EFFECT OF GANCICLOVIR THERAPY ON HEARING IN SYMPTOMATIC CONGENITAL CYTOMEGALOVIRUS DISEASE INVOLVING THE CENTRAL NERVOUS SYSTEM: A RANDOMIZED, CONTROLLED TRIAL

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Objective To evaluate the efficacy and safety of ganciclovir therapy in neonates with congenital cytomegalovirus (CMV) disease.

Study design Neonates with symptomatic CMV disease involving the central nervous system were randomly assigned to receive 6 weeks of intravenous ganciclovir versus no treatment. The primary end point was improved brainstem-evoked response (BSER) between baseline and 6-month follow-up (or, for patients with normal baseline hearing, normal BSER at both time points).

Results From 1991 to 1999, 100 patients were enrolled. Of these, 42 patients had both a baseline and 6-month follow-up BSER audiometric examination and thus were evaluable for the primary end point. Twenty-one (84%) of 25 ganciclovir recipients had improved hearing or maintained normal hearing between baseline and 6 months versus 10 (59%) of 17 control patients ($P = .06$). None (0%) of 25 ganciclovir recipients had worsening in hearing between baseline and 6 months versus 7 (41%) of 17 control patients ($P < .01$). A total of 43 patients had a BSER at both baseline and at 1 year or beyond. Five (21%) of 24 ganciclovir recipients had worsening of hearing between baseline and ≥ 1 year versus 13 (68%) of 19 control patients ($P < .01$). A total of 89 patients had absolute neutrophil counts determined during the course of the study; 29 (63%) of 46 ganciclovir-treated patients had grade 3 or 4 neutropenia during treatment versus 9 (21%) of 43 control patients ($P < .01$).

Conclusions Ganciclovir therapy begun in the neonatal period in symptomatically infected infants with CMV infection involving the central nervous system prevents hearing deterioration at 6 months and may prevent hearing deterioration at ≥ 1 year. Almost two thirds of treated infants have significant neutropenia during therapy. *(J Pediatr 2003;143:16-25)*

See editorial, p 4.

Congenital cytomegalovirus (CMV) infection is the most frequently identified viral cause of mental retardation[1,2] and is the leading nongenetic cause of neurosensory hearing loss in developed countries, including the United States.[3-5] It also is the most common congenital infection in human beings, with approximately 1% of all infants born alive in the United States being infected with CMV (approximately 40,000 infants per year).[2] Of infected fetuses, approximately 10% are symptomatic at birth, and 90% of symptomatic survivors have significant neurologic sequelae,[6-10] including hearing deficits in 30% to 65%.[7,11-13] The overall societal costs of providing specialized services for

ANC	Absolute neutrophil count	CSF	Cerebrospinal fluid
ALT	Alanine aminotransferase	CASG	Collaborative Antiviral Study Group
BSER	Brainstem-evoked response	CMV	Cytomegalovirus
CNS	Central nervous system		

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surviving infants and children with congenital CMV infections approaches $1.9 billion per year.[14]

No effective antiviral therapy exists for the treatment of congenital CMV disease. Despite its associated toxicities, ganciclovir is the most promising antiviral agent currently available for evaluation in this population. After completing a phase II pharmacokinetic/pharmacodynamic study,[15-17] the Collaborative Antiviral Study Group (CASG) of the National Institute of Allergy and Infectious Diseases conducted a randomized, controlled, phase III study of the effects of intravenous ganciclovir on hearing in the treatment of symptomatic congenital CMV disease involving the central nervous system (CNS).

METHODS

Study Population

Neonates with symptomatic (clinically apparent disease in the newborn period) congenital CMV disease involving the CNS were eligible for enrollment into this trial. All study subjects had confirmed isolation of CMV from a urine specimen obtained before study enrollment and within the first month of life,[15] and all had evidence of CNS disease, such as (1) microcephaly; (2) intracranial calcifications; (3) abnormal cerebrospinal fluid (CSF) for age; (4) chorioretinitis; and/or (5) hearing deficits. Infants ≤ 1 month of age, ≥ 32 weeks' gestation, and weighing ≥ 1200 g at birth were eligible for study participation. Patients were ineligible for the study if death was imminent, if they received other antiviral agents or immune globulin, had creatinine >1.5 mg/dL, were HIV-infected, or had hydranencephaly.

Study Design and Objectives

After informed consent from the parent(s) or legal guardian(s), patients were randomly assigned to receive ganciclovir treatment (6 mg/kg per dose administered intravenously every 12 hours for 6 weeks) or no treatment. A placebo arm was not used because of ethical concerns over maintaining intravenous access for 6 weeks. Institutional review boards at each participating study center approved the protocol. Ganciclovir was provided by F. Hoffmann-La Roche, Inc (Nutley, NJ).

The primary study end point was brainstem-evoked response (BSER) audiometry improvement by one gradation (eg, moderate impairment at baseline and mild impairment at follow-up) between baseline and the 6-month follow-up (or, for those patients with normal hearing at baseline, normal BSER at both time points). Nonprimary end points included evidence of laboratory (thrombocytopenia, hepatitis) and clinical (organomegaly, chorioretinitis) improvement, rate of growth, and death.

Audiologic Observations

Audiologic assessments were made by BSER at study entry, 6 weeks, 6 months, 1 year, and 2 years. For audiologic assessments beyond 2 years, only BSER hearing assessments were used in the efficacy analyses comparing baseline results and follow-up outcomes. The BSER thresholds were defined as normal hearing 0- to 20-dB thresholds, mild hearing loss 21- to 45-dB thresholds, moderate hearing loss 46 to 70 dB thresholds, and severe hearing loss ≥ 71 dB thresholds.[5,13] BSER threshold was defined as the lowest intensity level at which wave V could be detected and replicated. To eliminate variability between study sites, a single CASG Central Unit audiologist who was masked to randomization reviewed all BSER reports from all study patients and classified all evaluable ears as normal hearing, mild hearing loss, moderate hearing loss, and severe hearing loss.

Audiologic analyses were performed on best evaluable ear ("functional" assessment) and on total evaluable ears ("biological" assessment). The best-ear assessment correlates with functional hearing impairment in daily living (eg, a person with mild hearing impairment in one ear and severe hearing impairment in the other ear will function essentially as a mildly hearing impaired person).[18,19] Total ear assessment further assesses the biological effects of ganciclovir therapy. Odd numbers of total ears by treatment category are reported because at a given follow-up visit, a patient may have had only one ear that was evaluable (eg, otitis media on one side [nonevaluable], normal ear on the other [evaluable]).

Laboratory Observations

Patients randomly assigned to receive ganciclovir therapy had laboratory assessments for drug toxicity (complete blood counts, alanine aminotransferase [ALT], bilirubin, uric acid, creatinine) performed at study entry and on days 3, 5, 7, 10, 14, 17, 21, 28, 35, and 42. Patients randomly assigned to no therapy had laboratory assessments obtained weekly. Toxicity assessments were quantified with the use of the NIAID Division of AIDS Toxicity Tables, 1994.[20]

Modification of Dose

If a patient's absolute neutrophil count (ANC) fell below 500 cells/mm^3, ganciclovir was held until the ANC recovered to >750 cells/mm^3, at which time it was resumed at the full dose. If bone marrow suppression recurred, the ganciclovir dosage was decreased by 50% until the ANC rose above 500 cells/mm^3. If bone marrow suppression persisted at the 50% dosage, ganciclovir was discontinued.

Statistical Analysis

The Wilcoxon rank sum test and the Fisher exact test were used to compare the differences in baseline characteristics between the ganciclovir and the no-treatment groups or between evaluable (ie, patients who had both a baseline and a follow-up BSER assessment) and nonevaluable patients, by treatment category.

Treatment effect on change in BSER in the best ear was evaluated by means of the Fisher exact test. Logistic regression with generalized estimating equations[21] was used to assess change in BSER between the two treatment groups for total evaluable ears.

In addition, hearing assessments for best ear and total evaluable ears were performed with adjustment for potential influential factors. The factors explored in these logistic regression analyses included CT scan abnormalities, baseline intracranial calcifications, hepatomegaly, splenomegaly, microcephaly, chorioretinitis, growth retardation at birth, petechial rash, CSF protein concentration, seizures, ANC, bilirubin, creatinine, platelet, ALT, prematurity, and baseline BSER. Significant factors that were incorporated in the final multivariate model included baseline BSER, prematurity, CT scan abnormality, CSF protein concentration, chorioretinitis, and seizures. Since none of the ganciclovir recipients had worsening of hearing between baseline and the 6-month follow-up, the bayesian approach with Jeffreys prior shrinking group means toward zero[22] was used for evaluation of hearing deterioration at 6 months.

To investigate potential effects of patients who did not complete the study, comparisons of baseline demographic and clinical characteristics between evaluable and nonevaluable patients within each treatment group were performed. In addition, logistic regression analyses with adjustment for the potential influential factors on hearing were also performed, as above, to evaluate the treatment effect on hearing change to take into account the potential differences between the two treatment groups resulting from the high dropout rate.

The Fisher exact test was used to compare other clinical efficacy end points and safety evaluations between treatment groups. The Wilcoxon rank-sum test was used to assess the effect of ganciclovir on growth. The log-rank test was applied to analyze time to resolution of clinical and laboratory abnormalities and mortality rate between treatment groups. SAS software was used for all analyses.[23]

At the initiation of the study, sample size calculations projected 130 enrolled patients to provide 100 evaluable patients. Power calculations were based only on the primary end point. Interim analyses by the data and safety monitoring board were incorporated into the study protocol at the time of initial protocol development. Following the third of these interim analyses in December, 1999, the DSMB recommended early termination of the trial based on favorable preliminary study results and in recognition of the challenges in patient accrual and follow-up.

RESULTS

Population Characteristics

From 1991 through 1999, 100 patients from 18 CASG sites enrolled patients in this clinical trial. These sites and their corresponding enrollment numbers were University of Alabama at Birmingham, 15 subjects; University of Texas Southwestern Medical Center and University of Florida at Gainesville, 13 subjects each; Baylor College of Medicine, 11 subjects; University of Arkansas, 9 subjects; University of California at San Diego, 7 subjects; University of Alberta and Cook Fort Worth Children's Medical Center, 6 subjects each; Vanderbilt University, 5 subjects; Medical College of Virginia and University of Southern California, 3 subjects each; Tulane University and Children's Mercy Hospital in Kansas City, 2 subjects each; Carolinas Medical Center, University of Iowa, Maimonides Medical Center New York, Park Nicollet Medical Center Minnesota, and State University of New York, 1 subject each. Accrual by year was as follows: 1991, 4 subjects; 1992, 14 subjects; 1993, 12 subjects; 1994, 16 subjects; 1995, 9 subjects; 1996, 16 subjects; 1997, 13 subjects; 1998, 10 subjects; and 1999, 6 subjects.

Of these 100 subjects, 42 patients met all study entry criteria, had both a baseline and a 6-month follow-up BSER audiometric examination, and thus were evaluable for the primary end point. Two additional patients who had both baseline and 6-month follow-up BSERs did not meet all inclusion criteria (1 enrolled at 29 weeks' gestational age and randomly assigned to no treatment, 1 enrolled at 33 days of life and randomly assigned to ganciclovir), and 3 additional patients who had not had their 6-month follow-up at the time of data analysis. Of the remaining 53 patients, 18 had hearing assessments that were not BSERs; 15 had parental hardships necessitating their withdrawal from the study; 7 patients died before the 6-month follow-up; 5 patients had transportation difficulties; 5 patients relocated; and 3 patients refused follow-up visits.

Comparisons of the baseline demographic and clinical characteristics by treatment category of patients who were evaluable for the primary end point and of those who were nonevaluable are presented in Table I. No significant differences existed at baseline between the evaluable and nonevaluable patients with regard to clinical and laboratory measures of severity of congenital CMV disease (baseline BSER assessments, head circumference, intracranial calcifications, serum transaminase elevation, neutropenia, thrombocytopenia, hyperbilirubinemia, and organomegaly). Among the ganciclovir recipients, a higher percentage of nonevaluable patients were black, and a majority were born prematurely.

Baseline demographic and clinical characteristics for patients whose BSER assessments were available at both baseline and 6 months and at both baseline and ≥ 1 year are shown in Table II. All characteristics at baseline were comparable between the ganciclovir and the no-treatment groups.

More than three quarters of enrolled patients were evaluable for each of the nonprimary end points. The analyses that follow include all evaluable patients for each of the respective end points.

Hearing Efficacy Analyses

FOLLOW-UP AT 6 MONTHS. A total of 42 patients meeting all entry criteria were available for assessment of hearing change in the best ear at 6 months. Of these, 25 received ganciclovir and 17 received no treatment. For the biological total ear hearing evaluation, there were 85 ears with both baseline and 6-month BSER assessments, with 49 ears from ganciclovir recipients and 36 ears from control patients.

Table I. Comparison of baseline demographic and clinical characteristics of patients evaluable and nonevaluable at 6 months, by treatment category

Characteristic	Ganciclovir			No treatment		
	Evaluable (n = 25)	Nonevaluable (n = 21)	*P* value	Evaluable (n = 17)	Nonevaluable (n = 31)	*P* value
Median age (d)	8	14	.09	11	11	.46
Sex						
Female	10 (40%)	8 (38%)	1.00	9 (53%)	19 (61%)	.76
Male	15 (60%)	13 (62%)		8 (47%)	12 (39%)	
Race						
White	18 (72%)	7 (33%)	< .01	10 (59%)	17 (57%)	.92
Black	4 (16%)	12 (57%)		4 (24%)	6 (20%)	
Hispanic	3 (12%)	2 (10%)		2 (12%)	6 (20%)	
Other	0 (0%)	0 (0%)		1 (6%)	1 (3%)	
Prematurity (≤ 37 wk)	10/25 (40%)	14/18 (78%)	.03	8/17 (47%)	11/30 (37%)	.55
Median gestational age (wk)	38	35	< .01	38	38	.32
Median weight (kg)	2.55	2.2	.03	2.3	2.6	.20
Median head circumference (cm)	31	31	.36	31	31.5	.30
Abnormal CT (calcifications)	21/24 (88%)	15/21 (71%)	.27	14/16 (88%)	20/24 (83%)	1.00
Abnormal CSF indices	9/21 (43%)	12/18 (67%)	.20	9/15 (60%)	13/24 (54%)	.75
ALT ≥ 100 IU/L	5/23 (22%)	4/17 (24%)	1.00	3/17 (18%)	7/25 (28%)	.49
Platelet count ≤ 100,000/mm^3	10/24 (42%)	8/21 (38%)	1.00	7/17 (41%)	11/27 (41%)	1.00
Abnormal bilirubin	3/24 (13%)	7/20 (35%)	.15	4/16 (25%)	10/25 (40%)	.50
Splenomegaly	15 (60%)	11 (52%)	.77	13/17 (76%)	20/30 (67%)	.53
Hepatomegaly	16 (64%)	13 (62%)	1.00	13/17 (76%)	21/30 (70%)	.74
ANC Grade 3–4	4/24 (17%)	6/20 (30%)	.47	1/16 (6%)	2/24 (8%)	1.00
Baseline BSER (best ear)						
Normal	15/25 (60%)	6/11 (55%)	.12	10/17 (59%)	12/22 (55%)	.69
Mild	5/25 (20%)	0/11 (0%)		5/17 (29%)	4/22 (18%)	
Moderate	0/25 (0%)	1/11 (9%)		1/17 (6%)	2/22 (9%)	
Severe	5/25 (20%)	4/11 (36%)		1/17 (6%)	4/22 (18%)	
Unknown	0	10		0	9	
Baseline BSER (total ears)*						
Normal	23/49 (47%)	10/23 (43%)	.44	18/36 (50%)	18/41 (44%)	.26
Mild	8/49 (16%)	0/23 (0%)		11/36 (31%)	5/41 (12%)	
Moderate	3/49 (6%)	2/23 (9%)		3/36 (8%)	7/41 (17%)	
Severe	15/49 (31%)	11/23 (48%)		4/36 (11%)	11/41 (27%)	
Unknown	0	20		0	19	

*The denominator represents the number of total evaluable ears. The *P* value was obtained from a logistic regression analysis using generalized estimating equations.

Twenty-one (84%) of 25 ganciclovir recipients had hearing improvement or maintained normal hearing in their best ear at 6 months, compared with 10 (59%) of 17 patients in the no-treatment group (adjusted $P = .06$) (Tables III and IV). Inclusion in the best-ear analyses of the 2 additional patients who did not meet all entry criteria (above) yielded an adjusted *P* value of .03. For total evaluable ears, the effect of ganciclovir on hearing improvement or maintenance of normal hearing at 6 months was statistically significant in both the unadjusted and adjusted analyses (Tables III and IV).

No ganciclovir recipient had hearing deterioration at 6 months compared with 41% of control patients (adjusted $P < .01$) (Tables III and IV). Similar statistically significant effects on protection against hearing deterioration were seen in the total ear analyses as well (Tables III and IV).

For patients with best-ear hearing improvement between baseline and 6 months, the mean decibel change was >20 dB for ganciclovir recipients and was 25 dB for patients in the control group (Appendix 1). For patients with best-ear hearing deterioration between baseline and 6 months, the mean decibel change was >36.7 dB for patients in the control group (Appendix 1).

As noted above, 18 of the 53 patients who were nonevaluable for the primary end point had a follow-up

Table II. Comparison of baseline demographic and clinical characteristics in infants with evaluable hearing outcomes at 6 months and at ≥ 1 year

	BSER change evaluable at 6 months			BSER change evaluable at ≥ 1 year		
Characteristic	Ganciclovir (n = 25)	No treatment (n = 17)	*P* value	Ganciclovir (n = 24)	No treatment (n = 19)	*P* value
Median age (d)	8	11	0.68	9.5	12	0.44
Sex						
Female	10 (40%)	9 (53%)	0.53	11 (46%)	14 (74%)	0.12
Male	15 (60%)	8 (47%)		13 (54%)	5 (26%)	
Race						
White	18 (72%)	10 (59%)	0.66	15 (63%)	13 (68%)	0.91
Black	4 (16%)	4 (24%)		5 (21%)	3 (16%)	
Hispanic	3 (12%)	2 (12%)		4 (17%)	3 (16%)	
Other	0 (0%)	1 (6%)		0 (0%)	0 (0%)	
Prematurity (≤ 37 wk)	10/25 (40%)	8/17 (47%)	0.75	11 (46%)	5 (26%)	0.22
Median gestational age (wk)	38	38	0.22	38	38	0.50
Median weight (kg)	2.55	2.3	0.19	2.53	2.6	0.88
Median head circumference (cm)	31	31	0.17	31	31.5	0.81
Abnormal CT (calcifications)	21/24 (88%)	14/16 (88%)	1.00	19/23 (83%)	15/17 (88%)	1.00
Abnormal CSF indices	9/21 (43%)	9/15 (60%)	0.50	10/22 (45%)	8/17 (47%)	1.00
ALT ≥ 100 IU/L	5/23 (22%)	3/17 (18%)	1.00	4/22 (18%)	5/17 (29%)	0.46
Platelet count ≤ 100,000/mm^3	10/24 (42%)	7/17 (41%)	1.00	10/23 (43%)	7/18 (39%)	1.00
Abnormal bilirubin	3/24 (13%)	4/16 (25%)	0.41	4/23 (17%)	6/16 (38%)	0.26
Splenomegaly	15 (60%)	13 (76%)	.33	15 (63%)	16 (84%)	.17
Hepatomegaly	16 (64%)	13 (76%)	.50	16 (67%)	16 (84%)	.29
ANC grade 3-4	4/24 (17%)	1/16 (6%)	.63	3/23 (13%)	0/18 (0%)	.24
Baseline BSER (best ear)						
Normal	15 (60%)	10 (59%)	.39	12 (50%)	11 (58%)	.22
Mild	5 (20%)	5 (29%)		4 (17%)	5 (26%)	
Moderate	0 (0%)	1 (6%)		1 (4%)	2 (11%)	
Severe	5 (20%)	1 (6%)		7 (29%)	1 (5%)	
Baseline BSER (total ears)*						
Normal	23/49 (47%)	18/36 (50%)	.37	17/48 (35%)	17/36 (47%)	.11
Mild	8/49 (16%)	11/36 (31%)		7/48 (15%)	9/36 (25%)	
Moderate	3/49 (6%)	3/36 (8%)		5/48 (10%)	4/36 (11%)	
Severe	15/49 (31%)	4/36 (11%)		19/48 (40%)	6/36 (17%)	

*The denominator represents the number of total evaluable ears. *P* value was obtained from a logistic regression analysis using generalized estimating equations.

hearing assessment that was not a BSER. The alternative hearing tests performed were behavioral observation audiometry, visual reinforcement audiometry, and otoacoustics emissions. Of these 18 patients, 7 received ganciclovir (3 had hearing improvement, 3 maintained normal hearing, and 1 was unevaluable between baseline and 6 months) and 11 received no treatment (1 had hearing improvement, 1 maintained normal hearing, 1 maintained the same degree of hearing loss, 2 had worsened hearing [both of whom were deaf at follow-up] and 6 were unevaluable between baseline and 6 months).

Follow-up at or beyond 1 year. A total of 43 patients were available for evaluation of BSER hearing change in the

Table III. Unadjusted analyses of change in BSER

	Change between baseline and 6 months				Change between baseline and ≥ 1 year			
	Best ear assessment		Total ear assessment		Best ear assessment		Total ear assessment	
	Ganciclovir (n = 25)	No treatment (n = 17)	Ganciclovir (n = 49)	No treatment (n = 36)	Ganciclovir (n = 24)	No treatment (n = 19)	Ganciclovir (n = 48)	No treatment (n = 36)
Improved hearing between baseline and follow-up*	6 (24%)	5 (29%)	11 (22%)	6 (17%)	4 (17%)	0 (0%)	12 (25%)	0 (0%)
No change—normal hearing at baseline and follow-up	15 (60%)	5 (29%)	23 (47%)	8 (22%)	8 (33%)	5 (26%)	11 (23%)	8 (22%)
No change—same degree of hearing loss at both baseline and follow-up	4 (16%)	0 (0%)	15 (31%)	7 (19%)	7 (29%)	1 (5%)	15 (31%)	6 (17%)
Worsening hearing between baseline and follow-up*	0 (0%)	7 (41%)	0 (0%)	15 (42%)	5 (21%)	13 (68%)	10 (21%)	22 (61%)
	Improved + no change (normal to normal) vs other: $P = .086$ Worsening vs other: $P < .001$		Improved + no change (normal to normal) vs other: $P = .011$ Worsening vs other: $P < .001$		Improved + no change (normal to normal) vs other: $P = .133$ Worsening vs other: $P = .002$		Improved + no change (normal to normal) vs other: $P = .080$ Worsening vs other: $P = .002$	

*Improved or worsening hearing indicates changes in decibel, which result in movement to a different category of hearing (eg, normal to mild hearing, moderate to severe, moderate to mild, etc).

Table IV. Logistic regression analyses of change in BSER with adjustment for potential influential factors

Follow-up interval	Best ear analysis				Total ears analysis			
	Hearing improvement (or normal to normal)		Hearing deterioration		Hearing improvement (or normal to normal)		Hearing deterioration	
	OR (95% CI)*	P†	OR (95% CI)*	P†	OR (95% CI)‡	P‡	OR (95% CI)‡	P‡
6 mo	5.03 (0.84,45.94)	.06	21.11 (2.84, ∞)	< .01	9.96 (2.05,48.45)	< .01	92.40 (41.29,206.78)	< .01
≥ 1 y	4.77 (0.76,41.44)	.07	10.26 (1.79,81.92)	< .01	4.25 (1.25,14.44)	.02	4.38 (1.19,16.10)	.03

*Exact maximum conditional likelihood estimate and 95% CI.
†From exact conditional scores test.
‡From logistic regression analysis using generalized estimating equations.

best ear at 1 year or beyond. For subjects with multiple hearing assessments beyond 1 year (eg, at 1 year, at 2 years, and at 3 years), the final assessment (in this example, the one at 3 years) was used for the comparative analyses below. Of the 43 patients, 24 received ganciclovir, with a mean (± SD) follow-up time of 728 (± 465) days (median, 666 days). The remaining 19 patients were randomly assigned to the no-treatment group and had a mean (± SD) follow-up time of 702 (± 336) days (median, 672 days). For the biological total ear hearing evaluation, there were 84 ears with both baseline and ≥ 1 year BSER assessments, with 48 in ganciclovir recipients and 36 in control patients.

Significantly fewer ganciclovir-treated patients had hearing deterioration at 1 year or beyond compared with patients in the control group in both the unadjusted analysis (Table III) and logistic regression analysis (Table IV). This protection against hearing deterioration was noted in both the best-ear analysis (adjusted $P < .01$) and the total ear analysis (adjusted $P = .03$).

For patients with best-ear hearing improvement between baseline and ≥ 1 year, the mean decibel change was 25 dB for ganciclovir recipients (Appendix 2). For patients with best-ear hearing deterioration between baseline and ≥ 1 year, the mean dB change was 25 dB for ganciclovir recipients and >30.6 dB for patients in the no-treatment group (Appendix 2).

Of the 43 patients with BSER assessments both at baseline and ≥ 1 year, 32 also had a BSER assessment at 6 months. Hearing evaluation at 1 year or beyond from these 32 patients yielded similar results compared with those of the larger group of 43.

Other Clinical Efficacy Analyses

Patients treated with ganciclovir did not have a more rapid resolution of splenomegaly or hepatomegaly compared with patients in the control group. There was no statistically significant difference in time to resolution of CMV retinitis between the two treatment groups ($P = .23$), although only 8 patients had retinitis at baseline. Median weight gain between baseline and 6 weeks for ganciclovir recipients was 1.2 kg (n = 40), compared with 1.0 kg for control patients (n = 40) ($P = .02$). Similarly, median increase in head circumference between baseline and 6 weeks for ganciclovir-treated patients was 3.6 cm (n = 41), compared with 2.5 cm for control patients (n = 40) ($P<.01$). Similar results were also seen in growth at 6 weeks after adjustment for prematurity. These differences were not sustained at the 6-month follow-up or beyond.

Laboratory Efficacy Analyses

Among infants with abnormal ALT at baseline, ganciclovir-treated patients had more rapid resolution of ALT abnormalities compared with control patients (median time to ALT normalization, 19 days versus 66 days, respectively) ($P = .03$). Times to resolution of thrombocytopenia (median time, 9.5 days) and hyperbilirubinemia (median time, 16 days) were not significantly different between the two treatment groups.

Safety Evaluations

The primary toxicity in ganciclovir recipients was neutropenia (Table V), with 63% of ganciclovir recipients developing grade 3 or 4 neutropenia, compared with 21% of patients in the control group ($P < .01$). Of the 29 ganciclovir-treated patients developing neutropenia, 14 required dosage adjustments, but only 4 had the drug permanently discontinued. Two patients received granulocyte colony stimulating factor for their neutropenia. The mean time (± SD) of onset of grade 3 or 4 neutropenia for ganciclovir recipients was 14.2 (± 12.3) days and for control patients was 14.3 (± 13.1) days. Neutropenia in ganciclovir recipients resolved in 12.8 (± 13.6) days and in control patients, 14.2 (± 13.5) days.

Three ganciclovir recipients had catheter infections related to an indwelling intravenous catheter. One patient who had grade 3 neutropenia had Gram-negative septicemia but recovered fully. Neither of the other two patients had grade 3 or 4 neutropenia. No other infectious complications occurred that were judged by the participating investigator to be related to the study medication.

Table V. Development of significant toxicity during therapy

Laboratory test	Laboratory values constituting "Significant toxicity"*		Number of patients with stated laboratory abnormality: Ganciclovir (N = 47)†	No treatment (N = 50)‡	*P* value
Creatinine	< 7 days old:	≥ 2.5 mg/dL	1/44 (2%)	0/42 (0%)	1.00
	7–60 days old:	≥ 1.5 mg/dL			
	61–90 days old:	≥ 1.2 mg/dL			
ALT	≥ 540 IU/L (≥ 10X Upper limit normal)		0/40 (0%)	0/40 (0%)	–
		Preterm infants / Term infants			
Total bilirubin	3–6 days old:	> 25 mg/dL / >25 mg/dL	11/43 (26%)	7/39 (18%)	0.44
	7–30 days old:	≥ 36 mg/dL / ≥ 21 mg/dL			
	31–90 days old:	≥ 6 mg/dL / ≥ 3 mg/dL			
Platelets	< 50,000/mm^3		3/45 (7%)	2/41 (5%)	1.00
ANC	Grade 3–4 ANC		29/46 (63%)	9/43 (21%)	< 0.01
	Grade 3 ANC				
	2–7 days old:	750–1,249/mm^3	18/46 (39%)	8/43 (19%)	
	8–56 days old:	500–899/mm^3			
	57–90 days old:	250–399/mm^3			
	Grade 4 ANC				
	2–7 days old:	< 750/mm^3	11/46 (24%)	1/43 (2%)	
	8–56 days old:	< 500/mm^3			
	57–90 days old:	< 250/mm^3			

*Grade 3 or Grade 4 Toxicity. The data reflect treatment-emergent toxicities; that is, subjects whose baseline values were ≤ Grade 2 abnormalities and whose values rose to ≥ Grade 3 abnormalities during study.
†The mean (± SD) number of lab samples collected from subjects randomized to ganciclovir was 8.4 (± 2.1), with range of 2 to 15.
‡The mean (± SD) number of lab samples collected from subjects randomized to no treatment was 4.4 (± 1.7), with range of 1 to 9.

Death

Nine patients died during the course of this study: 3 were in the ganciclovir group and 6 were in the control group (P = .31). No death was related to complications of study drug. Causes of death for the 3 ganciclovir recipients included complications of CMV, necrotizing enterocolitis, and cardiopulmonary arrest. Causes of death for 6 patients in the control group included sudden infant death syndrome, pneumonia, necrotizing enterocolitis, *Candida* septicemia, dehydration, and *Escherichia coli* septicemia.

DISCUSSION

Six weeks of intravenous ganciclovir therapy prevents best-ear hearing deterioration at 6 months for patients with symptomatic congenital CMV disease involving the CNS. Ganciclovir therapy also may prevent best-ear hearing deterioration at or beyond 1 year. Although an understanding of the full clinical relevance of this audiologic effect awaits further long-term follow-up of these patients, the ability to prevent a patient from worsening from one level of hearing impairment (eg, mild) to another (eg, moderate) is of direct relevance to an individual's functional abilities, and preventing hearing deterioration can significantly affect a person's quality of life.[18,24-26]

The large number of patients who were nonevaluable for the primary end point raises the possibility of follow-up bias that could influence the conclusions of this trial. The potential for such bias cannot be eliminated. Among ganciclovir recipients, nonevaluable patients were more likely to be black and to be premature. Race has not been shown to correlate with severity of outcome in congenital CMV disease.[27] However, premature infants represent a population that may be at higher risk of adverse outcome, and while our adjusted logistic regression analyses controlled for prematurity, the possibility remains that this or other unrecognized imbalances could invalidate our findings. Reassuringly, other markers of severity of CMV disease were similar at baseline between the evaluable and nonevaluable patients. Furthermore,

analyses of the evaluable populations consistently demonstrated therapeutic benefit, including the subset of infants who had BSER assessments at baseline, 6 months, *and* ≥ 1 year. Developmental outcomes were not formally assessed in this study.

The difficulties in this trial with regard to loss to follow-up to a large degree mirror conditions in the "real world" that may limit the ability to use ganciclovir intravenously in patients with symptomatic congenital CMV disease involving the CNS. This was a rigorous trial that required major sacrifices on the part of study participants' families. Babies with symptomatic congenital CMV disease frequently are born to adolescent mothers and/or mothers with other young children, as both factors are known risks for maternal acquisition of CMV infection during pregnancy.[28-31] To have families with these circumstances continue the infants' stay in the hospital for 6 weeks or to have frequent follow-up visits was difficult. Given the toxicities of ganciclovir documented in this study, however, such close monitoring throughout the course of intravenous ganciclovir therapy is essential. A thorough assessment of a family's ability to complete a potentially difficult course of antiviral therapy must be considered before deciding to provide treatment.

Ganciclovir therapy was associated with significant hematologic toxicity in the majority of treated patients. The frequency of neutropenia in this study is similar to that seen in an earlier phase II trial,[15] although it is in contrast to the lower frequencies seen in another small, uncontrolled evaluation of ganciclovir therapy in congenital CMV disease.[32] Ganciclovir has both gonadal toxicity and carcinogenicity in animal models,[33] and its long-term safety after administration to young children is not established.

At this time, ganciclovir therapy administered intravenously for 6 weeks may be considered in patients with symptomatic congenital CMV disease involving the CNS. Patients receiving therapy should be monitored closely for neutropenia throughout the course of therapy. By study design, this trial included only symptomatic patients, who began therapy within the first month of life; demonstration of efficacy cannot be extrapolated to other settings. In determining whether to administer ganciclovir to a patient, the treating physician and family must weigh the potential benefit of therapy as interpreted by review of the data from this study against the significant risk of neutropenia and complications thereof, the potential for long-term gonadal toxicity or carcinogenicity,[33] and family circumstances that might impede completion of a full course of therapy.

This study is dedicated to Charles A. Alford, Jr, MD, whose vision and leadership were instrumental to this endeavor.

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Appendix 1. Sample of decibel readings of the best ear at baseline and 6 months

	Treatment assignment	Patient No	dB of best ear at Baseline	dB of best ear at 6 Months	Decibel change	Mean dB change
Improved hearing between baseline and 6 months	Ganciclovir	1 of 6	>90	80	>10	>20 dB improvement
		2 of 6	50	20	30	
		3 of 6	40	20	20	
	No Treatment	1 of 5	40	10	30	25 dB improvement
		2 of 5	55	30	25	
		3 of 5	40	20	20	
Worsening hearing between baseline and 6 months	Ganciclovir	(None of the 25 evaluable patients had hearing deterioration at 6 months)				NA
	No Treatment	1 of 7	30	60	30	>36.7 dB worsening
		2 of 7	75	>95	>20	
		3 of 7	35	>95	>60	

Several study centers completed the Case Record Forms for audiologic assessment in such a fashion that our independent audiologist could determine that the assessment of "normal," "mild," etc., was valid. The source documents (audiology reports) were not sent in, however, and thus dB cannot be reported for some patients.

Appendix 2. Sample of decibel readings of the best ear at baseline and ≥1 year

	Treatment assignment	Patient No	dB of best ear at Baseline	dB of best ear at ≥1 Year	Decibel change	Mean dB change
Improved hearing between baseline and ≥1 year	Ganciclovir	1 of 4	50	20	30	25 dB improvement
		2 of 4	40	20	20	
	No Treatment	(None of the 19 evaluable patients had hearing improvement at ≥1 Year)				NA
Worsening hearing between baseline and ≥1 year	Ganciclovir	1 of 5	20	40	20	25 dB worsening
		2 of 5	20	40	20	
		3 of 5	40	75	35	
	No Treatment	1 of 13	10	75	65	>30.6 dB worsening
		2 of 13	75	>95	>20	
		3 of 13	55	>95	>40	
		4 of 13	40	70	30	
		5 of 13	60	70	10	
		6 of 13	90	>100	>10	
		7 of 13	10	75	65	
		8 of 13	35	40	5	

Several study centers completed the Case Record Forms for audiologic assessment in such a fashion that our independent audiologist could determine that the assessment of "normal," "mild," etc., was valid. The source documents (audiology reports) were not sent in, however, and thus dB cannot be reported for some patients.