.
13. Emery VC, Cope AV, Bowen EF, Gor D, Griffiths PD. The dynamics of human cytomegalovirus replication in vivo. J Exp Med **1999**; 190: 177–82.
14. Ihaka R, Gentleman R. R: a language for data analysis and graphics. J Comput Graph Stat **1996**; 5:299–314.
15. 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.
16. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. N Engl J Med **1999**; 340:1462–70.
17. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. Proc Natl Acad Sci USA **2000**; 97:8039–44.
18. Humar A, Kumar D, Boivin G, Caliendo AM. Cytomegalovirus (CMV) virus load kinetics to predict recurrent disease in solid-organ transplant patients with CMV disease. J Infect Dis **2002**; 186:829–33.
19. Bacigalupo A, Bregante S, Tedone E, et al. Combined foscarnet-ganciclovir treatment for cytomegalovirus infections after allogeneic hemopoietic stem cell transplantation (Hsct). Bone Marrow Transplant **1996**; 18(Suppl 2):110–4.
20. Mylonakis E, Kallas WM, Fishman JA. Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. Clin Infect Dis **2002**; 34:1337–41.