

ORAL GANCICLOVIR FOR PATIENTS WITH CYTOMEGALOVIRUS RETINITIS TREATED WITH A GANCICLOVIR IMPLANT

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ABSTRACT

Background The intraocular ganciclovir implant is effective for local treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome (AIDS), but it does not treat or prevent other systemic manifestations of cytomegalovirus infection.

Methods Three hundred seventy-seven patients with AIDS and unilateral cytomegalovirus retinitis were randomly assigned to one of three treatments: a ganciclovir implant plus oral ganciclovir (4.5 g daily), a ganciclovir implant plus oral placebo, or intravenous ganciclovir alone. The primary outcome measure was the development of new cytomegalovirus disease, either contralateral retinitis or biopsy-proved extraocular disease.

Results The incidence of new cytomegalovirus disease at six months was 44.3 percent in the group assigned to the ganciclovir implant plus placebo, as compared with 24.3 percent in the group assigned to the ganciclovir implant plus oral ganciclovir ($P=0.002$) and 19.6 percent in the group assigned to intravenous ganciclovir alone ($P<0.001$). As compared with placebo, oral ganciclovir reduced the overall risk of new cytomegalovirus disease by 37.6 percent over the one-year period of the study ($P=0.02$). However, in the subgroup of 103 patients who took protease inhibitors, the rates of new cytomegalovirus disease were low and of similar magnitude, regardless of treatment assignment. Progression of retinitis in the eye that initially received an implant was delayed by the addition of oral ganciclovir, as compared with placebo ($P=0.03$). Treatment with oral or intravenous ganciclovir reduced the risk of Kaposi's sarcoma by 75 percent ($P=0.008$) and 93 percent ($P<0.001$), respectively, as compared with placebo.

Conclusions In patients with AIDS and cytomegalovirus retinitis, oral ganciclovir in conjunction with a ganciclovir implant reduces the incidence of new cytomegalovirus disease and delays progression of the retinitis. Treatment with oral or intravenous ganciclovir also reduces the risk of Kaposi's sarcoma. (N Engl J Med 1999;340:1063-70.)

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CYTOMEGALOVIRUS retinitis is the leading cause of visual loss in patients with the acquired immunodeficiency syndrome (AIDS).¹⁻³ Systemic administration of ganciclovir,^{4,6} foscarnet,⁴ or cidofovir^{7,8} results in the initial control of retinitis. However, the time to relapse is relatively short, in part because of the poor ocular bioavailability of most systemically administered compounds.⁹⁻¹¹ The ganciclovir implant delivers drug directly into the vitreous cavity, resulting in higher sustained intraocular levels than can be achieved with systemic therapy.¹² In two randomized clinical trials, the implant produced a longer-lasting therapeutic effect in the eye than has been achieved with systemic therapy.^{12,13} However, the implant does not produce measurable serum levels of ganciclovir, and patients therefore remain at risk for additional manifestations of cytomegalovirus disease.^{12,13} Oral ganciclovir is effective for preventing cytomegalovirus disease in patients infected with the human immunodeficiency virus (HIV) who do not have established cytomegalovirus end-organ disease.¹⁴ We hypothesized that it should also reduce the risk of additional manifestations of cytomegalovirus disease in patients with cytomegalovirus retinitis who are being treated with a ganciclovir implant.

We designed a randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of oral ganciclovir for the prevention of new cytomegalovirus disease in patients with unilateral cytomegalovirus retinitis who were being treated with a ganciclovir implant. We selected a dose of oral ganciclovir (4.5 g daily) that is higher than the currently approved dose (3 g daily), for two reasons. First, in one study that compared intravenous ganciclovir with 3 g daily of oral ganciclovir for maintenance treatment of cytomegalovirus retinitis, the incidence of new cytomegalovirus disease in the other eye was significantly higher in the group receiving oral ganciclovir.⁵ Second, in a pharmacokinetic study, 4.5 g dai-

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ly resulted in higher serum ganciclovir levels than 3 g daily (unpublished data), suggesting the possibility of better protection against cytomegalovirus end-organ disease with the higher dose.

METHODS

Study Design

The study protocol was reviewed and approved by the local institutional review boards at 27 clinical sites in the United States, and all patients gave written informed consent. The study subjects were adults with AIDS and unilateral cytomegalovirus retinitis that was newly diagnosed or that had been treated systemically for less than six months. Patients with previously treated disease could have had one prior progression of cytomegalovirus retinitis but had to have stable disease after at least four weeks of systemic anticytomegalovirus therapy. Patients were ineligible if they had past or present extraocular cytomegalovirus disease, had previously received oral ganciclovir for prophylaxis against cytomegalovirus disease for more than four months, or had previously received a ganciclovir implant. Other exclusion criteria were an absolute neutrophil count below 500 cells per cubic millimeter, a platelet count below 25,000 per cubic millimeter, an estimated creatinine clearance rate below 50 ml per minute, or a score below 60 on the Karnofsky performance scale.

The study was partially masked. Patients were stratified according to their status with respect to cytomegalovirus disease (newly diagnosed or previously treated) and randomly assigned, in a 1:1:1 ratio at each site, to receive one of the following three treatments: 1500 mg of oral ganciclovir (six 250-mg capsules) three times daily plus a ganciclovir implant; matching oral placebo (six capsules) three times daily plus a ganciclovir implant; or intravenous ganciclovir, at a dosage of 5 mg per kilogram of body weight twice daily for 14 to 21 days, followed by daily maintenance therapy of 5 mg per kilogram for patients with newly diagnosed disease and continued daily maintenance therapy of 5 mg per kilogram for patients with previously treated retinitis. Follow-up examinations were performed at weeks 2, 3, and 4, then every two weeks through week 16, and then every four weeks through week 52. Each study visit included determination of visual acuity with modified Bailey-Lovie charts,¹⁵ indirect ophthalmoscopy with eyes dilated, bilateral nine-field photography of the fundus, a limited physical examination, and laboratory tests.

Patients assigned to either of the two implant groups in whom contralateral retinitis developed were treated with an implant and continued to receive their originally assigned oral treatment. Patients assigned to intravenous ganciclovir who had two or more clinical progressions of retinitis in the initially involved eye after study enrollment were eligible to receive an implant, but they also continued to receive their assigned intravenous therapy. The ganciclovir implants were replaced if progression of retinitis occurred, but in some cases, they were preemptively replaced according to the investigators' best medical judgment. The exit point from the study was the development of extraocular cytomegalovirus disease, death, or the attainment of 52 weeks of follow-up.

Outcome Measures

The primary outcome measure was the development of new cytomegalovirus disease, manifested as contralateral retinitis or extraocular disease. The development of contralateral retinitis was identified by funduscopy or retinal photographs. Summaries describing all extraocular episodes of cytomegalovirus disease were reviewed independently by two clinical reviewers who were unaware of the patients' treatment assignments. Only cases that met protocol-defined criteria for biopsy-proved extraocular cytomegalovirus disease¹⁴ were included in the data analysis.

Other outcome measures were the progression of retinitis in the initially treated eye; the development of other opportunistic infections or Kaposi's sarcoma, diagnosed clinically; indicators of

the safety and tolerability of the treatment regimens; and survival. Progression of retinitis was defined as a movement of the border of a lesion by at least 750 μ m over a 750- μ m front or the development of a new area of cytomegalovirus retinitis at least 750 μ m in diameter. Progression was determined on the basis of central grading of fundus photographs by readers who were unaware of the patients' treatment assignments. The photographs obtained at week 3 were used as the base line for determining the time to progression of retinitis.

Statistical Analysis

The study was designed to have a power of 90 percent to detect a reduction of at least 50 percent in the incidence of new cytomegalovirus disease in the group treated with oral ganciclovir, as compared with the placebo group, during 52 weeks of treatment. We assumed that the incidence of new cytomegalovirus disease would be 50 percent in the placebo group and 25 percent in the group assigned to oral ganciclovir. Three interim analyses were performed and reviewed by an independent data and safety monitoring board. Using a conservative Lan-DeMets spending function to determine the guidelines for stopping the trial,¹⁶ the board did not recommend early termination or alteration of the study. Because of these interim analyses, the P value required for significance in the primary efficacy analysis was 0.043.

Kaplan-Meier analysis was used to estimate the rates of new cytomegalovirus disease, Kaposi's sarcoma, and progression of retinitis.¹⁷ The log-rank test was used to compare the time to the development of new cytomegalovirus disease and the time to the progression of retinitis in the involved eye among the three treatment groups. Relative risks, reductions in risk, and 95 percent confidence intervals were computed with a stratified Cox proportional-hazards analysis. Fisher's exact test was used to compare proportions in the study groups. All tests were two-sided. Analyses of survival and efficacy were performed on an intention-to-treat basis. For the analyses of safety, all subjects who actually received study medication were included.

RESULTS

Between May 1994 and July 1996, 377 patients were enrolled in the study: 123 were assigned to receive a ganciclovir implant plus oral ganciclovir, 122 to receive a ganciclovir implant plus placebo, and 132 to receive intravenous ganciclovir alone. There were no significant differences among the groups in base-line characteristics (Table 1). Twenty patients never received study medication. Eleven of these were assigned to intravenous ganciclovir, six to oral ganciclovir, and three to placebo. The mean duration of follow-up was 251 days for patients assigned to the ganciclovir implant plus oral ganciclovir, 211 days for patients assigned to the ganciclovir implant plus placebo, and 176 days for patients assigned to intravenous ganciclovir alone ($P=0.06$ for the comparison of oral ganciclovir with intravenous ganciclovir).

Cytomegalovirus Disease

The Kaplan-Meier estimates of the cumulative incidence of new cytomegalovirus disease (defined as either contralateral retinitis identified by photographs or funduscopy, or biopsy-proved extraocular cytomegalovirus disease) at six months were 44.3 percent (95 percent confidence interval, 34.4 to 54.2 percent) in the group assigned to the ganciclo-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS, ACCORDING TO STUDY GROUP.*

CHARACTERISTIC	GANCICLOVIR IMPLANT PLUS ORAL GANCICLOVIR (N=123)	GANCICLOVIR IMPLANT PLUS PLACEBO (N=122)	INTRAVENOUS GANCICLOVIR (N=132)
	Median age — yr	38	38
Male sex — no. (%)	113 (92)	118 (97)	124 (94)
Race or ethnic group — no. (%)†			
White	91 (74)	81 (66)	96 (73)
Black	13 (11)	16 (13)	13 (10)
Hispanic	16 (13)	21 (17)	18 (14)
Other	3 (2)	4 (3)	4 (3)
Category of retinitis — no. (%)			
Newly diagnosed	90 (73)	90 (74)	95 (72)
Previously diagnosed	33 (27)	32 (26)	37 (28)
Months since diagnosis of AIDS	36.2±25.6	27.9±20.8	31.9±25.8
CD4+ count — cells/mm ³ ‡			
Mean	21.5±25.1	19.9±25.5	22.2±20.1
Median	14.0	10.5	15.0
Range	0–142	0–177	1–94
Antiretroviral therapy — no. (%)			
Current	52 (42)	54 (44)	55 (42)
Previous	51 (41)	48 (39)	57 (43)
None	20 (16)	20 (16)	20 (15)
Karnofsky score	85.7±10.7	86.0±11.1	86.8±9.9

*Because of rounding, percentages may not total 100. Plus-minus values are means ±SD.

†For one patient in the intravenous-ganciclovir group, race was unknown.

‡The CD4+ count was available for 66 patients in the oral-ganciclovir group, 74 in the placebo group, and 67 in the intravenous-ganciclovir group.

vir implant plus placebo, 24.3 percent (95 percent confidence interval, 16.1 to 32.5 percent) in the group assigned to the ganciclovir implant plus oral ganciclovir, and 19.6 percent (95 percent confidence interval, 11.4 to 27.7 percent) in the group assigned to intravenous ganciclovir alone (oral ganciclovir vs. placebo, P=0.002; intravenous ganciclovir vs. placebo, P<0.001; oral ganciclovir vs. intravenous ganciclovir, P=0.42). Cytomegalovirus retinitis was more common than extraocular cytomegalovirus disease (Table 2).

During the one-year period of the study, the time to development of new cytomegalovirus disease was significantly longer in patients assigned to oral ganciclovir (P=0.02; risk reduction, 37.6 percent; 95 percent confidence interval, 6.5 to 58.3 percent) or intravenous ganciclovir (P=0.002; risk reduction, 51.6 percent; 95 percent confidence interval, 23.3 to 69.5 percent) than in those receiving placebo (Fig. 1). There was no significant difference between patients assigned to oral ganciclovir and those assigned to intravenous ganciclovir in the length of time to the development of new cytomegalovirus disease (P=0.32; risk reduction with intravenous ganciclovir,

TABLE 2. KAPLAN-MEIER ESTIMATES OF THE CUMULATIVE INCIDENCE OF NEW CYTOMEGALOVIRUS DISEASE AT SIX MONTHS.*

TYPE OF DISEASE	GANCICLOVIR IMPLANT PLUS ORAL GANCICLOVIR (N=123)	GANCICLOVIR IMPLANT PLUS PLACEBO (N=122)	INTRAVENOUS GANCICLOVIR (N=132)
	number (percent)		
All cytomegalovirus disease	26 (24.3)	46 (44.3)	19 (19.6)
Contralateral retinitis	24 (23.3)	41 (41.7)	17 (18.9)
Extraocular disease	3 (2.8)	9 (9.7)	3 (3.3)
Esophagitis	0	1 (1.0)	1 (1.2)
Gastroenteritis	0	3 (3.1)	0
Colitis	2 (1.8)	4 (4.4)	1 (0.8)
Hepatitis	0	1 (1.3)	0
Pneumonia	1 (1.1)	1 (1.3)	1 (1.3)
Polyradiculopathy	0	0	0
Other cytomegalovirus disease	0	0	0

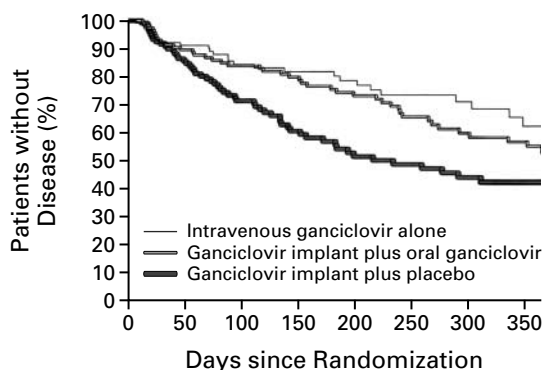
*New cytomegalovirus disease was defined as either contralateral retinitis identified in photographs or by funduscopy, or biopsy-proved extraocular cytomegalovirus disease.

vir, 22 percent; 95 percent confidence interval, -26.8 to 52.0 percent).

When only cases of photographically confirmed contralateral retinitis were included in the analysis, the six-month incidence of new cytomegalovirus disease was 37.8 percent in the group assigned to the ganciclovir implant plus placebo, 22.4 percent in the group assigned to the ganciclovir implant plus oral ganciclovir, and 17.1 percent in the group assigned to intravenous ganciclovir alone (oral ganciclovir vs. placebo, P=0.01; intravenous ganciclovir vs. placebo, P<0.001). In this analysis, the overall risk of new cytomegalovirus disease was reduced by 27 percent by oral ganciclovir as compared with placebo (P=0.14).

Effect of Protease Inhibitors

During the trial, 103 patients took protease inhibitors, with 89 of these patients (86 percent) starting after random assignment to a study group, as these agents became more widely available. In a post hoc subgroup analysis of the 274 patients who did not take protease inhibitors, oral ganciclovir was highly effective in preventing new cytomegalovirus disease (Fig. 2A). The six-month incidence was 61 percent in the group assigned to the ganciclovir implant plus placebo, 32 percent in the group assigned to the ganciclovir implant plus oral ganciclovir, and 25 percent in the group assigned to intravenous ganciclovir alone (oral ganciclovir vs. placebo, P<0.001; intravenous ganciclovir vs. placebo, P<0.001). However, in the 103 patients who took protease inhibitors, the rates of new cytomegalovirus disease were substan-



No. AT RISK

Oral ganciclovir	123	100	87	75	62	49	40	36
Placebo	122	98	71	51	38	34	26	23
Intravenous ganciclovir	132	92	71	57	48	34	28	20

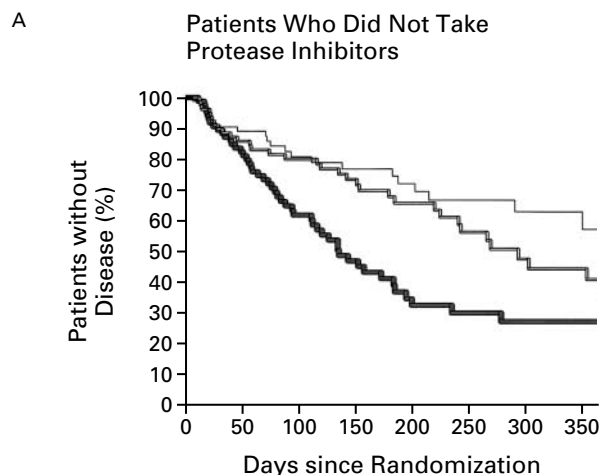
Figure 1. Kaplan–Meier Curves Showing the Cumulative Probability of New Cytomegalovirus Disease in Patients Treated with a Ganciclovir Implant plus Oral Ganciclovir, a Ganciclovir Implant plus Placebo, or Intravenous Ganciclovir Alone.

P=0.02 for the comparison of the patients assigned to the ganciclovir implant plus oral ganciclovir with those assigned to the ganciclovir implant plus placebo. P=0.002 for the comparison of the patients assigned to intravenous ganciclovir with those assigned to the ganciclovir implant plus placebo.

tially lower than in those who did not, with a six-month incidence of 9 percent in the placebo group, 11 percent in the oral-ganciclovir group, and 7 percent in the intravenous-ganciclovir group. No significant treatment effect could be identified in this subgroup (Fig. 2B). We repeated the primary analysis of new cytomegalovirus disease, using a Cox model to adjust for the use of protease inhibitors. In this analysis, the risk of new cytomegalovirus disease was reduced by 39 percent among patients taking oral ganciclovir as compared with placebo (P=0.02), confirming the primary result. Use of a protease inhibitor was a significant predictive factor in the model (P<0.001).

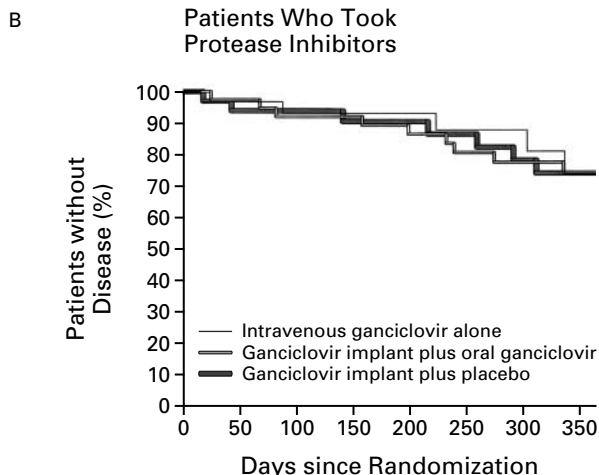
Progression of Retinitis

The ganciclovir implant was more effective than intravenous ganciclovir in controlling retinitis (P<0.001). The median time to progression of retinitis among patients assigned to intravenous ganciclovir was 66 days, whereas median progression rates were not reached in the two groups assigned to ganciclovir implants. The time to a 25 percent incidence of progression of retinitis was 180 days for the group assigned to the ganciclovir implant plus placebo and 267 days for the group assigned to the ganciclovir



No. AT RISK

Oral ganciclovir	85	63	52	41	31	22	15	13
Placebo	89	67	41	26	15	12	7	6
Intravenous ganciclovir	100	62	46	34	28	19	15	10

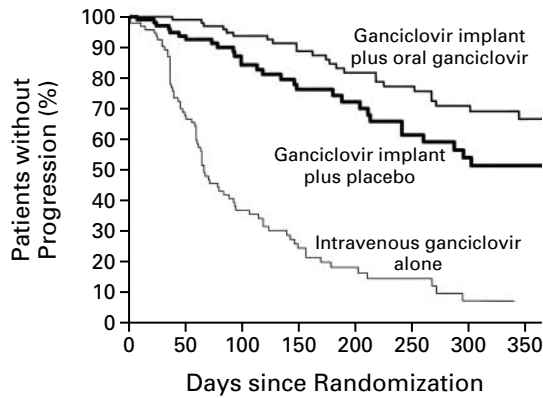


No. AT RISK

Oral ganciclovir	38	37	35	34	31	27	25	23
Placebo	33	31	30	25	23	22	19	17
Intravenous ganciclovir	32	30	25	23	20	15	13	10

Figure 2. Kaplan–Meier Curves Showing the Cumulative Probability of New Cytomegalovirus Disease in 274 Patients Who Did Not Take Protease Inhibitors (Panel A) and 103 Patients Who Took Protease Inhibitors (Panel B).

In Panel A, P<0.001 for the comparison of the patients assigned to the ganciclovir implant plus oral ganciclovir with those assigned to the ganciclovir implant plus placebo; P<0.001 for the comparison of the patients assigned to intravenous ganciclovir with those assigned to the ganciclovir implant plus placebo. In Panel B, P=0.94 for the comparison of the patients assigned to the ganciclovir implant plus oral ganciclovir with those assigned to the ganciclovir implant plus placebo; P=0.93 for the comparison of the patients assigned to intravenous ganciclovir with those assigned to the ganciclovir implant plus placebo.



No. AT RISK

Oral ganciclovir	109	98	84	69	56	50	42	16
Placebo	112	83	58	47	34	28	21	5
Intravenous ganciclovir	101	58	28	16	10	7	0	0

Figure 3. Kaplan–Meier Curves Showing the Cumulative Probability of Progression of Retinitis in Patients Treated with a Ganciclovir Implant plus Oral Ganciclovir, a Ganciclovir Implant plus Placebo, or Intravenous Ganciclovir Alone.

Of the 357 patients who began treatment, 35 patients (20 receiving intravenous ganciclovir, 8 receiving oral ganciclovir, and 7 receiving placebo) had insufficient photographic follow-up for the progression of retinitis to be determined. $P=0.03$ for the comparison of the patients assigned to the ganciclovir implant plus oral ganciclovir with those assigned to the ganciclovir implant plus placebo. $P<0.001$ for the comparison of the patients assigned to intravenous ganciclovir with those assigned to the ganciclovir implant plus placebo.

implant plus oral ganciclovir ($P=0.03$ by the log-rank test) (Fig. 3). Twenty-seven patients in the group assigned to the ganciclovir implant plus oral ganciclovir and 16 patients in the group assigned to the ganciclovir implant plus placebo underwent preemptive replacement of the implant before there was progression of retinitis. In an analysis in which data from these patients were censored at the time the implant was exchanged, the use of oral ganciclovir was still associated with a longer time to progression ($P=0.02$). In the subgroup of patients who did not take protease inhibitors, the median time to progression of retinitis in the group assigned to the ganciclovir implant plus placebo was 213 days, and a median time to progression was not achieved by 380 days in the group assigned to the ganciclovir implant plus oral ganciclovir ($P=0.03$ by the log-rank test). Cox-model analysis confirmed that the use of oral ganciclovir was an independent predictor of the time to the progression of retinitis even after adjustment for the concomitant use of protease inhibitors ($P=0.03$).

Kaposi’s Sarcoma and Other AIDS-Associated Conditions

Patients who received oral or intravenous ganciclovir had a significantly lower incidence of Kaposi’s

sarcoma than those who received placebo. Kaplan–Meier estimates of the six-month incidence of newly diagnosed Kaposi’s sarcoma were 11.3 percent (13 patients) in the group assigned to the ganciclovir implant plus placebo, 2.7 percent (3 patients) in the group assigned to the ganciclovir implant plus oral ganciclovir ($P=0.02$), and 1.5 percent (1 patient) in the group assigned to intravenous ganciclovir alone ($P=0.007$). The overall relative risk of Kaposi’s sarcoma was 0.25 in the group assigned to oral ganciclovir as compared with the group assigned to placebo ($P=0.008$; 95 percent confidence interval, 0.08 to 0.75) and 0.07 in the group assigned to intravenous ganciclovir alone as compared with the group assigned to placebo ($P<0.001$; 95 percent confidence interval, 0.01 to 0.56). Oral ganciclovir, as compared with placebo, also reduced the incidence of other new AIDS-associated infections ($P=0.02$), the number of hospitalizations ($P=0.02$), and the percentage of days spent in the hospital ($P=0.04$).

Cytomegalovirus Cultures

Urine cultures were positive for cytomegalovirus in 38 to 39 percent of the patients in all three groups at study entry. By week 8, the percentage of patients with positive cultures had been reduced to 5 percent in the group assigned to intravenous ganciclovir alone and to 7 percent in the group assigned to oral ganciclovir; this percentage had increased to 62 percent in the group assigned to placebo ($P<0.001$ for the comparison with either group receiving systemic ganciclovir).

Adverse Events

There were no significant differences among the treatment groups in the occurrence of gastrointestinal symptoms, the most common adverse events. Sepsis occurred in more patients assigned to intravenous ganciclovir than in either of the other two groups (21 percent of those assigned to intravenous ganciclovir, 9 percent of those assigned to oral ganciclovir, and 8 percent of those assigned to placebo; $P<0.001$ for the comparison between intravenous ganciclovir and placebo). Severe neutropenia, defined as an absolute neutrophil count below 500 cells per cubic millimeter, occurred in 28 percent of patients assigned to oral ganciclovir, as compared with 13 percent of those assigned to placebo ($P=0.006$) and 15 percent of those assigned to intravenous ganciclovir (oral ganciclovir vs. intravenous ganciclovir, $P=0.02$; intravenous ganciclovir vs. placebo, $P=0.70$). Patients assigned to receive oral ganciclovir took the drug for an average of 236 days, as compared with 168 days for patients assigned to intravenous ganciclovir.

A ganciclovir implant was placed in a total of 353 eyes during the trial. Endophthalmitis developed in one eye (0.3 percent) in the immediate postopera-

tive period. There were no significant differences in the incidence of retinal detachment between either of the groups assigned to receive implants and the group assigned to intravenous ganciclovir alone (13 percent for those assigned to the implant plus oral ganciclovir, 14 percent for those assigned to the implant plus placebo, and 18 percent for those assigned to intravenous ganciclovir alone). Retinal detachment occurred in five eyes at some time after implants had been placed in patients originally assigned to intravenous ganciclovir. When the data from these patients were excluded from the analysis, there were still no significant differences in the rate of detachment among treatment groups.

Survival

During the 12-month period of randomized treatment, there were 24 deaths in the group assigned to the ganciclovir implant plus oral ganciclovir, 31 in the group assigned to the ganciclovir implant plus placebo, and 26 in the group assigned to intravenous ganciclovir alone. The reduction in the risk of death in the group that received oral ganciclovir was 38.6 percent as compared with placebo (95 percent confidence interval, -4.9 to 64.1 percent; $P=0.07$) and 33.1 percent as compared with intravenous ganciclovir (95 percent confidence interval, -16.9 to 61.8 percent; $P=0.16$). The reduction in risk with intravenous ganciclovir as compared with placebo was 10.3 percent (95 percent confidence interval, -52.2 to 47.2 percent; $P=0.69$). When deaths after the termination of the study were included, the median survival was 568 days for patients assigned to oral ganciclovir, 426 days for patients assigned to intravenous ganciclovir, and 388 days for patients assigned to placebo ($P=0.15$ for oral ganciclovir vs. placebo, by the log-rank test).

DISCUSSION

Oral ganciclovir has previously been shown to be effective for the primary prevention of cytomegalovirus disease in patients who have AIDS but who do not have established cytomegalovirus end-organ disease.¹⁴ The current study shows that oral ganciclovir can prevent new cytomegalovirus disease in patients with established cytomegalovirus retinitis who are treated with a ganciclovir implant. This therapeutic effect was evident despite two potential sources of bias that worked against oral ganciclovir. First, patients assigned to oral ganciclovir remained in the study, and therefore at risk for an event, for a longer period than those who received placebo or intravenous ganciclovir. Second, pharmacokinetic sampling conducted throughout the study revealed measurable serum levels of ganciclovir in 21 percent of tested patients assigned to placebo (17 of 81), presumably resulting in part from surreptitious use of oral ganciclovir after it became commercially available.

A significant therapeutic effect of oral ganciclovir was observed only in the subgroup of patients who did not take protease inhibitors (Fig. 2A). Since the approval and widespread use of protease inhibitors beginning in the first half of 1996, many patients have had substantial improvement in immune function, and survival has been prolonged.¹⁸⁻²² Concomitant with this immune recovery, several studies have reported a substantial reduction in the incidence of opportunistic infections, including cytomegalovirus retinitis.²³⁻²⁵ Our trial confirms this observation. In the subgroup of patients who took protease inhibitors, the six-month incidence of new cytomegalovirus disease in patients given placebo was only 9 percent, as compared with 61 percent in patients given placebo who did not take protease inhibitors.

The principal question prompted by these data is whether patients taking protease inhibitors who have cytomegalovirus retinitis that is treated with an implant should receive oral ganciclovir. Although our trial was not specifically designed to answer this question, several points can be made. Most patients who took protease inhibitors in this study entered the trial with established cytomegalovirus retinitis, began taking protease inhibitors when they became available, and then presumably had some degree of immune recovery. For such patients, the data suggest that oral ganciclovir may be of limited benefit. However, since the majority of patients with advanced AIDS are now taking protease inhibitors, those in whom cytomegalovirus retinitis develops in the future will probably have limited options for additional immune recovery. In terms of the risk of additional cytomegalovirus end-organ disease and of the progression of retinitis, these patients may more closely resemble the patients in this study who never received protease inhibitors.

The ganciclovir implant was substantially more effective than intravenous ganciclovir in controlling retinitis. This finding is consistent with the results of a previous study in which the time to the progression of retinitis in eyes treated with an implant alone was 221 days, as compared with 71 days for those treated with intravenous ganciclovir.¹³ A somewhat unexpected finding in the current study was that oral ganciclovir extended the time to progression of retinitis in patients treated with an implant. The reasons for this are not entirely clear. One possible explanation is that providing drug to the retina through both its blood supply and the vitreous may produce higher retinal concentrations of ganciclovir than can be achieved with an implant alone. These levels may then decay more slowly with continued administration of oral ganciclovir after the implant runs out of drug.

Human herpesvirus 8 appears to have a critical role in the development of Kaposi's sarcoma.²⁶ Human herpesvirus 8 DNA sequences have been de-

tected in all forms of Kaposi's sarcoma,²⁷⁻³⁰ primarily in the neoplastic spindle cells.^{31,32} Infection with human herpesvirus 8 precedes the development of the tumor,³³⁻³⁵ and in various population studies, seropositivity for human herpesvirus 8 is strongly correlated with the risk of tumor development.³⁶⁻³⁸ Ganciclovir, foscarnet, and cidofovir have all been shown to have activity against human herpesvirus 8 in vitro.^{39,40} In a previous study of patients at risk for Kaposi's sarcoma who were randomly assigned to treatment with oral ganciclovir or placebo (for prophylaxis against cytomegalovirus disease),¹⁴ there was a non-significant trend toward a lower incidence of Kaposi's sarcoma in the group assigned to oral ganciclovir; the 12-month incidence was 8 percent in the group assigned to oral ganciclovir and 12 percent in the placebo group (P=0.15). The dose of oral ganciclovir (3 g daily) was lower than that used in the current study, and the risk of Kaposi's sarcoma may have been lower, because patients had no cytomegalovirus disease at base line and may have been healthier. In our study, the risk of Kaposi's sarcoma, a specified secondary end point, was reduced by 75 percent in patients treated with 4.5 g daily of oral ganciclovir and by 93 percent in patients treated with intravenous ganciclovir, as compared with patients given placebo. This reduced risk was not explained by the rate of use of protease inhibitors, which was essentially the same in all treatment groups.

In conclusion, 4.5 g of oral ganciclovir daily was well tolerated and reduced the risk of additional cytomegalovirus disease in patients with cytomegalovirus retinitis that was being treated with local intraocular therapy. In addition, the combination of the ganciclovir implant and oral ganciclovir controlled retinitis for the longest period reported to date. Finally, ganciclovir substantially reduced the risk of Kaposi's sarcoma. The potential role of ganciclovir implants and oral ganciclovir in the current environment of potent antiretroviral therapy requires further study.

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APPENDIX

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