

TREATMENT OF CYTOMEGALOVIRUS RETINITIS WITH A SUSTAINED-RELEASE GANCICLOVIR IMPLANT

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ABSTRACT

Background Sustained-release, intraocular implants that deliver ganciclovir are an alternative method for the treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome (AIDS).

Methods We conducted a randomized study of 188 patients with AIDS and newly diagnosed cytomegalovirus retinitis. The patients were randomly assigned to treatment with an implant delivering 1 μ g of ganciclovir per hour, an implant delivering 2 μ g of ganciclovir per hour, or intravenous ganciclovir. The primary outcome we studied was progression of cytomegalovirus retinitis.

Results The median time to progression of retinitis was 221 days with the 1- μ g-per-hour implant (75 eyes), 191 days with the 2- μ g-per-hour implant (71 eyes), and 71 days with ganciclovir administered intravenously (76 eyes; $P < 0.001$). The risk of progression of retinitis was almost three times as great among patients treated with intravenous ganciclovir as among those treated with a ganciclovir implant (risk ratio, 2.8; $P < 0.001$). However, the risk of disease in the initially uninvolved eye was lower with intravenous ganciclovir than with a ganciclovir implant (risk ratio, 0.5; $P = 0.19$). Patients treated with intravenous ganciclovir were also less likely to have extraocular cytomegalovirus infections (0, vs. 10.3 percent in the two implant groups; $P = 0.04$).

Conclusions For the treatment of cytomegalovirus retinitis, the sustained-release ganciclovir implant is more effective than intravenous ganciclovir, but patients treated with a ganciclovir implant alone remain at greater risk for the development of cytomegalovirus disease outside of the treated eye. (*N Engl J Med* 1997;337:83-90.)

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CYTOMEGALOVIRUS retinitis is the most common opportunistic infection of the eye in patients with the acquired immunodeficiency syndrome (AIDS).¹⁻⁶ If untreated, cytomegalovirus retinitis is invariably progressive, leading to retinal necrosis and loss of vision.¹⁻⁸ Three antiviral drugs — ganciclovir, foscarnet, and cidofovir — are approved for the treatment of cytomegalovirus retinitis. Although these drugs are initially effective in delaying the progression of cytomegalovirus retinitis,⁹⁻²⁴ relapse during intravenous maintenance therapy is common,¹²⁻²⁴ and such a finding is thought to be inevitable with sufficient follow-up.^{16,22}

Concern about limited efficacy, the toxicity of each drug,^{9-15,17-21,25-27} the effect of the indwelling catheters required to deliver long-term intravenous ganciclovir or foscarnet therapy on the quality of life,^{25,26,28} and the associated risk of sepsis prompted studies of local, intraocular therapy for cytomegalovirus retinitis. Injections of ganciclovir into the vitreous body are effective,²⁹⁻³³ but the short half-life of the drug requires weekly injections to maintain therapeutic levels. In order to achieve a longer-lasting therapeutic effect and to avoid intravitreal injections, a sustained-release delivery system for the treatment of cytomegalovirus retinitis was developed.³⁴ The surgically implanted device consists of a ganciclovir tablet coated with polyvinyl alcohol, which is permeable to ganciclovir, and then partially coated with ethylene vinyl acetate, which is impermeable to ganciclovir. Preliminary tests of the implant indicated successful stabilization of active cytomegalovirus retinitis in 27 of 30 consecutive treated eyes.^{35,36}

A recent clinical trial evaluated the use of the ganciclovir implant in treating newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS.³⁷ Patients were assigned to receive either the implant or deferred treatment. A significant difference ($P < 0.001$) was observed in the median time to the progression of cytomegalovirus retinitis (15 days in the deferred-treatment group [16 eyes] vs. 226 days in the implant group [14 eyes]). Although the magnitude of this difference was striking, questions remained about the efficacy and safety of the implant as compared with intravenous treatment.³⁸⁻⁴³ We conducted a randomized, controlled, multicenter clinical trial, in which patients with AIDS who had newly diagnosed cytomegalovirus retinitis were assigned to receive one of two intraocular ganciclovir implants, which varied only in the rate of release of the drug, or ganciclovir administered intravenously.

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METHODS

Patients

Patients with AIDS and newly diagnosed, active cytomegalovirus retinitis were enrolled at 18 clinical sites in the United States. Eligible patients had to be at least 18 years old, and their best corrected visual acuity had to be 20/200 or better in at least one affected eye. Exclusion criteria included opacities that would prevent visualization of the fundus, contraindications to intraocular surgery or to therapy with intravenous ganciclovir, the presence of overt signs or symptoms of extraocular cytomegalovirus infection, an absolute neutrophil count below 500 cells per cubic millimeter, a platelet count below 25,000 cells per cubic millimeter, a serum creatinine concentration above 1.5 mg per deciliter (133 μ mol per liter), and a Karnofsky score below 60. Informed consent was obtained from all patients.

Base-Line Evaluation and Randomization

Before randomization, patients underwent a complete base-line examination, which included nine-field fundus photography. The randomization was stratified so as to distribute patients with unilateral and bilateral cytomegalovirus retinitis equally among the three treatment groups, and blocking was used to assign patients equally to the treatment groups over time.

Treatment and Follow-up

Eligible patients were assigned with equal probability to receive one of three treatments: an intraocular implant (Vitrasert, Chiron Vision, Irvine, Calif.) with a release rate of 1 μ g of ganciclovir (Cytovene, Roche Laboratories, Nutley, N.J.) per hour, an intraocular implant with a release rate of 2 μ g of ganciclovir per hour, or intravenous ganciclovir. A 2- μ g-per-hour implant was included to determine whether a release rate higher than that used in a previous study³⁷ (1 μ g per hour) would have greater efficacy. Investigators and patients were unaware of the release rate of the ganciclovir implant. The surgical procedure to insert the implant has been described elsewhere.^{35,36} Patients assigned to receive intravenous ganciclovir received an induction dose of 5 mg per kilogram of body weight twice daily (total daily dose, 10 mg per kilogram) for at least 14 days, followed by maintenance therapy at a dose of 5 mg per kilogram once daily.

For patients in the implant groups, ophthalmic examinations were performed on postoperative days 1, 3, 4, 5, and 7. Patients in all three groups were examined at weeks 2, 4, 6, and 8 and then monthly until there had been eight months of progression-free follow-up or until progression of cytomegalovirus retinitis, death, or another event specified as leading to the termination of follow-up occurred. At follow-up visits from week 2 on, a complete ophthalmic examination was conducted, including measurement of visual acuity with modified Bailey-Lovie charts,⁴⁴ slit-lamp examination, indirect ophthalmoscopy with the eyes dilated, and bilateral, nine-field photography of the fundus.

Outcome Measures

Progression of cytomegalovirus retinitis in an eye involved at base line was the principal measure of outcome, and was defined as the extension of a lesion border by at least 750 μ m over a 750- μ m front; the development of a new area of cytomegalovirus retinitis at least 750 μ m in diameter; the occurrence of a retinal detachment in an area of active retinitis; or a decrease in best corrected visual acuity to less than 20/200 with active retinitis at or near the optic nerve. Progression was evaluated on the basis of central grading of photographs of the fundus by readers who were unaware of the patients' treatment assignments. Masking of the readers was achieved by creating artifactual implants on a portion of the fundus photographs of patients in the intravenous-ganciclovir group. The readers were informed of this procedure and knew they could not identify the study group by observing implant-shaped, darkened areas on the photographs they were

viewing. Other outcomes that were evaluated included clinically assessed progression of retinitis, the development of cytomegalovirus retinitis in a previously uninvolved eye, a diagnosis of extraocular cytomegalovirus disease, and death.

Statistical Analysis

Calculations of the power of the study were based on a sample size of 150 patients distributed equally among the three treatment groups. The assumptions included a recruitment time of 240 days, follow-up of 240 days, a median time to the progression of retinitis of 100 days for the intravenous-ganciclovir group, and a pooled comparison of the two implant groups' outcomes with that in the intravenous-ganciclovir group. The analyses indicated sufficient power (84 percent and 89 percent) to detect a doubling of the median time to the progression of retinitis in the implant groups as compared with the intravenous-ganciclovir group, allowing for a median time to withdrawal due to causes other than progression of retinitis of 20 and 30 weeks, respectively.

Time to the progression of cytomegalovirus retinitis was assessed with Kaplan-Meier product-limit analysis⁴⁵ and Cox proportional-hazards techniques.⁴⁶ We evaluated the risk of progression in all treated eyes, making use of an extension of the proportional-hazards regression model that adjusted for the correlation between the two eyes of a single patient.⁴⁷ SAS software (SAS Institute, Cary, N.C.) was used for all analyses.

RESULTS

From May 1993 through April 1994, 188 patients were enrolled: 63 were assigned to the 1- μ g-per-hour implant group, 61 to the 2- μ g-per-hour implant group, and 64 to the intravenous-ganciclovir group. Of the 188 patients, 15 (8.0 percent) were not treated because of voluntary withdrawal (8 from the intravenous-ganciclovir group and 4 from the implant groups), pretreatment complications (retinal detachment and cytomegalovirus colitis) that prevented study participation (2 from the implant groups), and determination of ineligibility after randomization (1 from an implant group). Therefore, 173 (92.0 percent) of the 188 randomized patients actually received treatment. Table 1 shows the age, sex, race, disease status, and base-line medication use of the treated patients in the three groups.

Progression of Cytomegalovirus Retinitis

Figure 1 shows Kaplan-Meier survival curves indicating the progression of cytomegalovirus retinitis for all eyes affected at base line in the three treatment groups. The median time to progression of cytomegalovirus retinitis was 221 days (lower 95 percent confidence limit, 181; the upper limit could not be estimated) in the 1- μ g-per-hour implant group, 191 days (95 percent confidence interval, 154 to 217) in the 2- μ g-per-hour implant group, and 71 days (95 percent confidence interval, 51 to 96) in the intravenous-ganciclovir group. For all eyes treated with implants (146 eyes for which the time to progression could be evaluated), the median time to progression was 196 days (95 percent confidence interval, 170 to 221). The median time to progression did not differ significantly between the two implant groups ($P=0.63$), but both groups, separately and

TABLE 1. BASE-LINE CHARACTERISTICS OF TREATED PATIENTS, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	1- μ g-PER-HOUR IMPLANT (N=62)	2- μ g-PER-HOUR IMPLANT (N=55)	INTRAVENOUS GANCICLOVIR (N=56)
Age (yr)	39.4 \pm 7.2	38.1 \pm 7.3	39.2 \pm 5.7
Male sex (%)	95.2	87.3	94.6
White race (%)†	83.9	83.6	69.6
Weight (lb)‡	146 \pm 22	151 \pm 20	150 \pm 24
Duration of HIV-positive status (yr)	4.1 \pm 2.6	4.6 \pm 2.9	4.0 \pm 2.7
Time from diagnosis of AIDS to study entry (yr)	2.1 \pm 1.9	2.0 \pm 1.7	2.0 \pm 1.4
Karnofsky score§	85 \pm 11	85 \pm 12	80 \pm 12
CD4+ count (cells/mm ³)	15.4 \pm 24.7	24.9 \pm 65.0	18.0 \pm 42.0
No AIDS-related conditions (%)¶	12.9	7.3	0.0
Bilateral CMV retinitis (%)	33.9	34.5	41.1
Medications used (%)			
Prophylaxis against <i>Pneumocystis carinii</i> pneumonia	75.8	83.6	76.4
Antiretroviral agents	54.8	63.6	61.8
Inhibitors of <i>Mycobacterium avium</i> complex	58.1	52.7	56.4
Antifungal agents	56.5	61.8	45.5
Acyclovir	41.9	41.8	43.6
Granulocyte colony-stimulating factor	9.7	5.5	12.7
Visual acuity in affected eye worse than 20/200 (%)	1.3	0.0	2.7

*Plus-minus values are means \pm SD. CMV denotes cytomegalovirus.

†P=0.05 by the chi-square test for the comparison between the combined implant groups and the intravenous-ganciclovir group.

‡To convert values in pounds to kilograms, divide by 2.2.

§P=0.01 by the independent Student's t-test for the comparison between the combined implant groups and the intravenous-ganciclovir group.

¶P=0.01 by Fisher's exact test for the comparison between the combined implant groups and the intravenous-ganciclovir group.

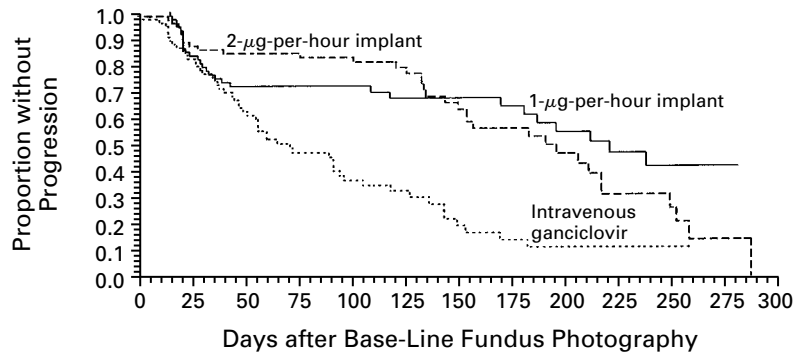
||The denominators used were the numbers of affected eyes, as follows: 75 eyes in the 1- μ g-per-hour implant group, 72 eyes in the 2- μ g-per-hour implant group, and 75 eyes in the intravenous-ganciclovir group.

together, were significantly different from the intravenous-ganciclovir group (P<0.001 by the log-rank test).

In order to adjust for base-line differences between the groups in measures of the severity of AIDS (the Karnofsky score and the presence of AIDS-related conditions) and of cytomegalovirus retinitis (the proportions of patients with bilateral vs. unilateral disease), as well as race and poor visual acuity (worse than 20/200) in the worse eye, we performed a proportional-hazards survival analysis with these factors as covariates (Table 2). The results indicated that the risk of progression in the affected eyes of patients in the intravenous-ganciclovir group was 2.83 times as great (95 percent confidence interval, 1.78 to 4.49) as that in the combined implant groups; the increase in risk was consistent in separate comparisons of the 1- μ g-per-hour and 2- μ g-per-hour implant groups with the intravenous-ganciclovir group. There was no significant difference in the risk of progression between the two implant groups (risk ratio, 1.01;

P=0.98). Of the covariates evaluated, bilateral retinitis at base line and a decrease of 10 points in the Karnofsky score were indicators of an increased risk of progression of retinitis.

In the analyses presented in Table 2 and Figure 1, some eyes were classified as having progression of retinitis within 28 days of the base-line photographs (this was defined as "early progression"). In the combined implant groups, early progression was identified in 22 eyes. Five eyes had involvement of the optic disk, and one eye had retinal detachment. Eleven of the remaining 16 eyes were the second eyes to receive an implant in patients who had bilateral retinitis at base line; in 3 of these 11 eyes, progression was recorded before the eye received an implant, and in the remainder there was a delay of 8 to 14 days between the base-line photographs and implantation. In the intravenous-ganciclovir group, early progression occurred in 13 eyes. Two eyes had active retinitis involving the optic disk, and for two eyes there were delays of eight and nine days be-



	0	25	50	75	100	125	150	175	200	225	250	275	300
Intravenous ganciclovir	76	59	43	27	20	13	7	5	3	3	1	0	0
1-µg-per-hour implant	75	60	47	41	33	27	24	20	16	10	3	2	0
2-µg-per-hour implant	71	61	57	52	47	38	26	18	14	8	5	2	0

Figure 1. Progression of Cytomegalovirus Retinitis in Eyes Affected at Base Line.

In the intravenous-ganciclovir group, 53 of the 76 affected eyes had progression, as compared with 29 of 75 in the 1-µg-per-hour implant group and 35 of 71 in the 2 µg-per-hour implant group ($P < 0.001$). Because of deficiencies in the base-line or follow-up photographs, the time to the progression of retinitis could not be calculated for eight eyes in the 1-µg-per-hour implant group, three eyes in the 2-µg-per-hour implant group, and three eyes in the intravenous-ganciclovir group.

tween the base-line photographs and the initiation of treatment. Thus, early progression attributable to limited or delayed efficacy of treatment occurred in no more than 5 of 146 implant-treated eyes (3.4 percent), and in 9 of 76 eyes treated with intravenous ganciclovir (11.8 percent).

Other Outcomes

Evaluation of outcomes other than progression of retinitis was limited by the fact that patients left the study at the time of the progression of retinitis (censoring); hence, the median follow-up was 156 days for the combined implant groups and 81 days for the intravenous-ganciclovir group. Since many patients treated with intravenous ganciclovir crossed over to treatment with an implant after the progression of retinitis, our ability to assess outcomes that occurred later in the course of disease was severely limited for patients treated intravenously, and our efforts to relate outcomes other than the progression of retinitis to the initial treatment assignment were confounded. Since no significant differences were found between the implant groups with respect to any outcome measures, the two implant groups were combined for subsequent analyses of outcomes.

Best corrected visual acuity was 20/40 or better in over 80 percent of the patients' affected eyes at base line (Table 3). Two weeks after the start of treatment, a significantly lower percentage of eyes with

ganciclovir implants had best corrected visual acuity of 20/40 or better (65 percent, as compared with 82 percent in the intravenously treated group; $P = 0.03$). After the second week, no significant differences were found between groups.

In the 177 eyes that received an implant (157 affected eyes that received an implant as initial treatment and 20 contralateral eyes in which retinitis developed that were treated later), there were no intraoperative complications. One week after implantation, vitreous hemorrhage was detected in 12 of the 154 eyes we examined (7.8 percent). These hemorrhages were transient and resolved by week 4 to 6 in nine eyes; further assessment of the other three eyes was prevented by death in two cases and by the development of endophthalmitis in one. Endophthalmitis was reported in a total of three eyes with implants: it occurred on postoperative day 7, two months after implant surgery, and after cataract extraction and insertion of an intraocular lens six months after implant surgery.

Among the 177 treated eyes (in 117 patients) in the two implant groups, there were 21 instances of retinal detachment (11.9 percent). Four cases of detached retina (5.1 percent) were observed in the 79 affected eyes (in 56 patients) that were treated with intravenous ganciclovir. Analysis of the time to retinal detachment showed no significant difference between the implant groups and the intravenous-gan-

ciclovir group with respect to the incidence of retinal detachment (P=0.23).

The most frequently observed systemic adverse effect of treatment was a decrease in the absolute neutrophil count to below 500 cells per cubic millimeter. This complication was reported more frequently in the intravenous-ganciclovir group (in 10 patients [17.9 percent]) than in the implant groups (8 patients [6.8 percent]). The use of granulocyte colony-stimulating factor was required during follow-up by 13.5 percent of the patients treated with an implant (15 of the 111 for whom information was available), and by 41.2 percent of the patients treated intravenously (21 of the 51 for whom information was available, P<0.001). Catheter-related sepsis was reported in two patients treated with intravenous ganciclovir.

We used Kaplan–Meier survival curves to analyze the time to involvement of the contralateral eye in patients who had unilateral retinitis at base line. The 25th percentile of time to involvement was 87 days for patients in the two implant groups, as compared with 119 days in the intravenous-ganciclovir group (P=0.28). The risk of involvement of the contralateral eye in the intravenous-ganciclovir group was half of that in the combined implant groups (risk ratio, 0.5; 95 percent confidence interval, 0.2 to 1.4; P=0.19).

A total of 13 extraocular cytomegalovirus infections were reported in 12 of 117 patients in the two implant groups (10.3 percent) and in none of 56 patients in the intravenous-ganciclovir group (P=0.04 by the log-rank test). The sites of involvement were the gastrointestinal tract (five infections), the lungs (five infections), and the central nervous system (three infections).

Follow-up for mortality was conducted through September 1995. As shown in Figure 2, no differences were found between the groups in the time to death (P=0.80). The median survival was 268 days for implant-treated patients and 262 days for patients treated intravenously.

DISCUSSION

The results of this randomized, controlled trial demonstrate a substantial and clinically important benefit of treating cytomegalovirus retinitis with ganciclovir released from an intraocular implant, as compared with intravenous administration. The median times to the progression of retinitis in the two implant groups were more than twice as long as that in the intravenous-ganciclovir group. These results are consistent with the results of Martin et al. for 14 eyes assigned to immediate treatment with an implant (median time to progression, 226 days).³⁷ The advantage of delivering ganciclovir through an intraocular implant may be due to the achievement of higher levels of ganciclovir in the vitreous body.

TABLE 2. RESULTS OF COX REGRESSION ANALYSIS OF THE PROGRESSION OF CYTOMEGALOVIRUS RETINITIS IN ALL AFFECTED EYES.

COMPARISON AND COVARIATES	RISK RATIO FOR PROGRESSION (95% CI)*	P VALUE
Intravenous ganciclovir vs. combined implant groups	2.83 (1.78–4.49)	<0.001
Bilateral retinitis	1.91 (1.26–2.90)	0.002
Karnofsky score 10 points lower	1.27 (1.06–1.52)	0.01
White race	0.89 (0.59–1.34)	0.56
AIDS-related conditions	1.78 (0.71–4.46)	0.22
Visual acuity <20/200	1.79 (0.72–4.41)	0.21
Intravenous ganciclovir vs. 1-μg-per-hour implant	2.45 (1.40–4.30)	0.002
Bilateral retinitis	2.31 (1.39–3.84)	0.001
Karnofsky score 10 points lower	1.30 (1.08–1.57)	0.006
White race	0.83 (0.53–1.30)	0.42
AIDS-related conditions	2.66 (0.64–11.08)	0.18
Visual acuity <20/200	1.65 (0.56–4.90)	0.37
Intravenous ganciclovir vs. 2-μg-per-hour implant	3.42 (1.95–6.01)	<0.001
Bilateral retinitis	1.43 (0.91–2.26)	0.12
Karnofsky score 10 points lower	1.31 (1.07–1.61)	0.01
White race	0.94 (0.56–1.58)	0.81
AIDS-related conditions	1.18 (0.42–3.28)	0.75
Visual acuity <20/200	0.80 (0.37–1.74)	0.58
1-μg-per-hour implant vs. 2-μg-per-hour implant	1.01 (0.61–1.66)	0.98
Bilateral retinitis	2.21 (1.26–3.86)	0.006
Karnofsky score 10 points lower	1.16 (0.89–1.52)	0.27
White race	0.80 (0.46–1.37)	0.41
AIDS-related conditions	1.48 (0.54–4.04)	0.44
Visual acuity <20/200	4.42 (1.62–12.09)	0.004

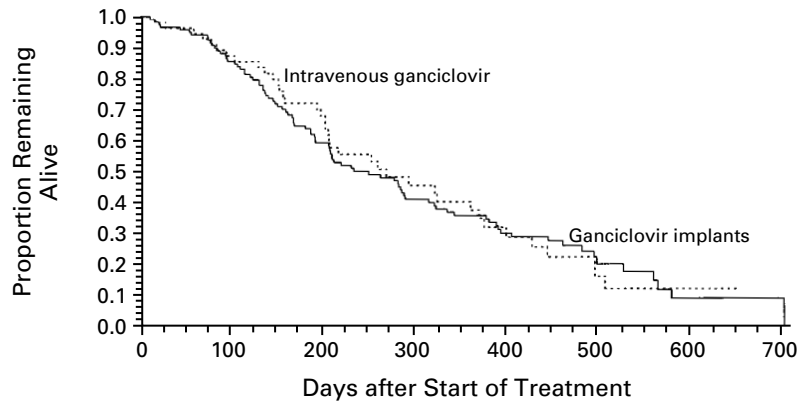
*Overall risk-ratio estimates have been adjusted for the presence or absence of bilateral retinitis at base line, the base-line Karnofsky score (each 10-point decrease), race (white vs. nonwhite), the presence or absence of AIDS-related conditions at base line, and the presence or absence of visual acuity worse than 20/200 in the affected eye at base line. CI denotes confidence interval.

TABLE 3. BEST CORRECTED VISUAL ACUITY, ACCORDING TO TREATMENT GROUP.*

TIME OF ASSESSMENT	COMBINED IMPLANT GROUPS		INTRAVENOUS-GANCICLOVIR GROUP	
	NO. OF EYES	20/40 OR BETTER (%)	NO. OF EYES	20/40 OR BETTER (%)
Base line	147	83	75	84
Week 2†	104	65	47	82
Week 4	108	77	55	78
Week 6	109	78	54	81
Month 2	98	74	49	83
Month 3	86	79	34	88
Month 4	71	80	22	81

*For implant-treated patients, the number of eyes shown is the number of eyes treated at entry for which information on visual acuity was available; for intravenously treated patients, the number of eyes shown is the number of affected eyes at entry for which visual-acuity information was available.

†P=0.03 by the chi-square test for the comparison with the combined implant groups.



	NO. OF PATIENTS AT RISK							
	0	100	200	300	400	500	600	700
Intravenous ganciclovir	56	47	33	17	10	5	1	0
Ganciclovir implants	117	100	65	40	24	9	2	1

Figure 2. Survival among Patients with Cytomegalovirus Retinitis.

In the intravenous-ganciclovir group, 38 of the 56 patients died, as did 87 of 117 in the combined implant groups ($P = 0.80$).

During the intravenous administration of ganciclovir, a mean vitreous ganciclovir concentration of 0.8 to 0.9 μg per milliliter has been reported.^{48,49} This concentration is below the level required to achieve 50 percent inhibition of viral plaque formation for many cytomegalovirus strains that had no prior exposure to ganciclovir.^{50,51} In contrast, Martin et al. reported a mean vitreous ganciclovir level of 4.1 μg per milliliter in eight eyes treated with implants releasing 1 μg per hour,³⁷ a level that exceeds the 50 percent plaque-inhibition level for most moderately resistant cytomegalovirus isolates.⁵²

Differences in outcome between the two implant groups were nonsignificant. The lower rate of release of ganciclovir (1 μg per hour) may be sufficient to treat the retinitis effectively or, alternatively, the actual rates of release in vivo may be so similar for implants designed to release the drug at 1 μg per hour and those designed to release 2 μg per hour that a difference would not be expected.

When the progression of retinitis was assessed clinically, the estimated median times to progression were longer than estimates resulting from assessments of fundus photographs in all three groups (results not shown), but comparisons of the time to progression yielded results consistent with those based on central grading of photographs of the fundus. Visual acuity was reduced two weeks after the placement of the implants. After this time, visual acuity was similar in eyes treated intravenously and those treated with implants. These results are consistent

with the findings of Martin et al.³⁷ Patients considering treatment with an implant must be informed of the likelihood of a temporary decrease in visual acuity, lasting several weeks after surgery, in the operated eye. Candidates for placement of implants must also be informed that intraocular surgery entails other risks, such as that of endophthalmitis.

Retinal detachment is a known complication of cytomegalovirus retinitis. The probability of retinal detachment depends on the extent, activity, and duration of retinitis.^{53,54} Estimates of the incidence of this condition have ranged from 24 to 50 percent.⁵⁴⁻⁶⁰ The frequency of retinal detachment in our study was somewhat lower. Although the Kaplan-Meier curves suggest that retinal detachment may be an earlier event in the implant groups (data not shown), the overall rate of retinal detachment in these groups is low.

The marked difference in efficacy between intravenous ganciclovir and ganciclovir implants resulted in many intravenously treated patients' being offered implants after early progression. Such crossing over limited our ability to assess outcomes that occurred later in the course of disease among patients treated intravenously and confounded any attempt to relate subsequent events to the initial treatment assignment. Follow-up of eyes that initially had no signs of cytomegalovirus retinitis was of particular interest, given the local treatment provided by the implant. The estimated risk ratio for retinitis in the contralateral eye (0.5), adjusted for severity of

disease, indicated that the risk was halved for eyes treated with intravenous ganciclovir, as compared with either ganciclovir implant. This finding suggests a need to monitor carefully the contralateral eyes of patients receiving therapy with ganciclovir implants alone for the appearance of cytomegalovirus disease.

An additional concern regarding treatment with a ganciclovir implant alone was the possibility that the incidence of extraocular cytomegalovirus infections would be increased and that survival would be adversely affected. New extraocular cytomegalovirus infections were reported in 12 patients who received implants. This finding, which suggests that the systemic coverage provided by intravenous ganciclovir prevented extraocular manifestations of cytomegalovirus, must be tempered by the limited follow-up for patients treated intravenously, as compared with implant-treated patients. There was no indication of a significant difference in mortality between the groups, and the median survival for patients in this study corresponds closely with that observed by Martin et al.³⁷ in patients who received implants (295 days in 26 patients) and with the results of a study of intravenous ganciclovir in 127 patients (median survival, 8.5 months).²⁶

With the availability of oral ganciclovir,⁶¹ it may be reasonable to offer patients who receive the ganciclovir implant the option of concurrent, systemic prophylaxis. Such combination therapy is currently being evaluated in a multicenter clinical trial, which is addressing the risk of extraocular cytomegalovirus disease and retinitis in the contralateral eyes of patients with unilateral retinitis at base line who receive a ganciclovir implant in combination with oral ganciclovir.

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Dr. Musch is a consultant to Chiron Vision, Inc. Drs. Kuppermann and Martin have received payment from Chiron Vision, Inc., for participation in a Food and Drug Administration advisory-panel meeting on the ganciclovir implant.

APPENDIX

The participants in the Ganciclovir Implant Study Group were as follows: M.H. Heinemann (principal investigator), S. Campbell, and S. Boddice, New York; J.S. Duker (principal investigator), K. Naughton, and J. McGeary, Boston; L.P. Chong (principal investigator), F. Walonker, and L. Levin, Los Angeles; B.D. Kuppermann (principal investigator), K. Lopez, and A. Gomes, Irvine, Calif.; J.L. Davis (principal investigator), T. Simmons, and R. Vandenbrook, Miami; R.H. Fish (principal investigator) and C. Hutchison, Houston; E. Ai (principal investigator), A. Luckie, and D. Tashayyod, San Francisco; R. Anand (principal investigator), Dallas; E.L. Chuang (principal investigator) and B. Lawrence, Seattle; M.R. Robinson (principal investigator) and K. Champagne, Rochester, N.Y.; H.L. Cantrill (principal investigator) and A. Brallier, Minneapolis; W.R. Freeman (principal investigator) and C. Jarman, La Jolla, Calif.; M.R. Wieland (principal investigator) and V. Coverstone, San Jose, Calif.; J.K. Ligh (principal investigator) and R. Hutt, New York; B.C. Norman (principal investigator) and J. Cristiano, Newport, Calif.; R. Neger (principal investigator) and K. Crawford, San Francisco; D.V. Weinberg (principal investigator) and A. Munana, Chi-

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Drs. Ashton and Smith are inventors of the ganciclovir implant, and as such they have a proprietary interest in its development and use. Dr. Dieterich has received payment from Chiron Vision, Inc., for participation in a Food and Drug Administration advisory-panel meeting on the ganciclovir implant.

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