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Oral Valganciclovir Is Noninferior to Intravenous Ganciclovir for the Treatment of Cytomegalovirus Disease in Solid Organ Transplant Recipients

A. Åsberg[a,‡], A. Humar [b,‡], H. Rollag[c], A. G. Jardine[d], H. Mouas[e], M. D. Pescovitz[f], D. Sgarabotto[g], M. Tuncer[h], I. L. Noronha[i] and A. Hartmann[j,*] on behalf of the VICTOR Study Group[†]

[a] *Department of Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Oslo, Norway*
[b] *University of Alberta, Edmonton, Canada*
[c] *Institute of Microbiology, University of Oslo, Norway*
[d] *Department of Medicine, University of Glasgow, Glasgow, UK*
[e] *Hoffmann-La Roche Ltd, Basel, Switzerland*
[f] *Department of Surgery, Indiana University,Indianapolis, IN*
[g] *Department of Tropical and Infectious Diseases, Padua General and Teaching Hospital, Padua, Italy*
[h] *Department of Nephrology, Akdeniz University Medical Faculty, Antalya, Turkey*
[i] *Department of Nephrology, Hospital Beneficiencia Portuguesa, Sao Paulo, Brazil*
[j] *Department of Medicine, Rikshospitalet-Radiumhospitalet Medical Centre, University of Oslo, Oslo, Norway*
* *Corresponding author: Anders Hartmann, anders.hartmann@rikshospitalet.no*
[†] *Members of the study group are listed in the appendix*
[‡] *These authors contributed equally to this work*

Intravenous ganciclovir is the standard treatment for cytomegalovirus disease in solid organ transplant recipients. Oral valganciclovir is a more convenient alternative. In a randomized, international trial, recipients with cytomegalovirus disease were treated with either 900 mg oral valganciclovir or 5 mg/kg i.v. ganciclovir twice daily for 21 days, followed by 900 mg daily valganciclovir for 28 days. A total of 321 patients were evaluated (valganciclovir [n = 164]; i.v. ganciclovir [n = 157]). The success rate of viremia eradication at Day 21 was 45.1% for valganciclovir and 48.4% for ganciclovir (95% CI −14.0% to +8.0%), and at Day 49; 67.1% and 70.1%, respectively (p = NS). Treatment success, as assessed by investigators, was 77.4% versus 80.3% at Day 21 and 85.4% versus 84.1% at Day 49 (p = NS). Baseline viral loads were not different between groups and decreased exponentially with similar half-lives and median time to eradication (21 vs. 19 days, p = 0.076). Side-effects and discontinuations of assigned treatment (18 of 321 patients) were comparable. Oral valganciclovir shows comparable safety and is not inferior to i.v. ganciclovir for treatment of cytomegalovirus disease in organ transplant recipients and provides a simpler treatment strategy, but care should be taken in extrapolating to organ transplant recipients not properly represented in the present study.

Key words: Cytomegalovirus disease, ganciclovir, posttransplant, valganciclovir, viral kinetics

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Introduction

Cytomegalovirus (CMV) is a significant viral pathogen affecting solid organ transplant recipients and is responsible for substantial morbidity. The clinical manifestations of CMV include an acute viral syndrome and tissue invasive disease, such as pneumonitis, hepatitis and gastrointestinal disease (1). In addition, CMV is associated with indirect immunomodulatory effects including opportunistic infections and acute and chronic allograft injury and rejection (1). Given the clinical consequences of CMV, many transplant centers have adopted prevention strategies. Although prophylaxis is effective in decreasing both the incidence and severity of CMV disease, it remains a common problem and both simple and efficient treatment options are needed (2).

Intravenous ganciclovir, currently the recommended standard treatment for CMV disease in solid organ transplant recipients, requires frequent hospitalizations, long-term i.v. catheter access, and is expensive and inconvenient for patients (3–5). A safe and effective oral therapy would significantly improve and simplify the management of posttransplant CMV disease. Valganciclovir, an oral prodrug of ganciclovir, is absorbed and rapidly metabolized to ganciclovir in the intestinal wall and liver (6). The bioavailability of ganciclovir from valganciclovir is approximately 60%, and the systemic exposure from 900 mg valganciclovir once daily provides similar systemic exposure to that of 5 mg/kg/day i.v. ganciclovir (7–9). While valganciclovir is effective for treatment of CMV retinitis in patients with AIDS (10,11) and for CMV prophylaxis in solid organ transplant recipients, its safety and efficacy for the treatment of

posttransplant CMV disease has yet to be assessed in an adequately powered study.

Material and Methods

Study design

A randomized, open-label, parallel-group, active drug-controlled, multicenter noninferiority trial in adult solid organ transplant recipients with CMV disease (ClinicalTrials.gov NCT00431353) was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines and applicable local regulatory requirements. The trial protocol was approved by local institutional review board at the 42 centers: 25 in Europe, six in Brazil, four in India, two in Canada, two in Venezuela, one in Mexico, one in Australia, and one in New Zealand. Written informed consent was obtained from each patient by the local investigator prior to randomization.

Adult solid organ transplant recipients with both virological and clinical evidence of CMV disease, (regardless of donor or recipient CMV serostatus) were eligible for enrollment. Patients were ineligible if their CMV disease was considered life-threatening by the investigator, had a history of significant adverse reaction to ganciclovir, valganciclovir, acyclovir or valacyclovir, had proven ganciclovir resistance, had received an investigational new drug within the last 30 days or had a calculated creatinine clearance of <10 mL/min using the Cockcroft-Gault equation. The concomitant treatment with any of the following medications were prohibited; oral ganciclovir, acyclovir, valacyclovir, famacyclovir, cidofovir, inter-ferons, CMV hyperimmune globuline, foscarnet, lobucavir, leflunomide, HBIg, probenecid, other investigational drugs.

Between April 2004 and June 2006, 333 patients were screened for the study, resulting in 326 patients being randomized. A total of 321 patients received at least one dose of assigned medication; the 164 patients randomized to treatment with 900 mg twice daily valganciclovir and 157 patients to 5 mg/kg twice daily i.v. ganciclovir were the intention-to-treat population. Both treatments were administered for an induction period of 21 days, followed by 900 mg daily valganciclovir until Day 49. Doses were adjusted to the individual renal function in according to the following criteria. Treatment dose of oral valganciclovir; 900 mg twice daily for Cockcroft-Gault calculated creatinine clearance (CL_{creat}) $\geq$ 60 mL/min, 450 mg twice daily for CL_{creat} from 40 to <60 mL/min, 450 mg once daily for CL_{creat} from 25 to <40 mL/min and 450 mg every second day for CL_{creat} from 10 to <25 mL/min. Maintenance dose of oral valganciclovir; 900 mg once daily for CL_{creat} $\geq$60 mL/min, 450 mg once daily for CL_{creat} from 40 to <60 mL/min, 450 mg every second day for CL_{creat} from 25 to <40 mL/min and 450 mg twice per week for CL_{creat} from 10 to <25 mL/min. Treatment dose of IV ganciclovir: 5 mg/kg twice daily for CL_{creat} $\geq$70 mL/min, 2.5 mg/kg twice daily for CL_{creat} from 50 to <70 mL/min, 2.5 mg/kg once daily for CL_{creat} from 25 to <50 mL/min and 1.25 mg/kg daily for CL_{creat} from 10 to <25 mL/min.

Outcome measures

The primary outcome was treatment success defined as the eradication of CMV viremia at Day 21. Viral loads were determined in all patients at Days 0, 3, 7, 10, 14, 17, 21, 28, 35, 42 and 49 and were measured in plasma at a central laboratory facility, blinded with regards to treatment allocation, using the Amplicor CMV Monitor® Test (Roche Diagnostics, USA). For the primary analysis, the viral cutoff value for defining eradication was set (a priori) at 600 copies/mL plasma. Although the limit of detection was 200 copies/mL, the cutoff of 600 copies represents the validated and reproducible quantitative cutoff point of this PCR assay (as per kit instructions).

Secondary outcome measures included clinical assessment of CMV disease activity, time to viremia below the limit of detection (i.e. <200 copies/mL), viral load kinetics and safety and tolerability of each treatment. Viral kinetics, including half-life and slope, were determined by plotting best-fit viral decay curves for each patient.

Definition of CMV disease

CMV disease was defined as the presence of CMV in the blood by a local assay including shell vial culture, antigenemia assay, or accredited nucleic acid detection assay plus the presence of compatible symptoms. For viral syndrome, the definition was consistent with current American Society of Transplantation recommendations for use in clinical trials; at least one of the following was required: body temperature $\geq$38°C, new or increased significant malaise, leucopaenia (white blood cell count of <3500/μL), atypical lymphocytosis of $\geq$5%, or thrombocytopaenia (platelet count of <100 000/μL) (12). Tissue invasive disease was defined based on evidence of localized CMV infection (CMV inclusion cells or *in situ* detection of CMV antigen or DNA by immunization or hybridization, respectively) in a biopsy or other appropriate specimen (e.g. bronchoalveolar lavage, cerebrospinal fluid) and/or relevant symptoms or signs of organ dysfunction that is unlikely to be due to other causes. If the affected organ was the allograft, acute rejection was to be excluded as a possible cause for the patient's clinical findings.

Statistical methods

This trial was designed as a noninferiority study. The primary endpoint (eradication of CMV viremia at Day 21) was expected to be approximately 65% in the i.v. ganciclovir group. The valganciclovir test group was considered noninferior if the proportion of eradication was 50% or greater (accepted range of noninferiority –15%-points absolute). A sample size of 159 patients per group had 80% power to detect statistically significant inferiority ($p < 0.05$). The primary endpoint was analyzed by contingency tables according to the intention-to-treat principle; patients who dropped out of treatment and those who had missing viral loads at Day 21 were considered treatment failures. Statistical analyses used chi-square with relative risk and 95% confidence interval (CI) estimates for eradication rates; analysis of variance (ANOVA), Kruskal–Wallis and Kaplan–Meier survival analyses were used for secondary endpoints.

Results

Baseline characteristics

Demographic and baseline characteristics were similar between the two groups (Table 1). Transplant types were kidney (73.8%), liver (7.2%), heart (5.6%) and other or combined (13.4%). Clinical presentation was comparable between groups. Fever was present in 25% of valganciclovir-treated patients and 17.8% of ganciclovir patients. Forty-six percent of patients had tissue invasive disease (valganciclovir, 48.8%; i.v. ganciclovir, 42.7%). The number of patients having received previous anti-CMV therapy (prophylaxis or treatment) was 73 of 164 patients (44.5%) in the valganciclovir arm and 73 of 157 patients (46.6%) in the i.v. ganciclovir arm. Recipient and donor serostatus at the time of transplantation is given in Table 1. Recipient IgG serostatus at the time of randomization was available for 175 patients (18 seronegative and 157 seropositive) and was comparable in both arms.

Analysis of efficacy

In the intention-to-treat population, viral eradication (<600 copies/mL) was achieved in 45.1% of the valganciclovir-treated patients and in 48.4% of the ganciclovir-treated

Table 1: Baseline characteristics and demographics of the intention-to-treat population

		Valganciclovir (n = 164)	Ganciclovir (n = 157)	p-Values
Sex N (%)	Male	106 (64.6)	93 (59.2)	0.319[1]
	Female	58 (35.4)	64 (40.8)	
Ethnicity n (%)	Caucasian	127 (77.4)	118 (75.2)	0.780[1]
	Black	7 (4.3)	4 (2.5)	
	Oriental	16 (9.8)	16 (10.2)	
	Hispanic	8 (4.9)	11 (7.0)	
	Other	6 (3.6)	8 (5.1)	
Age at randomization (years)	Mean ± SD	46.2 ± 13.7	44.4 ± 13.5	0.252[2]
	Range	18–72	19–70	
Weight at randomization (kg)		68.1 ± 15.5	68.6 ± 16.6	0.780[2]
HLA-A mismatches at last transplant	No mismatch	18	18	0.925[1]
	1 or 2 mismatch	85	88	
	Missing	61	49	
HLA-B mismatches at last transplant	No mismatch	15	18	0.611[1]
	1 or 2 mismatch	88	87	
	Missing	61	49	
Transplant n (%)	Kidney	122 (74.4)	115 (73.2)	0.644[1]
	Liver	15 (9.1)	8 (5.1)	
	Heart	9 (5.5)	9 (5.7)	
	Lung	11 (6.7)	8 (5.1)	
	Pancreas	1 (0.6)	2 (1.3)	
	Multiple organs	6 (3.7)	15 (9.6)	0.039[3]
Days after transplantation	Mean ± SD	367 ± 1002	325 ± 729	0.156[4]
	Range	10–9257	20–5028	
Clinical diagnosis	No clinically detectable pathology	5 (3.0%)	3 (1.9%)	0.390[1]
	CMV syndrome	79 (48.2%)	87 (55.4%)	
	TI CMV disease	80 (48.8%)	67 (42.7%)	
Type of TI-disease	TI-pneumonia	11 (6.7%)	16 (10.2%)	0.316[5]
	TI-hepatitis	22 (13.4%)	12 (7.6%)	0.105[5]
	TI-gastrointestinal disease	46 (28.0%)	47 (29.9%)	0.714[5]
	TI disease of CNS, PNS, retina	2 (1.2%)	1 (0.6%)	1.000[5]
	other	24 (14.6%)	16 (10.2%)	0.242[5]
Indication of previous anti-CMV therapy	Prophylactic	96 (65.3%)	116 (72.0%)	0.397[1]
	Pre-emptive	17 (11.6%)	13 (8.1%)	
	Treatment of disease	34 (23.1%)	32 (19.9%)	
	N/A	–	12	
Previous anti-CMV therapy	Acyclovir	27 (18.4%)	19 (11.0%)	0.018[1]
	CMV IgG	2 (1.4%)	7 (4.0%)	
	Ganciclovir	56 (38.1%)	88 (50.9%)	
	Valaciclovir	10 (6.8%)	4 (2.3%)	
	Valganciclovir	52 (35.4%)	55 (31.8%)	
Donor (D)/recipient (R) serostatus at transplantation	D+/R–	22 (18.6)	32 (29.4)	0.080[1]
	D+/R+	78 (66.1)	56 (51.4)	
	D–/R+	12 (10.2)	10 (9.2)	
	D–/R–	6 (5.1)	11 (10.1)	
N (%)	Missing	46	48	

[1] chi-square.
[2] *t*-test.
[3] Cochran-Mantel-Haenzel; the odds ratio that a patient had a multiple organ transplant in the valganciclovir group was 0.36 (95% CI: 0.14–0.95).
[4] Mann-Whitney.
[5] Fisher's exact test.

patients at Day 21 (95% CI for the difference in proportions was –14.0 to +8.0%), fulfilling the criteria for noninferiority (Figure 1A; Kaplan–Meier survival analysis). Viral eradication at Day 49 was 67.1% in valganciclovir- and 70.1% in ganciclovir-treated patients (Figure 1A, p = NS). Clinical resolution of CMV disease, as assessed by the investigator in according to protocol definitions, occurred at a mean of 15.1 days (95% CI 13.0–17.2) and 15.1 days (95% CI 13.0–17.3) (p = 0.880) for the valganciclovir and ganciclovir groups, respectively. At Day 21, clinical success was achieved in 127 of 164 valganciclovir-treated patients (77.4%) and 126 of 157 patients (80.3%) in the i.v.

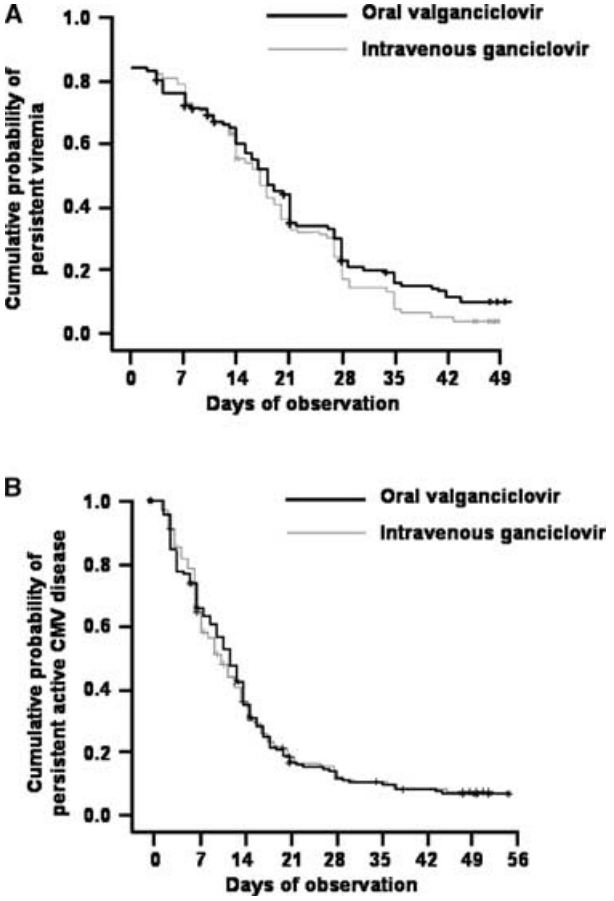

Figure 1: Kaplan–Meier curves showing cumulative probability of persistence of clinical symptoms and viral eradication in patients treated with either oral valganciclovir or i.v. ganciclovir (intention-to-treat population). There were no differences between treatment groups. Black lines denote the valganciclovir treatment arm and gray lines represent the i.v. ganciclovir treatment arm. (A) Cumulative probability of persistent viremia (cutoff level of 600 copies/mL plasma). (B) Cumulative probability of persistent active CMV disease (as assessed by the investigator).

ganciclovir arm; by Day 49 clinical success was achieved in 140 of 164 patients (85.4%) and 132 of 157 patients (84.1%), respectively (Figure 1B; Kaplan–Meier survival analysis). Resolution of fever and disappearance of active disease (Figure 1B) occurred at similar time points in both arms.

The per-protocol population included only patients with confirmed baseline viral load $\geq$600 copies/mL (valganciclovir, n = 133; ganciclovir, n = 126). The intention-to-treat and per-protocol analyses showed consistent results (Table 2A and 2B). Detailed viral kinetic analyses were only performed on the per-protocol population. Median baseline viral loads were not different between the groups (Table 2B). Viral clearance (<600 copies/mL) at Day 21 was achieved in 74 of 133 patients (55.6%) in the valganciclovir group and 76 of 126 patients in the ganciclovir group (60.3%; p = NS), and increased to 110 of 133 patients (82.7%) and 110 of 126 patients (87.3%), respectively, at Day 49 (p = NS).

Viral loads decreased following approximate first-order kinetics, and decay curves were almost identical in both treatment arms (Figure 2). In most of the patients there was a lag-time before the reduction of viral load was seen. The mean time to a clinically relevant drop in viral load ($\geq$0.3 natural log units) was 6.1 $\pm$ 4.5 days (n = 120) for valganciclovir and 6.6 $\pm$ 4.7 days (n = 116) for ganciclovir (p = NS). Median times to viral eradication (Kaplan–Meier estimates) using either the 600 copies or 200 copies cutoff were similar in both arms and are shown in Table 2B (per-protocol population).

The median viral load half-life was 11.5 days (8.3–16.5 days) and 10.4 days (7.9–14.5 days) for valganciclovir- (n = 113) and ganciclovir- (n = 112) treated patients, respectively (p = 0.932). The median slope of viral load decay (k_{decay}) was comparable in both arms (Table 2B).

Adverse events

During the first 21 days, treatment was discontinued in 11 (6.7%) valganciclovir versus 7 (4.5%) ganciclovir patients, respectively (p = NS). The most frequent adverse events are listed in Table 3. There were no major differences in the frequencies of adverse events between the treatment groups. A total of 44 of 321 patients (13.7%) reported at least one serious adverse event during the induction phase of treatment (valganciclovir: 25 of 164 patients, 15.2%, and ganciclovir: 19 of 157 patients, 12.1%; p = 0.107). Leucopenia occurred in 11.8% of patients (valganciclovir, 11.6%; ganciclovir, 12.1%). Three patients treated with valganciclovir and seven patients treated with ganciclovir developed subsequent opportunistic infections (p = 0.484). Overall, 47 of 164 valganciclovir-treated patients reported at least one potentially treatment-related adverse event during induction therapy, compared to 40 of 157 i.v. ganciclovir-treated patients during induction treatment (relative risk 1.08; 95% CI 0.86–1.36; p = 0.514).

Overall, 22 patients had 25 episodes of acute graft rejection either at the start of treatment (n = 1) or during the study period (n = 24). The incidence of acute rejection was comparable in both arms. No episodes of graft loss were noted during the treatment and study periods, but two patients in each arm died due to septicemia and one valganciclovir treated patient died of fungal infection during the 49 days of treatment. None of these were treatment-attributable deaths.

Potential factors affecting outcome

Factors potentially related to treatment success/failure at Day 21 were assessed. Donor or recipient CMV pretransplant serostatus or serostatus at randomization, the

Table 2: Analysis of efficacy

Response	Valganciclovir	Ganciclovir	Difference (95% CI)
(A) Intention-to-treat population	n = 164	n = 157	
viremia eradication at Day 21	74 (45.1%)	76 (48.4%)	−14% to +8%
viremia eradication at Day 49	110 (67.1%)	110 (70.1%)	−13% to +7%
Clinical resolution of CMV disease at Day 21	127 (77.4%)	126 (80.3%)	−12% to +6%
Clinical resolution of CMV disease at Day 49	140 (85.4%)	132 (84.1%)	−7% to +9%
(B) Per-protocol population	Valganciclovir (n = 133)	Ganciclovir (n = 126)	
Median baseline viral load[1] (copies/mL)	19 750 (3470–84 500)	16 675 (3520–83 500)	
Time to viral eradication (≤600 copies) (days)	21 (95% CI: 19.3–22.7)	19 (95% CI: 16.8–21.2)	
Time to viral eradication (≤200 copies) (days)	21 (95% CI: 17.1–24.9)	21 (95% CI: 17.2–24.8)	
Calculated decay slope (log copies/day)[2]	–0.060 (–0.084 to –0.042)	–0.067 (–0.088 to –0.048)	
Calculated viral load half-life (days)[2]	11.5 (8.3–16.5)	10.4 (7.9–14.5)	

[1]Inter-quartile range is shown in parentheses.
[2]Range is shown in parentheses.

presence of tissue invasive disease, previous anti-CMV therapy and type of organs transplanted or number of HLA-A or HLA-B locus mismatches had no significant influence on treatment success. The only factor predictive of viral eradication was the baseline viral load (Figure 3). Patients with a baseline viral load of <10 000 copies/mL had a univariate relative chance for eradication of viremia (cutoff: 600 copies/mL) at Day 21 of 6.41 (95% CI 3.61–11.36; $p < 0.001$) and at Day 49 of 2.56 (95% CI 1.29–5.08; $p = 0.001$), compared to those with a viral load of ≥10 000 copies/mL.

Discussion

This is the first randomized controlled trial comparing oral valganciclovir to i.v. ganciclovir for the treatment of CMV disease in solid organ transplant recipients. The current American Society of Transplantation recommendation for the treatment of CMV disease is i.v. ganciclovir and this was the chosen comparator (5). The results of this trial show that 900 mg of oral valganciclovir twice daily is non-inferior to 5 mg/kg of i.v. ganciclovir twice daily for the treatment of CMV disease. This was confirmed by both intention-to-treat and per-protocol analyses at Day 21 and Day 49. In the per-protocol population viral clearance by Day 21 was almost 60%, increasing to about 85% at the end of treatment (Day 49). Viral clearance kinetics based on plotting best-fit decay curves for each patient was almost identical in the two arms. In addition, clinical parameters such as resolution of fever and clinical resolution of CMV disease (as assessed by the investigator) were the same in both arms, with very high clinical success rates observed by Day 49 (valganciclovir, 85.4%; ganciclovir, 84.1%). Thus, both clinical and viral parameters were equivalent for valganciclovir- and ganciclovir-treated patients at all time points until Day 49.

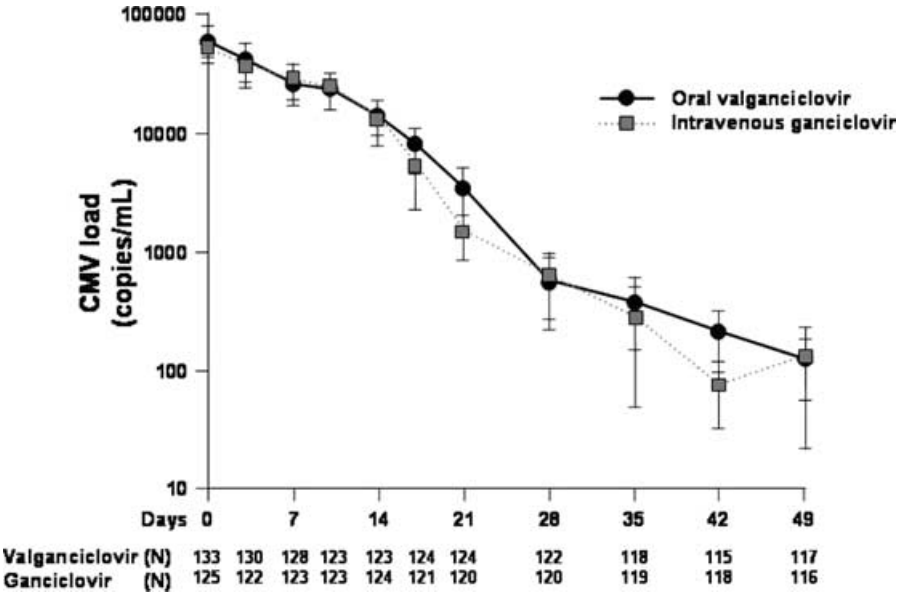

Figure 2: Reduction in CMV viral load with time in patients treated with oral valganciclovir or i.v. ganciclovir. There was no difference in viral load reduction rate between the treatment groups (200 copies/mL as assay cutoff; per-protocol population).

Table 3: Distribution of main reported adverse events by treatment group (number of patients with at least 1 episode)

Adverse event	Valganciclovir	Ganciclovir	p-Value (Cochran-Mantel-Haenszel)
Leucopenia	19 (11.6%)	19 (12.1%)	0.886
Diarrhea	12 (7.3%)	20 (12.7%)	0.109
Urinary tract infection	15 (9.1%)	17 (10.8%)	0.616
Anemia	20 (12.2%)	11 (7.0%)	0.120
Respiratory disorders	14 (8.5%)	9 (5.7%)	0.333
Cough	8 (4.9%)	7 (4.5%)	0.859
Abdominal pain	5 (3.0%)	9 (5.7%)	0.247
Nausea/vomiting	7 (4.3%)	7 (4.5%)	0.933
Diabetes	4 (2.4%)	4 (2.5%)	0.950
Sore throat	6 (3.7%)	–	0.015[1]
Dyspepsia	4 (2.4%)	3 (1.9%)	0.747
Flu-like symptoms	2 (1.2%)	2 (1.3%)	0.965
Tremors	2 (1.2%)	2 (1.3%)	0.965
Neutropenia	2 (1.2%)	–	0.499[1]
Any other event	92 (56.1%)	78 (49.7%)	0.260
Total patients with events	115 (70.1%)	100 (63.7%)	0.221

[1]Fisher's exact test.

Several studies have demonstrated the importance of CMV viral load in the pathogenesis of CMV disease in transplant recipients (13–16) and the clinical utility of monitoring CMV viral load in transplant recipients is well established (13–17). In our study up to 12 viral load measurements were performed during the treatment period, enabling us to perform a detailed and sensitive analysis of viral kinetics, such as half-life and slope of decay. Median half-lives appear longer than those reported in smaller observational studies using the same therapies (14,18). Reasons for these differences may include sample size, the frequency of viral load measurements, and differences in immunologic parameters, such as CMV specific T-cell responses in different populations (19). However, the viral load reductions of 1.06% and 1.07% copies/mL/day for the valganciclovir and ganciclovir groups, respectively, are similar to those achieved in allogenic stem cell transplantation (20). A median initial lag phase of approximately 6 days was commonly observed before a sustained reduction in viral load was achieved, especially in patients with high initial viral loads. This novel observation may be secondary to a true delay in viral clearance in heavily immunosuppressed patients, or potentially due to release of nonviable viral DNA from cells into the plasma component after the initiation of anti-viral therapy.

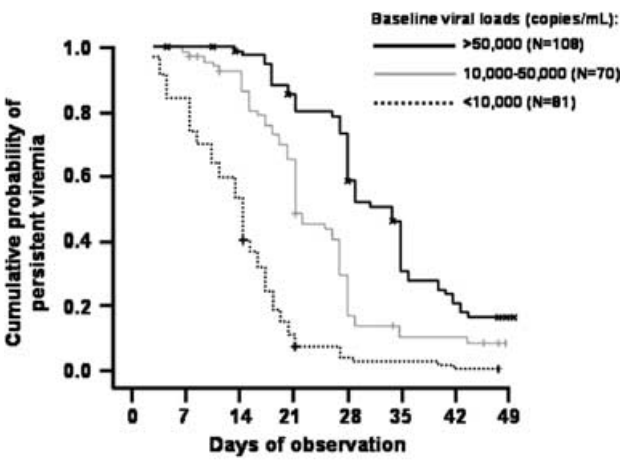

Figure 3: Kaplan–Meier curves showing the influence of three different baseline viral load levels on efficacy of treatment (viral eradication with cutoff level of 600 copies/mL plasma; per-protocol population) ($p < 0.001$, log-rank test).

Symptomatic CMV disease is generally treated with a 2–4 week course of i.v. ganciclovir (3,5,21). We chose a treatment length of 21 days followed by a maintenance period of 28 days. In transplant recipients treated for CMV disease, the risk of recurrent CMV disease after treatment is estimated to be 25–30% (22,23). The most important predictor of disease recurrence after treatment of CMV disease is persistent viremia at the end of anti-viral therapy (14,24). Therefore, current guidelines recommend treatment until eradication of CMV viremia (3,5). Based on our study, it is apparent that viral eradication is only achieved in approximately 58% of patients with 21 days of therapy despite the resolution of symptoms in a significantly larger fraction of patients. Prolongation of therapy is therefore warranted for a substantial number of patients and should likely be individualized based on serial viral load measurements.

We also analyzed predictors of viral eradication. Amongst the factors analyzed, only the baseline viral load was a significant predictor of viral eradication. Low baseline viral loads increased the likelihood of viral eradication severalfold. Therefore, viral load is clearly an important prognostic indicator for length of treatment. However, the absolute treatment length cannot be adequately predicted without viral monitoring. The pretransplant donor seropositive/recipient seronegative sub-group of patients is well known to be at higher risk of CMV disease. Interestingly, we found that these patients responded just as well to treatment as CMV seropositive patients. This finding cannot be explained by differences in baseline viral loads (multivariate logistic regression) and further substantiates that response to anti-viral therapy is likely dependent on a complex interaction between the virus and the host (25,26).

Both valganciclovir and ganciclovir were well tolerated, compliance was high and similar, and there was no difference in the adverse event profile, including leucopenia and neutropenia, between treatment arms.

One of the limitations of this study was that treatment allocation was not blinded. It was felt that the use of i.v. placebo would be difficult to justify for ethical reasons and since the primary endpoint is an objective outcome, it is believed that this will only induce an insignificant bias to the study. Occasionally patients with severe tissue invasive disease, especially gastrointestinal disease, may have low or negative peripheral viral loads. Due to the design of this study, such patients would either have been excluded, or the use of viral loads would not be an appropriate outcome measure to evaluate response to therapy in this sub-group. In the present study we also excluded life-threateningly ill patients (based on the decision of the investigator) and no patient had extremely high viral loads (typically $>10^6$ copies). Extrapolation to these patient categories may not be relevant. Single kidney transplant recipients also comprised more than 70% of the patients in the study with a relatively small number of other types of organ recipients which somewhat limits the validity of the results in nonkidney transplants. Finally, since this study did not include pediatric patients, oral treatment in this population should still be given with great care until more data are available.

In conclusion, for solid organ transplant recipients with CMV disease, oral valganciclovir has comparable safety and is not inferior to standard i.v. ganciclovir treatment for eradication of viremia and clinical success. These findings have major implications for the management of CMV disease, for patients, physicians and health-care providers, but care should be taken in extrapolating to organ transplant recipients not properly represented in the present study, such as nonkidney transplants, pediatric patients and patients with severe CMV disease.

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Appendix: Victor study group

North America

Sandra Cockfield

Latin

Anabela Arminio
Luis F.A. Camargo
Valter Duro Garcia
Carmen Gracida
Carlos Henriquez
Marilda Mazzali
Elias David Neto
Jose Osmar Medina Pestana
Rafael Reyes

Asia, Pacific Islands and Australia

Ian Dittmer
Allan Glanville
George T. John
Vijay Kher
R.K. Sharma
C.M.Thiagarajan

Europe and Middle East

Jose Maria Aguado
Emel Akoglu
Hofman Blazenka
Felix Burkhalter
Magdalena Durlik
Antonio Franco Esteve
Maciej Glyda
Abdul Hammad
Rajko Hrvacevic
Madis Ilmoja
Marian Klinger
Dirk Kuypers
Phil Mason
Miguel Montejo
Ercan Ok
Mai Ots
Patrik Peters
Rafails Rozentals
Boleslaw Rutkowski
Sabine Schmaldienst
Juerg Steiger
Zbigniew Wlodarczyk
Michael Zakliczynski