

A CONTROLLED TRIAL OF VALGANCICLOVIR AS INDUCTION THERAPY FOR CYTOMEGALOVIRUS RETINITIS

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ABSTRACT

Background Valganciclovir is an orally administered prodrug that is rapidly hydrolyzed to ganciclovir. We compared the effects of oral valganciclovir with those of intravenous ganciclovir as induction therapy for newly diagnosed cytomegalovirus retinitis in 160 patients with the acquired immunodeficiency syndrome (AIDS).

Methods The primary end point was photographically determined progression of cytomegalovirus retinitis within four weeks after the initiation of treatment. Secondary end points included the achievement of a prospectively defined satisfactory response to induction therapy and the time to progression of cytomegalovirus retinitis. After four weeks, all patients received valganciclovir as maintenance therapy.

Results Eighty patients were randomly assigned to each treatment group. Of the patients who could be evaluated, 7 of 70 assigned to intravenous ganciclovir (10.0 percent) and 7 of 71 assigned to oral valganciclovir (9.9 percent) had progression of cytomegalovirus retinitis during the first four weeks (difference in proportions, 0.1 percentage point; 95 percent confidence interval, -9.7 to 10.0). Forty-seven of 61 patients (77.0 percent) assigned to intravenous ganciclovir and 46 of 64 (71.9 percent) assigned to valganciclovir had a satisfactory response to induction therapy (difference in proportions, 5.2 percentage points; 95 percent confidence interval, -20.4 to 10.1). The median times to progression of retinitis were 125 days in the group assigned to intravenous ganciclovir and 160 days in the group assigned to oral valganciclovir. The mean values for the area under the curve for the ganciclovir dosage interval were similar at both induction doses and maintenance doses. The frequency and severity of adverse events were similar in the two treatment groups.

Conclusions Orally administered valganciclovir appears to be as effective as intravenous ganciclovir for induction treatment and is convenient and effective for the long-term management of cytomegalovirus retinitis in patients with AIDS. (N Engl J Med 2002; 346:1119-26.)

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CYTOMEGALOVIRUS retinitis remains the leading cause of visual loss in patients with the acquired immunodeficiency syndrome (AIDS).¹⁻³ Induction therapy with intravenous ganciclovir,^{4,5} foscarnet,^{5,6} or cidofovir,^{7,8} followed by maintenance therapy, can effectively make cytomegalovirus retinitis inactive. If recovery of immune function is not possible, indefinite treatment is needed, and an indwelling catheter and daily intravenous medication may be required. The cost, the risk of sepsis, and the adverse effect on the quality of life associated with an indwelling catheter spurred the development of an oral formulation of ganciclovir.⁹ When administered orally, ganciclovir requires three doses (up to 12 capsules per day) and has a bioavailability of only 6 to 9 percent¹⁰; it therefore cannot be used for induction therapy. Local treatment with a ganciclovir implant can control intraocular disease but does not obviate the need for systemic treatment.^{11,12} Concomitant treatment with oral ganciclovir can reduce the risk of additional cytomegalovirus disease in patients with a ganciclovir implant.¹³ An oral agent is needed that is effective for both induction and maintenance therapy, with a convenient dosing schedule and a low daily pill burden.

Valganciclovir is a monovalyl ester prodrug that, when administered orally, is rapidly hydrolyzed to the active compound ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is 60 percent,¹⁴ and a dose of 900 mg (two 450-mg tablets) results in ganciclovir blood levels similar to those obtained with a dose of 5 mg of intravenous ganciclovir per kilogram of body weight.^{15,16} We conducted a randomized, controlled clinical trial to compare the safety and efficacy of oral valganciclovir and intravenous ganciclovir as therapy for newly diagnosed cytomegalovirus retinitis.

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METHODS

Study Design

The study protocol was reviewed and approved by the local institutional review boards at 42 clinical sites: 22 in the United States, 11 in Europe, 3 in Mexico, 3 in Canada, 2 in Australia, and 1 in Brazil. All patients gave written informed consent. The study patients were adults with AIDS and newly diagnosed cytomegalovirus retinitis. Because the use of an oral agent had not been studied as induction therapy, enrollment was initially restricted to patients with retinitis located more than 1500 μm from the fovea. After a masked review of photographs from the first 43 patients, the entry criteria were expanded to include patients with more posterior retinitis.

Patients were ineligible if they had a history of treated cytomegalovirus retinitis, had received systemic anticytomegalovirus therapy for more than three weeks, or had received any systemic anticytomegalovirus therapy within three months before randomization. Eligible patients may have received up to three months of prophylaxis with oral ganciclovir. Other exclusion criteria were the presence of severe uncontrolled diarrhea (more than three watery stools per day), an absolute neutrophil count below 750 cells per cubic millimeter, a platelet count below 75,000 per cubic millimeter, an estimated creatinine clearance below 70 ml per minute, or a score below 70 on the Karnofsky performance scale.

Patients were randomly assigned in a 1:1 ratio at each site to receive either 5 mg of intravenous ganciclovir per kilogram twice daily for three weeks (induction therapy), followed by 5 mg per kilogram once daily for one week (maintenance therapy), or 900 mg of oral valganciclovir (two 450-mg tablets) twice daily for three weeks (induction therapy), followed by 900 mg once daily for one week (maintenance therapy). Antiretroviral therapy was to remain unchanged during the first four weeks of the study. Ocular examinations were performed at base line and weeks 2 and 4 and included determination of visual acuity with the use of charts from the Early Treatment Diabetic Retinopathy Study¹⁷ or Snellen charts, indirect ophthalmoscopy, and bilateral nine-field fundus photography. Laboratory evaluations were performed at base line and then weekly for four weeks and included qualitative and quantitative polymerase-chain-reaction (PCR) assays of blood for cytomegalovirus and a quantitative assay for the human immunodeficiency virus (HIV), as well as routine blood chemical and hematologic tests. Urine (and occasionally semen or blood) was collected at base line and week 4 for cytomegalovirus culture. CD4+ cell counts were determined at base line and week 4. Complete steady-state pharmacokinetic profiles were obtained at selected centers at week 1 (induction dosing) and week 4 (maintenance dosing).

At the end of week 4, patients in both groups received 900 mg of oral valganciclovir once daily for continued maintenance therapy. Follow-up examinations, similar to those performed during the first four weeks of the study, were performed every two weeks until week 16 and then monthly until progression of retinitis occurred. Patients in whom retinitis progressed were offered induction therapy followed by maintenance therapy with valganciclovir and were examined on a monthly basis until valganciclovir therapy was discontinued or death occurred.

Outcome Measures

The primary outcome measure was the progression of retinitis during the first four weeks of therapy, as determined by treatment-masked grading of retinal photographs. Progression of retinitis was defined as movement of a border of the lesion by at least 750 μm over a 750- μm front or the development of a new area of cytomegalovirus retinitis at least 750 μm in diameter.

Secondary outcome measures included the achievement of a satisfactory response to induction treatment during the first four weeks, as determined by analysis of retinal photographs. A satisfactory response was achieved when all of the following criteria were met:

no movement of a lesion border by 1500 μm or more and no development of a new lesion 1500 μm or more in diameter between base line and week 4, no movement of a lesion border by 750 μm or more and no development of a new lesion 750 μm or more in diameter between week 2 and week 4, no increase in retinitis activity between week 2 and week 4, and a decrease in retinitis activity between base line and week 4 by at least two steps on the six-step activity scale of the Fundus Photograph Reading Center at the University of Wisconsin.

Other secondary outcome measures were the time to progression of retinitis as determined by examination of photographs, the effect of treatment on cytomegalovirus cultures and plasma PCR results, the safety and tolerability of the treatment regimens, the development of contralateral and extraocular cytomegalovirus disease, and survival. All photographically derived outcomes were determined by independent grading of retinal photographs, performed by graders at the Fundus Photograph Reading Center who were unaware of treatment assignments.

Statistical Analysis

The sample size was based on the need to provide an estimate of the difference (intravenous ganciclovir minus oral valganciclovir) in the proportion of patients with progression of cytomegalovirus retinitis by week 4 with a relatively narrow confidence interval, with constraints on enrollment due to the decline in cytomegalovirus retinitis associated with highly active antiretroviral therapy taken into account. On the basis of these considerations, we calculated that 75 patients per treatment group would be needed. We assumed that 20 percent of patients in each study group would have progression at week 4, on the basis of a previous study that reported that progression had occurred at week 4 in 23 percent of patients assigned to intravenous ganciclovir and 86 percent of patients for whom treatment was deferred.⁴ Using a noninferiority study design, we defined an acceptable range of efficacy as a lower 95 percent confidence limit for the difference in proportions (intravenous ganciclovir minus oral valganciclovir) that was greater than -0.25 .

The 95 percent confidence interval for the difference in proportions of progressions and other binary end points at week 4 was based on the normal approximation to the binomial distribution. Long-term data on the time to progression were evaluated with the use of Kaplan–Meier survival analysis,¹⁸ and the mean, median, and lower and upper quartiles (and their confidence intervals) were derived. All P values were two-sided. There were no interim analyses of efficacy. All authors had full access to all data and take responsibility for the integrity of the data, the accuracy of the analysis, and the content of the article.

RESULTS

Between January 1997 and March 1999, 160 patients were enrolled in the study; 80 were randomly assigned to receive intravenous ganciclovir and 80 to receive oral valganciclovir. There were no substantial differences between the groups in base-line characteristics (Table 1).

For the analyses of efficacy, seven patients in each group were excluded for the following reasons defined by the protocol: absence of photographic confirmation of cytomegalovirus retinitis at study entry (three assigned to intravenous ganciclovir and two assigned to valganciclovir); noncompliance with study therapy, defined as use of treatment on fewer than 21 of 28 days (one assigned to intravenous ganciclovir and three assigned to valganciclovir); absence of efficacy data reported after randomization (one assigned to intrave-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	INTRAVENOUS GANCICLOVIR (N=80)	ORAL VALGANCICLOVIR (N=80)
Age — yr*	36.5±7.3	39.0±7.6
Male sex — no. (%)	73 (91)	72 (90)
Race or ethnic group — no. (%)		
White	42 (52)	43 (54)
Black	9 (11)	9 (11)
Hispanic	25 (31)	25 (31)
Other	4 (5)	3 (4)
Karnofsky score†	85.9±10.3	82.9±10.1
Retinitis in zone 1 — no. (%)	19 (24)	19 (24)
Bilateral retinitis — no. (%)	20 (25)	20 (25)
Duration of use of protease inhibitors — no. (%)‡		
None	21 (26)	26 (32)
90 days	16 (20)	14 (18)
91–365 days	18 (22)	17 (21)
>365 days	25 (31)	23 (29)
Plasma HIV load§		
No. of patients tested	66	63
Median — log copies/ml	4.9	4.8
Mean — log copies/ml†	4.5±1.4	4.5±1.2
CD4+ count		
No. of patients tested	74	75
Median — cells/mm ³	26	20
Mean — cells/mm ³ †	53.6±67.6	58.0±80.8
Range — cells/mm ³	2–365	2–390
Cytomegalovirus culture — no. (%)		
Patients tested	71	71
Patients with a positive culture	46 (65)	33 (46)
Cytomegalovirus qualitative PCR of plasma¶		
No. of patients tested	76	77
Patients with positive PCR results — no. (%)	39 (51)	31 (40)
Cytomegalovirus quantitative PCR of plasma		
— log copies/ml		
Median	3.4	3.6
Mean†	3.5±0.8	3.6±0.7

*Plus–minus values are medians ±SD.

†Plus–minus values are means ±SD.

‡Use of protease inhibitors was considered a marker for highly active antiretroviral therapy.

§Values were measured with an Amplicor HIV Monitor (Roche Diagnostic Systems). HIV denotes human immunodeficiency virus.

¶Values were measured with an Amplicor CMV Monitor (Roche Diagnostic Systems) and were log-transformed with use of a base 10 scale.

||Values were measured with a Cobas Amplicor CMV Monitor (Roche Diagnostic Systems) and were log-transformed with use of a base 10 scale. The internal quantitation standard was a plasmid DNA with primer-binding sites identical to those of cytomegalovirus but with a unique probe-binding region.

nous ganciclovir and two assigned to valganciclovir); presence of a ganciclovir implant in one eye (one assigned to intravenous ganciclovir); and nonreceipt of any doses of study drug (one assigned to intravenous ganciclovir). For this study design, the most conservative analysis excludes these patients. An intention-to-treat analysis was also performed and yielded the same results. For the analyses of safety, we excluded one patient in the valganciclovir group who had no safety data after randomization and one patient in the ganciclovir group who did not receive any doses of the study drug.

This report contains all safety and efficacy data

through September 30, 1999, six months after the last patient was enrolled. The results of additional analyses of such data through April 2000 were similar. The median duration of follow-up was 419 days for patients originally assigned to intravenous ganciclovir and 376 days for patients originally assigned to oral valganciclovir.

Progression of Retinitis and Response to Induction Therapy

For the analysis of the progression of retinitis during the first four weeks, sets of photographs could be evaluated for 70 patients assigned to intravenous gan-

ciclovir and 71 assigned to oral valganciclovir. Progression occurred in 7 of 70 patients assigned to intravenous ganciclovir (10.0 percent) and in 7 of 71 assigned to oral valganciclovir (9.9 percent). The difference in proportions was 0.1 percentage point (95 percent confidence interval, -9.7 to 10.0). Progression of retinitis in 13 of 14 patients was due to movement of a lesion border by at least $750\ \mu\text{m}$, and progression in 5 of 7 patients in each group occurred between base line and week 2.

For the analysis of the response to induction therapy, 61 patients assigned to intravenous ganciclovir and 64 assigned to oral valganciclovir had a set of photographs that could be evaluated. A satisfactory response to induction therapy (Fig. 1A and 1B) was achieved in 47 of 61 patients assigned to intravenous

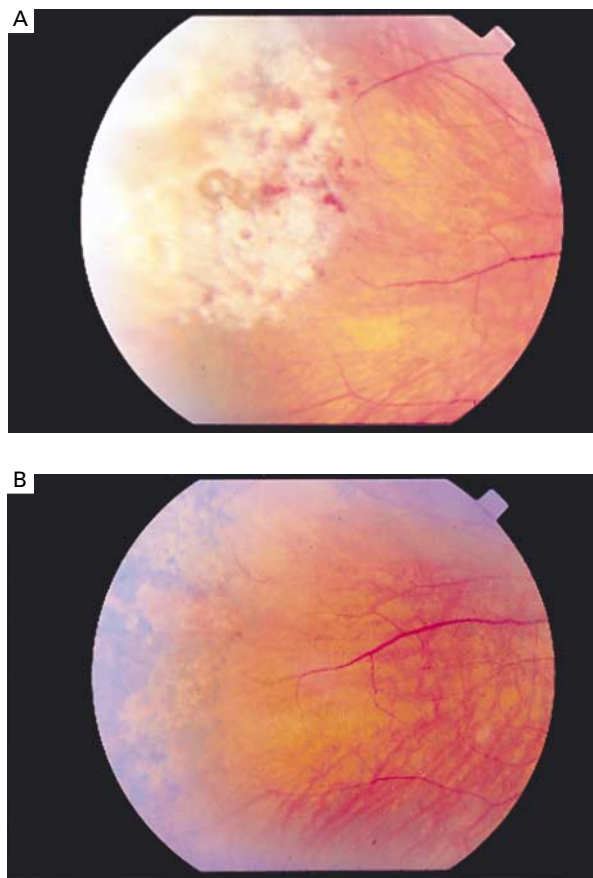


Figure 1. Response of Cytomegalovirus Retinitis to Treatment with Oral Valganciclovir.

The photograph in Panel A shows active cytomegalovirus in the retina of the left eye at base line. The photograph of the same eye in Panel B shows resolution of cytomegalovirus retinitis after four weeks of treatment with oral valganciclovir.

ganciclovir (77.0 percent) and 46 of 64 patients assigned to oral valganciclovir (71.9 percent). The difference in proportions was 5.2 percentage points (95 percent confidence interval, -20.4 to 10.1). The most common reason for an unsatisfactory response was failure of the retinitis activity to decrease by two or more steps (13 of 14 patients with unsatisfactory responses in the ganciclovir group and 17 of 18 in the valganciclovir group).

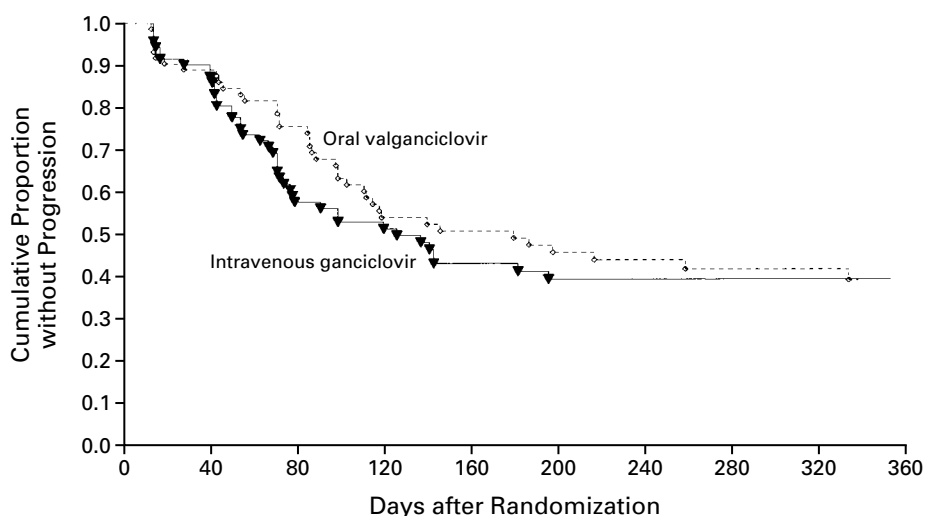
The median time to progression of retinitis for patients originally assigned to intravenous ganciclovir was 125 days (95 percent confidence interval, 74 to a value that could not be estimated) and that for patients assigned to oral valganciclovir was 160 days (95 percent confidence interval, 99 to a value that could not be estimated) (Fig. 2). The relative risk of progression of retinitis in the valganciclovir group as compared with the ganciclovir group, calculated from the Cox proportional-hazards model, was 0.90 (95 percent confidence interval, 0.58 to 1.38).

Virologic Assessment

There were no substantial changes in HIV load or CD4+ cell count during the four weeks of randomized treatment. Median HIV loads, expressed as the log (on a base 10 scale) of the number of copies of HIV RNA per milliliter, were similar at base line (4.9 log copies per milliliter in the ganciclovir group and 4.8 log copies per milliliter in the valganciclovir group), and there was little change at week 4 (4.8 log copies per milliliter in the ganciclovir group and 5.0 log copies per milliliter in the valganciclovir group). Median CD4+ cell counts were similar at base line (26 cells per cubic millimeter in the ganciclovir group and 20 cells per cubic millimeter in the valganciclovir group), and there was little change at week 4 (20 cells per cubic millimeter in each group).

Cultures of urine (predominantly), blood, or semen were positive for cytomegalovirus at base line in 46 of 71 patients assigned to intravenous ganciclovir (65 percent) and in 33 of 71 patients assigned to oral valganciclovir (46 percent, $P=0.03$) (Table 1). After four weeks of treatment, only 4 of 64 patients assigned to ganciclovir (6 percent) and 4 of 58 patients assigned to valganciclovir (7 percent) had a positive cytomegalovirus culture.

Cytomegalovirus viremia as determined by qualitative PCR was present at base line in 39 of 76 patients assigned to intravenous ganciclovir (51 percent) and in 31 of 77 patients assigned to valganciclovir (40 percent, $P=0.17$). By quantitative PCR assay, the median log cytomegalovirus DNA load at base line was 3.4 in the ganciclovir group (mean, 3.5) and 3.6 in the valganciclovir group (mean, 3.6) (Table 1). After four weeks of treatment, only 2 of 70 patients assigned to ganciclovir (3 percent) and 3 of 71 patients assigned



No. AT RISK										
Oral valganciclovir	72	65	39	33	25	21	18	17	15	14
Intravenous ganciclovir	74	62	49	34	32	26	22	18	16	14

Figure 2. Kaplan–Meier Curves Showing the Cumulative Proportion of Patients without Progression of Retinitis.

to valganciclovir (4 percent) had positive PCR results for cytomegalovirus.

Adverse Events

During randomized treatment, diarrhea was the most common adverse event and occurred more often in the valganciclovir group than in the ganciclovir group (19 percent vs. 10 percent, $P=0.11$). Intravenous-catheter-related events occurred in 9 percent of patients in the ganciclovir group and in 4 percent of patients in the valganciclovir group (catheters were in place for reasons unrelated to valganciclovir treatment). Neutropenia was reported with similar frequency in the two groups (13 percent in the ganciclovir group and 14 percent in the valganciclovir group). In the long-term extension phase of the study, an absolute neutrophil count below 500 cells per cubic millimeter developed in 24 percent of patients. Neither the hemolytic-uremic syndrome nor thrombotic thrombocytopenia purpura developed in any patient.

Retinal detachment occurred in 7 patients (5 in the ganciclovir group and 2 in the valganciclovir group) during the first four weeks and in a total of 30 of 158 patients (19 percent) over the course of the study (15 in each group). On the basis of ophthalmologic assessment, contralateral cytomegalovirus retinitis developed in 1 patient in the valganciclovir group during the first four weeks and, over the course of the study, in 18 of 120 patients who entered the study

with unilateral retinitis (15 percent). Two deaths occurred (one in each group) during randomized treatment.

Pharmacokinetic Studies

Blood levels of the prodrug valganciclovir were low; mean values for the area under the curve at steady state and the maximal concentration of valganciclovir were approximately 1 percent and 2 percent, respectively, of those of ganciclovir (Fig. 3). At both induction and maintenance doses, systemic exposure to ganciclovir was similar after the administration of oral valganciclovir and intravenous ganciclovir (Fig. 3 and Table 2). The maximal concentration of ganciclovir achieved with oral valganciclovir was 59 to 67 percent of that achieved with intravenous ganciclovir. The relative bioavailability of ganciclovir derived from oral valganciclovir, as compared with intravenous ganciclovir, was 1.16 (90 percent confidence interval, 0.98 to 1.36) at week 1 and 1.09 (90 percent confidence interval, 0.91 to 1.31) at week 4. The absolute bioavailability of ganciclovir derived from 900 mg of oral valganciclovir administered twice daily was 64 percent, and the bioavailability derived from the once-daily regimen was 59 percent.

DISCUSSION

The results of our study indicate that a twice-daily dose of 900 mg of oral valganciclovir for induction

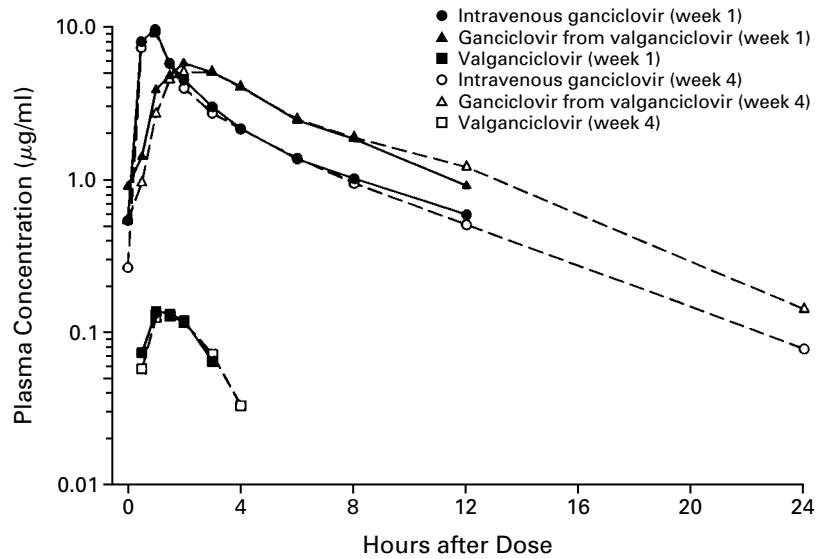


Figure 3. Mean Steady-State Ganciclovir and Valganciclovir Concentrations after Treatment with Intravenous Ganciclovir or Oral Valganciclovir.

The scale for plasma concentrations is logarithmic. Week 1 denotes induction therapy, and week 4 maintenance therapy.

TABLE 2. PHARMACOKINETIC VALUES FOR GANCICLOVIR AFTER TREATMENT WITH INTRAVENOUS GANCICLOVIR OR ORAL VALGANCICLOVIR.*

TREATMENT	NO. OF PATIENTS	AUC	C _{max}	T _{max}	T _{1/2}
		µg·hr/ml	µg/ml		hr
Week 1 (induction therapy)					
Intravenous ganciclovir	18	28.6±9.0	10.4±4.9	1.0	3.99±0.85
Oral valganciclovir	25	32.8±10.1	6.71±2.12	2.0	3.90±1.11
Week 4 (maintenance therapy)					
Intravenous ganciclovir	18	30.7±7.7	9.86±3.14	1.0	4.32±0.69
Oral valganciclovir	20	34.9±13.3	5.87±1.81	2.0	4.12±0.86

*Plus-minus values are means ±SD. AUC denotes the area under the time-concentration curve (measured at 12 hours for induction therapy and at 24 hours for maintenance therapy); C_{max} denotes the maximal concentration of the drug; T_{max} denotes the median time at which maximal concentration was achieved; and T_{1/2} denotes the half-life of ganciclovir.

therapy in patients with cytomegalovirus retinitis has an efficacy and safety profile that is similar to the profile for intravenous ganciclovir. The proportions of patients with progression of retinitis during the first four weeks were similar for the two regimens. A similar proportion of patients in each group had a satisfactory response to induction therapy. Almost all patients in the study had negative cytomegalovirus cultures and PCR results at the end of four weeks of treatment. The pharmacokinetic profiles showed that systemic

exposure to ganciclovir after the administration of valganciclovir is similar to that with intravenous ganciclovir. Rates of adverse events, particularly neutropenia, were also similar. The main difference in safety between the two treatments was related to the mode of administration, with more diarrhea in the oral valganciclovir group and more catheter-related complications in the intravenous group.

Our study was not designed to evaluate the differences between these treatments for maintenance ther-

apy, which would require a randomized comparison of patients followed up to the time of the progression of retinitis. We originally designed such a study but concluded that it would be difficult to conduct, given the nonintravenous treatment options available and the declining incidence of cytomegalovirus retinitis. However, on the basis of its efficacy for induction and the pharmacokinetic data, we would expect valganciclovir to compare favorably with both intravenous and oral ganciclovir for maintenance therapy. The area under the curve at 24 hours for ganciclovir derived from oral valganciclovir exceeds the area under the curve at 24 hours for 3 g of oral ganciclovir (34.9 vs. 14.7 $\mu\text{g}\cdot\text{hr}$ per milliliter,¹⁰ respectively) and is similar to that for 5 mg of intravenous ganciclovir per kilogram (30.7 $\mu\text{g}\cdot\text{hr}$ per milliliter) for maintenance therapy. In addition, the reduced pill burden and once-daily dosing with oral valganciclovir for maintenance treatment may increase adherence and therefore improve outcomes.

The median times to progression of retinitis were 125 days for patients originally assigned to intravenous ganciclovir and 160 days for patients originally assigned to oral valganciclovir, which are longer than any effect of treatment observed in trials of ganciclovir conducted before the availability of highly active antiretroviral therapy. Although there is no evidence, on the basis of HIV loads and CD4+ cell counts, that highly active antiretroviral therapy affected our primary outcome at four weeks, it almost certainly influenced the observed times to progression of retinitis. The proportion of patients in whom progression developed over a one-year period was 61 percent, whereas in studies conducted before the advent of highly active antiretroviral therapy, 85 percent of patients receiving intravenous ganciclovir had progression of retinitis by four months.⁵ For patients with no recovery of immune function, it would be expected that the time to progression of retinitis would be similar to the medians of 47 to 71 days^{4,5,9,12} observed before highly active antiretroviral therapy became available. Because of the heterogeneity in the immune response to highly active antiretroviral therapy, the time to the progression of retinitis may vary widely from patient to patient. Careful surveillance for progression of retinitis is therefore recommended throughout treatment.

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APPENDIX

The members of the Valganciclovir Study Group were as follows: D.F. Martin (Emory University, Atlanta); J. Sierra-Madero (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico); G. Ortega (Hospital Médica Sur, Mexico City, Mexico); S. Walmsley and J. Hopkins (Toronto General Hospital, Toronto); R.A. Wolitz and H. Bloom (Kaiser Permanente Medical Center, San Francisco); R. Lalonde and J. Deschênes (McGill University Health Centre, Montreal); L. Nieto (Hospital Regional de Zona Gabriel Mancera, Del Valle, Mexico); B.D.

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CORRECTION

**A Controlled Trial of Valganciclovir as Induction
Therapy for Cytomegalovirus Retinitis**

A Controlled Trial of Valganciclovir as Induction Therapy for Cytomegalovirus Retinitis . The Appendix on page 1125 should have included Peter McCluskey (St. Vincent's Hospital, Sydney, Australia) as a member of the Valganciclovir Study Group.