

ORAL GANCICLOVIR AS MAINTENANCE TREATMENT FOR CYTOMEGALOVIRUS RETINITIS IN PATIENTS WITH AIDS

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Abstract Background. *Cytomegalovirus retinitis, a sight-threatening infection associated with the acquired immunodeficiency syndrome (AIDS), currently requires lifelong intravenous treatment. An effective oral treatment would be an important advance.*

Methods. *We compared oral with intravenous ganciclovir in an open-label, randomized study in patients with AIDS and newly diagnosed, stable cytomegalovirus retinitis (the disease was stabilized by three weeks of treatment with intravenous ganciclovir). Sixty subjects were randomly assigned to maintenance therapy with intravenous ganciclovir at a dose of 5 mg per kilogram of body weight daily, and 63 to maintenance therapy with oral ganciclovir at a dose of 3000 mg daily. The subjects were followed for up to 20 weeks, with photography of the fundi conducted every other week. The photographs were evaluated at the completion of the study by an experienced grader who was unaware of the subjects' treatment assignments.*

Results. *Efficacy could be evaluated in 117 subjects; photographs were ungradable for 2 of the 117. On the basis of the masked assessment of photographs from*

115 subjects, the mean time to the progression of retinitis was 62 days in those given intravenous ganciclovir and 57 days in those given oral ganciclovir ($P=0.63$; relative risk [oral vs. intravenous], 1.08; 95 percent confidence interval for the difference in means, -22 to $+12$ days). On the basis of funduscopy by ophthalmologists who were aware of the subjects' treatment assignments, the mean time to progression was 96 days in subjects given intravenous ganciclovir and 68 days in subjects given oral ganciclovir ($P=0.03$; relative risk [oral vs. intravenous], 1.68; 95 percent confidence interval for the difference in means, -45 to -11 days). Survival, changes in visual acuity, the incidence of viral shedding, and the incidence of adverse gastrointestinal events were similar in the two groups. Neutropenia, anemia, intravenous-catheter-related adverse events, and sepsis were more common in the group given intravenous ganciclovir.

Conclusions. *Oral ganciclovir is safe and effective as maintenance therapy for cytomegalovirus retinitis and is more convenient for patients to take than intravenous ganciclovir. (N Engl J Med 1995;333:615-20.)*

CYTOMEGALOVIRUS retinitis is an infection associated with the acquired immunodeficiency syndrome (AIDS) that, if left untreated, causes progressive retinal destruction with partial or complete visual loss. Retinitis develops in up to 40 percent of patients with AIDS.¹⁻⁶ Intravenous formulations of two agents, ganciclovir (Cytovene-IV) and foscarnet (Foscavir), are approved in the United States for the treatment of cytomegalovirus retinitis. Lifelong maintenance treatment can slow the progression of retinitis and minimize vision loss.⁷⁻¹⁴ Daily intravenous therapy is associated with substantial cost, inconvenience, and risk of catheter-related complications. An effective oral treatment would be an important advance.

A capsule form of ganciclovir (Cytovene) for oral administration has been studied. The absolute bioavailability of ganciclovir administered orally in a dosage of 1000 mg three times daily with food averaged 9 percent.¹⁵ Daily doses of 3000 mg or more yielded average serum ganciclovir concentrations exceeding 0.5 μg per milliliter,¹⁶ a concentration sufficient to inhibit most

clinical isolates of cytomegalovirus in vitro.¹⁷ Oral ganciclovir also reduced viral shedding and viral titers in urine and semen. Oral ganciclovir was tolerated at doses of up to 6000 mg daily; the rate of neutropenia was higher at doses of 6000 mg daily.¹⁶

We compared the efficacy and safety of oral ganciclovir at a daily dose of 3000 mg with that of intravenous ganciclovir at a daily dose of 5 mg per kilogram of body weight as maintenance therapy for cytomegalovirus retinitis. The disease was first stabilized with intravenous ganciclovir.

METHODS

Subjects

After approval by the institutional review boards, the study was conducted at 15 centers in the United States and Canada. Eligible subjects were at least 13 years of age, had been given a diagnosis of AIDS, and had been given a diagnosis of cytomegalovirus retinitis of one or both eyes within one month before entry. No exclusions were made on the basis of the location or extent of retinitis. Patients who had signs and symptoms of serious gastrointestinal disease, an absolute neutrophil count below 1000 cells per cubic millimeter, a platelet count below 50,000 per cubic millimeter, or a creatinine clearance rate of less than 70 ml per minute were ineligible.

Randomization and Treatment

After providing informed consent, enrolled subjects received 21 days of induction therapy with intravenous ganciclovir at a dose of 5 mg per kilogram twice daily for 14 days, followed by a dose of 5 mg per kilogram once daily for 7 days. All subjects whose retinitis stabilized (defined as no progression on two consecutive ophthalmologic evaluations on weeks 2 and 3 after the start of induction therapy) were randomly assigned (on a 1:1 basis) to open-label maintenance treatment with either intravenous ganciclovir (5 mg per kilogram

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once daily) or oral ganciclovir (500 mg six times daily during waking hours; total, 3000 mg per day), taken with food.

The subjects were followed for up to 20 weeks after the start of maintenance therapy. If retinitis was judged by experienced ophthalmologists to have progressed, the subjects received a second course of induction therapy with intravenous ganciclovir. If retinitis again stabilized, the originally assigned maintenance treatment was resumed. Subjects in whom retinitis progressed a second time were withdrawn from the study.

Clinical and Ophthalmologic Evaluations

The subjects were evaluated every two weeks after starting maintenance treatment, and a limited history was taken to collect data regarding adverse events, concomitant medications, and AIDS-related clinical events. Hematologic and serum chemical tests were performed every two weeks; CD4+ lymphocyte counts were made at the start of maintenance therapy and on weeks 4 and 20.

Urine cultures for cytomegalovirus were scheduled at entry, at the start of maintenance therapy, and on week 20 or in the event of early withdrawal from the study, progression of retinitis, or the development of extraocular cytomegalovirus disease. Other cultures (e.g., of blood or semen) were encouraged, and if they were done, the results were included in the analysis. Isolates from positive cultures were tested for susceptibility to ganciclovir in diploid-fibroblast cultures with a plaque-reduction assay.¹⁸ Resistance was defined as a 50 percent inhibitory concentration in excess of 2.9 μg per milliliter or a 90 percent inhibitory concentration in excess of 7.4 μg per milliliter.¹⁹

Ophthalmologic evaluations were conducted every two weeks and were the basis for treatment decisions. Best corrected visual acuity on Snellen's test was determined, and the subjects were asked to assess their functional vision using the following scale: 1, able to read newspaper print; 2, able to identify people and objects; 3, able to distinguish light from dark; and 4, unable to see anything. Ophthalmologists performed an indirect ophthalmoscopic examination of the fundi in patients' dilated eyes (funduscopy). Progression of retinitis was defined as advancement of the border of a lesion by at least 750 μm (approximately half the optic-disk diameter) or the appearance of a new lesion of at least 750 μm in a previously uninvolved area of either fundus.

Photographs of the fundi were taken every two weeks. At most centers, a wide-angle camera (50 or 60 degrees) was used. Photographs included all of zone 1 of each eye (the area within 1500 μm of the edge of the optic disk and within 3000 μm of the fovea), whether or not the eye was affected by retinitis. Additional photographs were taken to document the location and extent of all lesions noted on funduscopy. At the completion of the study, all photographs were evaluated by a single grader, who was unaware of the patients' treatment assignments. Photographs taken closest to the date of randomization served as the base line. The definition of progression on the basis of photographic assessment was identical to that for funduscopy.

Efficacy End Points

The primary efficacy end point was the length of time from the start of maintenance therapy to the progression of retinitis. Other specific ophthalmologic outcomes included the proportions of subjects in whom existing lesions increased in size by at least 750 μm , new lesions developed in either eye, retinitis extended into zone 1, active lesion borders developed, retinal detachment developed, and changes in visual acuity or functional vision were recorded. Other secondary end points were survival, the development of extraocular cytomegalovirus disease, the occurrence of other AIDS-associated infections and malignant conditions, changes in the counts of CD4+ lymphocyte subgroups, the occurrence of positive cultures for cytomegalovirus, and the development of ganciclovir-resistant strains of cytomegalovirus.

Safety End Points

Adverse events were monitored throughout ganciclovir treatment with the use of history taking, physical examinations, and laboratory tests.

Statistical Analysis

The mean time from the start of maintenance therapy to the progression of retinitis was the primary end-point measure. On the basis

of clinical experience, the mean time to the progression of retinitis during maintenance therapy with intravenous ganciclovir was expected to be approximately 70 days. A sample of 120 subjects was considered sufficient to give the study 80 percent power to detect a difference of 25 days or more in the mean time to progression between treatment groups with use of a two-sided test at the 0.05 level.

The time to the progression of retinitis was compared in the two groups by Kaplan–Meier curves and the log-rank test and analyzed with a proportional-hazards regression model. The relative risk of progression was expressed as the ratio of the rate of progression during oral ganciclovir maintenance therapy to that during intravenous ganciclovir maintenance therapy; a relative risk greater than 1 indicated an increased risk of progression with oral maintenance therapy.

The proportions of subjects in each group with deterioration of visual acuity and functional vision, extension of retinitis into zone 1, increase in the size of existing lesions, new lesions, development of active lesion borders, and development of retinal detachment were compared with Fisher's exact test. The time to the deterioration of visual acuity was analyzed by Kaplan–Meier curves and the log-rank test. Three broad categories of visual acuity were defined: 20/40 or better, 20/50 to 20/100, or 20/200 or worse. Deterioration of visual acuity was defined as a change from one category to a worse category for either eye on two consecutive visits or on the last visit during the study.

Adverse events specifically reported as related to intravenous catheters or infusion sites were categorized as catheter-related adverse events.

To determine the survival rate, all subjects, including those who withdrew early from the study, were followed until October 25, 1994. Survival was assessed according to randomized treatment assignment (intention to treat), and the results were compared with Kaplan–Meier curves and the log-rank test.

RESULTS

A total of 161 subjects were enrolled between March 1991 and June 1992. Thirty-eight subjects were not randomly assigned to maintenance treatment for the following reasons: unstable retinitis after the three weeks of induction therapy ($n=18$), abnormal laboratory results ($n=11$), a decision by the subject not to participate ($n=4$), administrative problems ($n=3$), or death ($n=2$). Thus, 123 subjects were randomly assigned to receive maintenance treatment with intravenous ganciclovir ($n=60$) or oral ganciclovir ($n=63$). Six subjects were excluded from the efficacy analyses: two did not receive maintenance treatment, two received laser photocoagulation treatment that made it impossible to evaluate whether retinitis had progressed, and two had been given a diagnosis of cytomegalovirus retinitis that could not be confirmed photographically. Thus, efficacy could be evaluated in 117 subjects (95 percent of those randomized): 57 given intravenous ganciclovir and 60 given oral ganciclovir. Photographs for 2 subjects were ungradable; therefore, 115 subjects (57 given intravenous ganciclovir and 58 given oral ganciclovir) were included in the analysis of the time to progression on the basis of fundus photography. The safety analysis included all 121 subjects who received maintenance treatment.

The characteristics of the treatment groups at the start of maintenance therapy are shown in Table 1. There were two significant differences between the groups. The mean number of months since the diagnosis of AIDS (according to criteria established in 1987 by the Centers for Disease Control and Prevention) was 11.0 for subjects randomly assigned to intravenous ganciclovir as compared with 16.8 months for subjects randomly assigned to oral ganciclovir ($P=0.02$). More subjects in the intravenous-ganciclovir group than in the

oral-ganciclovir group had Karnofsky scores of 30 to 60 (16 percent vs. 2 percent, $P=0.02$).

The mean time from the start of maintenance treatment to withdrawal from the study was 116 days in the intravenous-ganciclovir group (median, 140) and 100 days in the oral-ganciclovir group (median, 160; $P=0.04$).

Time to Progression of Cytomegalovirus Retinitis

On the basis of the masked assessment of fundus photographs, the mean time from the start of maintenance therapy to progression of retinitis was 62 days with intravenous ganciclovir and 57 days with oral ganciclovir, with a 5-day difference between the means ($P=0.63$ by the log-rank test; relative risk of progression in the oral-ganciclovir group as compared with the intravenous-ganciclovir group, 1.08) (Fig. 1 and Table 2). On the basis of the results of funduscopy by unmasked ophthalmologists, the mean time to progression was 96 days with intravenous ganciclovir and 68 days with oral ganciclovir, with a 28-day difference between the means, as shown in Table 2 ($P=0.03$ by the log-rank test; relative risk of progression with oral ganciclovir, 1.68). Progression of retinitis was detected earlier by photographic assessment in 56 percent of the subjects and by funduscopy in 8 percent of the subjects.

Several covariates were examined, including age, time since the diagnosis of AIDS, base-line Karnofsky score, the presence of bilateral retinitis at base line, and use of antiretroviral therapy. In a Cox proportional-hazards model, the only covariate that was significantly correlated with time to progression was the concomitant use of antiretroviral medication. The relative risk of progression in the oral-ganciclovir group with the best adjusted Cox model was 1.05, confirming the results of the primary analysis.

Other Ophthalmologic Outcomes

The proportions of subjects who had new retinal detachment, new active lesion borders, any extension of retinitis into zone 1, or new lesions of retinitis in previously involved eyes during treatment were similar in the two treatment groups (Table 3). On the basis of masked photographic readings, there was no significant difference between the treatment groups in the development of new retinitis lesions in previously uninvolved eyes. On the basis of funduscopy assessment, however, there was a significantly greater incidence of new bilateral lesions in the oral-ganciclovir group ($P=0.005$). Changes in visual acuity and in the subjects' assessment of their functional vision, shown in Table 3, were similar in the two groups.

Other Clinical Outcomes

None of the subjects were given a diagnosis of extraocular cytomegalovirus disease during the study. The incidence of new episodes of AIDS-associated opportunistic infections or cancer was similar in the two groups: 36 percent among subjects given intravenous ganciclovir and 26 percent among those given oral ganciclovir. Herpes simplex infections developed in

Table 1. Characteristics of the Subjects at the Start of Maintenance Therapy.*

CHARACTERISTIC	INTRAVENOUS GANCICLOVIR (N = 57)	ORAL GANCICLOVIR (N = 60)	P VALUE†
Mean age (yr)	37.7	40.4	0.05
Sex (M/F)	55/2	57/3	1.00
Race or ethnic group (%)			0.68
Black	9	8	
White	79	83	
Other	12	8	
Mean interval since AIDS diagnosis (mo)	11.0	16.8	0.02
Karnofsky score (%)			0.02
30–60	16	2	
70–80	46	48	
90–100	39	50	
Mean Karnofsky score	79.0±15.7	84.7±9.1	
History of <i>Pneumocystis carinii</i> pneumonia (%)	39	43	0.71
Prior antiretroviral therapy (%)‡	77	75	0.83
Mean CD4+ count (cells/mm ³)	15.5	22.2	0.22
Mean interval since diagnosis of cytomegalovirus retinitis (days)	27.8	29.6	0.24
Retinal detachment (%)	4	2	0.61
Unilateral retinitis (%)§	58 (60)	72 (72)	0.13 (0.17)
Zone 1 retinitis (%)§	42 (49)	45 (47)	0.85 (0.85)
Active lesion borders (%)	42	47	0.71
Snellen score of 20/40 or better (%)			
Worse eye	86	82	0.63
Better eye	98	95	0.62
Able to read newspaper (%)	100	98	1.00

*Plus-minus values are means ±SD. Because of rounding, not all categories total 100 percent.

†P value by Fisher's exact test or Pearson's chi-square test and t-test for age, months since the diagnosis of AIDS, and days since the diagnosis of cytomegalovirus retinitis.

‡Within four weeks before study entry.

§Parentheses indicate results based on masked reading of fundus photographs.

two subjects in each group; there were no reports of herpes zoster infection. The use of antiretroviral drugs was similar in the two groups: 70 percent of subjects given intravenous ganciclovir and 61 percent of those given oral ganciclovir received some concomitant antiretroviral treatment. The use of granulocyte or granulocyte-macrophage colony-stimulating factor was more frequent in the intravenous-ganciclovir group than in the oral-ganciclovir group (42 percent vs. 24 percent, $P=0.05$ by Fisher's exact test). Mean changes in CD4+ lymphocyte counts from the start of maintenance therapy to the completion of the study or at withdrawal were -2.8 cells per cubic millimeter and -9.1 cells per cubic millimeter in the intravenous-ganciclovir and oral-ganciclovir groups, respectively ($P=0.36$ by analysis of covariance, with use of the CD4+ count at the start of maintenance therapy as the covariate).

Survival

Kaplan-Meier analysis showed no difference in survival between the treatment groups. The subjects in both groups survived a mean of 13 months (median, 11) after randomization (data not shown).

Cytomegalovirus Cultures and Viral Resistance

A total of 74 subjects had cultures at the start of maintenance therapy: 5 of 37 subjects given intrave-

nous ganciclovir (14 percent) had positive cultures, as did 9 of 37 subjects given oral ganciclovir (24 percent). Of the 92 subjects who had one or more cultures after the start of maintenance therapy, 3 of 48 subjects given intravenous ganciclovir (6 percent) and 4 of 44 given oral ganciclovir (9 percent) had positive cultures. Isolates from four of the seven subjects were available for in vitro testing of sensitivity to ganciclovir. One isolate from a subject given intravenous ganciclovir was resistant to ganciclovir (50 percent inhibitory concentration, 2.48 μg per milliliter; 90 percent inhibitory concentration, 12.00 μg per milliliter).

Adverse Events

Neutropenia, anemia (minimal hemoglobin value, <8.0 g per deciliter; $P=0.02$), and intravenous-catheter-related adverse events ($P=0.006$), including catheter-related sepsis, were reported more often in the intravenous-ganciclovir group (Table 4). Gastrointestinal adverse events were frequent, but were equally common in both groups.

DISCUSSION

For patients with AIDS, lifelong intravenous treatment of cytomegalovirus retinitis is inconvenient and is accompanied by the risk of catheter-related infections. We compared oral ganciclovir at a dose of 3000 mg per day with standard, once-daily intravenous ganciclovir as maintenance therapy for cytomegalovirus retinitis in subjects whose retinitis had been stabilized by induction therapy with intravenous ganciclovir. Comparison of the efficacy of oral and intravenous ganciclovir by masked assessment of retinal photographs showed a mean difference in the time to progression of retinitis of five days in favor of intravenous treatment. These photographic data indicate with 95 percent certainty that the difference in the mean time to progression of retinitis in subjects with newly diagnosed, stabilized retinitis who are given maintenance therapy with oral ganciclovir is between -22 and $+12$ days of the mean for those who receive intravenous ganciclovir maintenance therapy.

The difference in the median time to progression (49 days vs. 29 days) is greater than the difference in the mean time to progression (62 days vs. 57 days). The

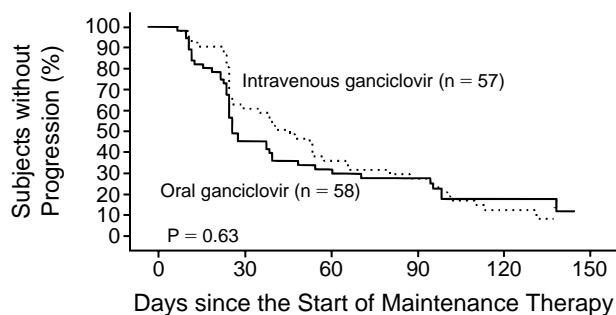


Figure 1. Time from the Start of Maintenance Therapy to Progression of Cytomegalovirus Retinitis, According to Photographic Assessment.

The P value was determined by the log-rank test.

Table 2. Days from the Start of Maintenance Therapy to Progression of Cytomegalovirus Retinitis.

OUTCOME VARIABLE	INTRAVENOUS GANCICLOVIR	ORAL GANCICLOVIR
Photographic assessment		
No. of subjects	57	58
Days to progression		
Mean (95% confidence interval for the difference in means)*	62 (-22 to $+12$)	57
1st quartile	28	25
Median	49	29
3rd quartile	99	99
Relative risk (oral vs. intravenous) (95% confidence interval)	—	1.08 (0.7 to 1.7)
Funduscopy assessment		
No. of subjects	57	60
Days to progression		
Mean (95% confidence interval for the difference in means)†	96 (-45 to -11)	68
1st quartile	52	30
Median	105	48
3rd quartile	NC‡	125
Relative risk (oral vs. intravenous) (95% confidence interval)	—	1.68 (1.1 to 2.7)

* $P=0.63$ for the comparison between groups by the log-rank test.

† $P=0.03$ for the comparison between groups by the log-rank test.

‡NC denotes not calculable.

large difference in the medians reflects the unusually wide separation of the Kaplan–Meier curves at the 50 percent progression point (Fig. 1). The difference in the means reflects differences between treatment groups that were averaged over the entire study population, which provides a more representative comparison of the two treatments.

On the basis of funduscopy assessment, the difference in the mean time to the progression of retinitis was 28 days in favor of intravenous treatment. In this open-label study, both the ophthalmologist and the primary care physician were aware of the subjects' treatment assignments. This may have influenced decisions regarding the need for a second course of induction therapy with intravenous ganciclovir; ophthalmologists may have been less inclined to have subjects who were receiving standard intravenous treatment undergo a second course of induction therapy than subjects who were receiving experimental oral therapy. Thus, differences in the time to progression favoring intravenous treatment would be greater when assessed by unmasked funduscopy. The use of masked assessment of fundus photographs avoids this potential observer bias. Another possibility is that oral ganciclovir was less effective than intravenous ganciclovir, and funduscopy changes in the group treated orally, although not satisfying the study definition of progression, concerned ophthalmologists enough for them to begin a second course of induction treatment earlier.

The effect on the time to progression when determined by unmasked funduscopy as compared with the masked grading of photographs was similar to that seen in another clinical trial of retinitis.^{20,21} The time to progression was shorter in both treatment groups when masked photographic assessment was used, reflecting

Table 3. Ophthalmologic Outcomes during the Study.

OUTCOME VARIABLE	INTRAVENOUS GANCICLOVIR	ORAL GANCICLOVIR	P VALUE*
	% (total no. of subjects assessed)		
Increase in size of lesion by $\geq 750 \mu\text{m}$			
Photographic assessment	77 (57)	78 (58)	1.00
Funduscopy assessment	54 (57)	67 (60)	0.19
New lesion in previously involved eye			
Photographic assessment	33 (57)	21 (58)	0.15
Funduscopy assessment	26 (57)	30 (60)	0.69
New lesion in previously uninvolved eye†			
Photographic assessment	9 (34)	21 (42)	0.21
Funduscopy assessment	6 (33)	33 (43)	0.005
Extension into zone 1‡			
Photographic assessment	6 (52)	11 (56)	0.49
Funduscopy assessment	8 (51)	16 (57)	0.25
Development of active lesion borders§	35 (48)	50 (54)	0.16
Development of retinal detachment	18 (57)	13 (60)	0.61
Deterioration of Snellen acuity	25 (57)	20 (60)	0.66
Deterioration of functional vision	4 (57)	7 (60)	0.68

*Calculated with Fisher's exact test.

†The development of bilateral retinitis in subjects with unilateral retinitis at base line.

‡Percentage of those at risk for extension of retinitis into zone 1.

§In subjects without bilateral lesion-border activity at base line on the basis of funduscopy.

the greater ability of this method to detect subtle manifestations of disease progression. The comparison of retinal photographs among visits, using precise measuring tools, is inherently different from a "real-time," clinical evaluation.

Retinitis often involves both eyes. In a recent study, retinitis developed in the contralateral eye in 14 of 21 patients with unilateral retinitis (67 percent) treated locally with an intraocular sustained-release ganciclovir implant.²² Even with systemic treatment, retinitis may develop in a previously uninvolved eye. In one study, bilateral retinitis developed in 17 percent of 126 patients with unilateral retinitis who were assigned to intravenous ganciclovir or foscarnet maintenance treatment.²⁰ In the present study, there was no significant difference between the groups in the development of new lesions in the contralateral eye on the basis of masked assessment of fundus photographs (9 percent of subjects given intravenous ganciclovir, as compared with 21 percent of those given oral ganciclovir). On the basis of funduscopy, however, new contralateral lesions were detected in 6 percent of subjects treated intravenously as compared with 33 percent of those treated orally, a significant difference. In eight subjects the results of the two methods of assessment were in disagreement (in both directions). In five of these subjects, the basis for the disagreement was the extent of retinitis at the start of maintenance therapy (unilateral vs. bilateral). The involved lesions were all peripheral, and such lesions are difficult to assess funduscopically and even more difficult to photograph. Lesions in zone 3 (the most anterior part of the retina) can be missed, since it is not technically possible to photograph all of zone 3.

Oral ganciclovir and intravenous ganciclovir were equally effective in preserving vision. The frequencies of extension of lesions into zone 1 and of retinal detachment — the most common causes of visual loss — were

similar in the two groups. Although visual acuity gradually declined despite treatment, there was no difference in visual acuity between the groups, on the basis of Snellen measurements or broad categories of functional vision, the latter of which is admittedly an insensitive measure.

The antiviral activity of an oral dose of 3000 mg of ganciclovir daily could not be differentiated from that of intravenous ganciclovir. In both groups the proportion of subjects with positive cultures decreased to less than 10 percent after the start of maintenance therapy. One cytomegalovirus isolate obtained after 28 days of intravenous ganciclovir treatment was resistant *in vitro*. The subject from whom this strain was isolated had a sensitive strain of cytomegalovirus at study entry. The

relative infrequency of resistance as compared with the rate in an earlier report¹⁹ may reflect the shorter observation time in the present study.

Mean survival after randomization was similar in both groups: approximately 13 months (median, 11). In a study of intravenous ganciclovir and foscarnet for the treatment of retinitis, median survival was 8.5 and 12.6 months, respectively.²¹ The longer survival of ganciclovir-treated subjects in our study may reflect differences in study design. In our study, subjects whose retinitis was not stable after three weeks of induction therapy (11 percent of enrolled subjects) were not randomly assigned to maintenance therapy. Those with a response to induction therapy may have had a survival advantage.

Oral ganciclovir was well tolerated and had fewer

Table 4. Incidence of Selected Adverse Events after the Start of Maintenance Therapy.*

ADVERSE EVENT	INTRAVENOUS GANCICLOVIR (N = 59)	ORAL GANCICLOVIR (N = 62)	P VALUE†
	<i>percent</i>		
Neutropenia (minimal absolute neutrophil count, $< 500/\text{mm}^3$)	37	24	0.17
Anemia (minimal hemoglobin value, $< 8.0 \text{ g/dl}$)	24	15	0.02
Minimal platelet count, $< 25,000/\text{mm}^3$	3	2	1.00
Sepsis‡	19	8	0.15
Any catheter-related complication‡	31	10	0.006
Diarrhea	54	50	0.72
Nausea	29	34	0.56
Anorexia	22	23	1.00
Vomiting	15	15	1.00

*Includes events reported during second courses of induction and maintenance therapies.

†Calculated by Fisher's exact test.

‡Including catheter-related sepsis.

side effects than intravenous ganciclovir, with fewer episodes of anemia, neutropenia, sepsis, and catheter-related adverse events. The incidence of neutropenia with intravenous ganciclovir was similar to that reported in other trials of intravenous ganciclovir as maintenance therapy for cytomegalovirus retinitis.^{7,23} The incidence rates of anemia and catheter-related adverse events, including catheter-related sepsis, were significantly lower in the oral-ganciclovir group. It is likely that fewer intravenous catheters were used in the subjects in this group, since catheters were not necessary for maintenance treatment (catheters may have been present for other reasons). Avoidance of the use of catheters decreases the risk of all catheter-related complications.

In summary, this study demonstrates that oral ganciclovir is an effective and safe alternative to intravenous ganciclovir as maintenance therapy for stable cytomegalovirus retinitis in persons with AIDS. Oral ganciclovir offers greater ease of administration and convenience than intravenous ganciclovir — advantages that likely outweigh the small differences in efficacy. Careful clinical judgment and monitoring must be exercised in cases of retinitis lesions adjacent to the optic nerve or fovea, where even a limited degree of progression can have major visual consequences. The close cooperation of the ophthalmologist and the physician overseeing the treatment of AIDS is vital to the successful management of cytomegalovirus retinitis. The availability of an oral agent for maintenance therapy expands the treatment options for those who face the prospect of lifelong treatment for cytomegalovirus retinitis.

APPENDIX

Other members of the Syntex Cooperative Oral Ganciclovir Study Group are as follows: W. Freeman, L. Meixner, and T.C. Meng (University of California, San Diego); C.L. Brosgart, C. Borkert, G. Feldman, C. Ferrell, and R. Sorenson (East Bay AIDS Center, Berkeley, Calif.); M. Braffman (Pennsylvania Hospital, Philadelphia); P. Phillips, S. Guillemi, S. Holland, J. Lindley, D. Anderson, and P. Nash (St. Paul's Hospital, Vancouver, B.C.); K. Squires (University of Alabama, Birmingham); D. Busch and T. Dwyer (California Pacific Medical Center, San Francisco); A. Chachoua, J. Ligh, and A. McMeeking (New York University Medical Center, New York); M. Heath-Chiozzi (Leahi Hospital, Honolulu); G. Dickinson and J. Edelstein (Miami Veterans Affairs Medical Center, Miami); R. Pollard (University of Texas, Galveston); J. Lavelle and P. Kumar (Georgetown University Hospital, Washington, D.C.); E. Chuang (University of Washington, Seattle); and S.J. Tan (Syntex Research, Palo Alto, Calif.).

REFERENCES

- Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Acquired immune deficiency syndrome: ocular manifestations. *Ophthalmology* 1983; 90:859-73.
- Pepose JS, Holland GN, Nestor MS, Cochran AJ, Foos RY. Acquired immune deficiency syndrome: pathogenic mechanisms of ocular disease. *Ophthalmology* 1985;92:472-84.
- Palestine AG, Rodrigues MM, Macher AM, et al. Ophthalmic involvement in acquired immunodeficiency syndrome. *Ophthalmology* 1984;91:1092-9.
- Jabs DA, Green WR, Fox R, Polk BF, Bartlett JG. Ocular manifestations of acquired immune deficiency syndrome. *Ophthalmology* 1989;96:1092-9.
- Jabs DA, Enger C, Bartlett JG. Cytomegalovirus retinitis and acquired immunodeficiency syndrome. *Arch Ophthalmol* 1989;107:75-80.
- Drew WL. Cytomegalovirus infection in patients with AIDS. *J Infect Dis* 1988;158:449-56.
- Holland GN, Sidikaro Y, Kreiger AE, et al. Treatment of cytomegalovirus retinopathy with ganciclovir. *Ophthalmology* 1987;94:815-23.
- Jabs DA, Newman C, De Bustros S, Polk BF. Treatment of cytomegalovirus retinitis with ganciclovir. *Ophthalmology* 1987;94:824-30.
- Orellana J, Teich SA, Friedman AH, Lerebours F, Winterkorn J, Mildvan D. Combined short- and long-term therapy for the treatment of cytomegalovirus retinitis using ganciclovir (BW B759U). *Ophthalmology* 1987;94:831-8.
- Jacobson MA, O'Donnell JJ, Brodie HR, Wofsy C, Mills J. Randomized prospective trial of ganciclovir maintenance therapy for cytomegalovirus retinitis. *J Med Virol* 1988;25:339-49.
- Jacobson MA, Causey D, Polsky B, et al. A dose-ranging study of daily maintenance intravenous foscarnet therapy for cytomegalovirus retinitis in AIDS. *J Infect Dis* 1993;168:444-8.
- Jacobson MA, O'Donnell JJ, Mills J. Foscarnet treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. *Antimicrob Agents Chemother* 1989;33:736-41.
- Lehoang P, Girard B, Robinet M, et al. Foscarnet in the treatment of cytomegalovirus retinitis in acquired immune deficiency syndrome. *Ophthalmology* 1989;96:865-74.
- Walmsley SL, Chew E, Read SE, et al. Treatment of cytomegalovirus retinitis with trisodium phosphonoformate hexahydrate (foscarnet). *J Infect Dis* 1988;157:569-72.
- Anderson RD, Griffy KG, Jung D, Dorr A, Hulse JD, Smith RB. Ganciclovir absolute bioavailability and steady-state pharmacokinetics after oral administration of two 3000-mg/d dosing regimens in human immunodeficiency virus- and cytomegalovirus-seropositive patients. *Clin Ther* 1995;17:425-32.
- Spector SA, Busch DF, Follansbee S, et al. Pharmacokinetic, safety and antiviral profiles of oral ganciclovir in persons infected with human immunodeficiency virus: a phase I/II study. *J Infect Dis* 1995;171:1431-7.
- Plotkin SA, Drew WL, Felsenstein D, Hirsch MS. Sensitivity of clinical isolates of human cytomegalovirus to 9-(1,3-dihydroxy-2-propoxymethyl)guanine. *J Infect Dis* 1985;152:833-4.
- Drew WL, Miner R, Saleh E. Antiviral susceptibility testing of cytomegalovirus: criteria for detecting resistance to antivirals. *Clin Diagn Virol* 1993;1: 179-85.
- Drew WL, Miner RC, Busch DF, et al. Prevalence of resistance in patients receiving ganciclovir for serious cytomegalovirus infection. *J Infect Dis* 1991;163:716-9.
- Studies of Ocular Complications of AIDS Research Group, AIDS Clinical Trials Group. Foscarnet-ganciclovir cytomegalovirus retinitis trial. 4. Visual outcomes. *Ophthalmology* 1994;101:1250-61.
- Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. *N Engl J Med* 1992;326:213-20.
- Martin DF, Parks DJ, Mellow SD, et al. Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol* 1994;112:1531-9.
- Fletcher CV, Balfour HH Jr. Evaluation of ganciclovir for cytomegalovirus disease. *DICP* 1989;23:5-12.