

ORAL GANCICLOVIR FOR THE PREVENTION OF CYTOMEGALOVIRUS DISEASE IN PERSONS WITH AIDS

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Abstract Background. In the advanced stages of the acquired immunodeficiency syndrome (AIDS), cytomegalovirus (CMV) disease, particularly vision-damaging retinitis due to CMV, is common. We evaluated prophylactic treatment with orally administered ganciclovir as a way to prevent CMV disease.

Methods. We conducted a prospective, randomized, double-blind, placebo-controlled study of CMV-infected persons with AIDS with either CD4+ lymphocyte counts of ≤ 50 per cubic millimeter or counts of ≤ 100 per cubic millimeter in those with a history of an AIDS-defining opportunistic infection. Patients were randomly assigned, in a 2:1 ratio, to receive either oral ganciclovir (1000 mg three times daily) or placebo.

Results. The study was stopped after a median of 367 days of follow-up. In an intention-to-treat analysis, the 12-month cumulative rates of confirmed CMV disease were 26 percent in the placebo group (n = 239) and

14 percent in the ganciclovir group (n = 486), representing an overall reduction in risk of 49 percent in the ganciclovir group (P < 0.001). The incidence of CMV retinitis after 12 months was 24 percent in the placebo group and 12 percent in the ganciclovir group (P < 0.001). The prevalence of CMV-positive urine cultures at base line was 42 percent; after two months it was 43 percent in the placebo group and 10 percent in the ganciclovir group (P < 0.001). The one-year mortality rate was 26 percent in the placebo group and 21 percent in the ganciclovir group (P = 0.14). Therapy with granulocyte colony-stimulating factor was more frequent in the ganciclovir group (24 percent) than in the placebo group (9 percent).

Conclusions. In persons with advanced AIDS, prophylactic oral ganciclovir significantly reduces the risk of CMV disease. (N Engl J Med 1996;334:1491-7.)

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HUMAN cytomegalovirus (CMV) is an important pathogen in persons with the acquired immunodeficiency syndrome (AIDS), and at autopsy as many as 90 percent of patients with AIDS have evidence of CMV infection.¹⁻⁵ CMV retinitis affects 25 to 40 percent of those with AIDS²⁻⁷; other diseases related to CMV in patients with AIDS include gastrointestinal disease, encephalitis, polyradiculitis, and, less frequently, pneumonia.^{2-5,8-10} CMV is also an important pathogen in other immunocompromised people, including recipients of organ transplants, persons with cancer, and congenitally infected infants.¹¹

Currently, two antiviral agents, ganciclovir and foscarnet, are approved for the treatment of some CMV-related conditions.¹²⁻¹⁶ Despite treatment, however, CMV disease, and particularly CMV retinitis, tends to recur; retinitis may progress and result in the loss of vision. Both ganciclovir and foscarnet must be administered intravenously in the initial treatment of active CMV disease, and long-term intravenous treatment necessitates placement of a central venous catheter.

Studies of the bioavailability of oral ganciclovir have

demonstrated that the plasma levels attained are sufficient to inhibit the growth in vitro of most clinically important strains of CMV.¹⁷ Oral ganciclovir has also been shown to be effective as maintenance therapy for patients with AIDS who have newly diagnosed, as well as recurrent, CMV retinitis.^{18,19}

Considerable progress has been made in the prevention of opportunistic infections in people with AIDS, including *Pneumocystis carinii* pneumonia, disease caused by the *Mycobacterium avium* complex, and serious fungal infections.^{4,20-24} The high frequency of CMV disease in patients with AIDS makes prophylaxis against the condition a high priority. In this study we evaluated the safety and efficacy of oral ganciclovir in the prevention of CMV disease in persons with AIDS.

METHODS

Study Design

The study protocol was reviewed and approved by the appropriate local institutional review boards, and all participants gave written informed consent. The study subjects were adults infected with the human immunodeficiency virus (HIV) who had had two CD4+ lymphocyte counts performed in the 30 days before entry into the study that were ≤ 50 cells per cubic millimeter or, in those with a documented history of an AIDS-defining opportunistic infection, were ≤ 100 per cubic millimeter.²⁵ All subjects had CMV infection, confirmed by antibody test or urine culture. Patients were ineligible if they had past or present CMV disease or a history of treatment for CMV, active gastrointestinal disease, an absolute neutrophil count below 750 cells per cubic millimeter, a platelet count below 50,000 per cubic millimeter, an estimated creatinine clearance rate below 70 ml per minute, or a score below 60 on the Karnofsky scale.

At base line, all study subjects underwent a complete history taking, a physical examination, and an ophthalmologic examination. Base-line laboratory evaluations included complete and differential blood counts, an analysis of serum chemistry, determination of T-cell-

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subgroup levels, and a urine culture for CMV. Experienced ophthalmologists performed dilated-eye examinations in order to exclude patients with CMV retinitis before randomization.

After stratification according to base-line CD4+ lymphocyte count (≤ 50 or > 50 per cubic millimeter), subjects were randomly assigned, in a 2:1 ratio, to receive either 1000 mg of ganciclovir (in 250-mg capsules) or a matched placebo three times a day with food. Subjects were evaluated on the 14th day after the start of treatment and then at 2-month intervals during treatment. At each study visit, a limited interim history was taken, and a physical examination and laboratory tests were performed. Every two months, an examination of the subjects' dilated eyes was performed by an experienced ophthalmologist, and urine was obtained for CMV culture.

Antiretroviral therapy was recommended for all subjects. Therapy with oral acyclovir was allowed, in doses of no more than 1000 mg per day, for the suppression of recurrent infection with herpes simplex virus. Higher doses of acyclovir for the treatment of acute herpesvirus infection were allowed up to a maximum of four weeks of oral acyclovir or two weeks of intravenous acyclovir.

End Points

The primary study end point was the development of confirmed CMV disease according to defined criteria. The presence of CMV retinitis was determined through examination of the fundus of the dilated eye and through indirect ophthalmoscopy by ophthalmologists experienced in the diagnosis of the condition. Summaries describing all extraocular episodes of CMV disease were reviewed independently by the study chairperson and a clinical reviewer not associated with the study, both of whom were unaware of the subjects' treatment assignments.

A diagnosis of CMV gastrointestinal disease was confirmed by the presence of signs and symptoms of disease in the upper or lower gastrointestinal tract and by endoscopy with biopsy. The biopsy had to reveal the presence of cells with CMV inclusions or evidence of CMV on immunostaining, immunofluorescence, or in situ hybridization; inflammation or necrosis; and the absence of other pathogens. A diagnosis of CMV pneumonia required confirmation by either open-lung biopsy or transbronchial lung biopsy. The lung biopsy had to reveal cells with CMV inclusions, or the tissue had to test positive for CMV on immunostaining, immunofluorescence, or in situ hybridization; in addition, there had to be no evidence of *P. carinii* or other pathogens. At least two of the following were also required for a confirmed diagnosis of CMV pneumonia: interstitial infiltrates seen on chest x-ray films, dyspnea, a need for supplemental oxygen or ventilatory assistance, and decreased partial pressure of oxygen. The diagnosis of CMV polyradiculopathy required confirmation of CMV in the cerebrospinal fluid by culture or the polymerase chain reaction, as well as progressive flaccid paraparesis, polymorphonuclear pleocytosis, and decreased glucose levels and elevated protein in the cerebrospinal fluid. Other types of CMV disease required confirmation by biopsy and had to fulfill the histopathological and virologic criteria described above.

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 CMV disease after 18 months of treatment, with an expected incidence of CMV disease of 30 percent in the placebo group and 15 percent in the ganciclovir group. Two interim analyses were scheduled to be reviewed by an independent Data and Safety Monitoring Board that would use the O'Brien-Fleming boundary as the criterion for early termination of the study.^{26,27} We used Kaplan-Meier analysis to compute rates of CMV disease in the placebo and ganciclovir groups.²⁸ The time to the development of CMV disease in the two study groups was compared with the stratified log-rank test, and the groups were stratified according to base-line CD4+ lymphocyte counts. Relative risks, reductions in risk, and 95 percent confidence intervals were computed with a stratified Cox proportional-hazards analysis. We used Fisher's exact test to compare proportions in the study groups. All tests were two-sided.

RESULTS

A total of 725 subjects were enrolled at 19 sites from November 1992 through December 1993. The ran-

domized portion of the study ended on July 15, 1994, after the review of the first interim analysis by the Data and Safety Monitoring Board determined that the criteria for stopping the trial had been satisfied. All subjects were then offered open-label ganciclovir. The analysis of survival included all deaths of study subjects through August 18, 1994, the earliest date on which subjects could have started open-label treatment. For the primary analyses of efficacy and survival, all subjects randomly assigned to the study groups were included according to intention-to-treat criteria. In the secondary analyses of efficacy and safety, all subjects who actually received study medication were included.

Study Population

Of the 725 subjects, 486 were randomly assigned to therapy with oral ganciclovir and 239 to placebo. Thirteen subjects, eight assigned to the ganciclovir group and five to placebo, never received study medication. The majority of subjects were white (82 percent) and male (99 percent). CMV infection was confirmed by serologic testing in 90 percent of the subjects, by urine culture in 6 percent, and by both in 4 percent. The mean age was 39 years, and the median CD4+ lymphocyte count was 22 per cubic millimeter. In the month before entry into the study, 94 percent of the subjects had received antiretroviral medication; 54 percent of the subjects had had an AIDS-defining opportunistic infection. Base-line characteristics were similar in both treatment groups (Table 1).

The mean duration of treatment with ganciclovir was 269 days (median, 265), as compared with 240 days (median, 244) for placebo. Of the subjects, 33 percent in the ganciclovir group and 27 percent in the placebo group were treated for more than 365 days (maximum, 621 days in the ganciclovir group and 618 days in the placebo group). The mean length of observation from randomization through July 15, 1994, including follow-up, was 355 days (median, 372) for the ganciclovir group and 343 days (median, 360) for the placebo group.

CMV Disease

Kaplan-Meier estimates of the rate of protocol-defined CMV events at 12 months were 26 percent in the placebo group and 14 percent in the ganciclovir group, producing an overall reduction in risk of 49 percent (relative risk, 0.51; 95 percent confidence interval, 0.36 to 0.73; $P < 0.001$) (Fig. 1A and Table 2). The rate of investigator-reported CMV events at 12 months was 33 percent in the placebo group and 18 percent in the ganciclovir group (relative risk, 0.50; 95 percent confidence interval, 0.37 to 0.69; $P < 0.001$) (Table 2).

CMV retinitis was the most frequent and usually the first type of CMV disease in both study groups. The 12-month incidence of CMV retinitis was 24 percent in the placebo group and 12 percent in the ganciclovir group ($P < 0.001$). The 12-month incidence of protocol-defined colitis was 2 percent in both groups ($P = 0.50$). The

Table 1. Base-Line Characteristics of the Subjects, According to Study Group.

CHARACTERISTIC	PLACEBO (N = 239)	GANCICLOVIR (N = 486)
Median age — yr	38	39
Sex — M/F	237/2	480/6
Previous diagnosis of AIDS — no. (%) [*]	162 (68)	302 (62)
History of AIDS-defining opportunistic infection — no. (%)	132 (55)	256 (53)
History of <i>P. carinii</i> pneumonia — no. (%)	93 (39)	170 (35)
Antiretroviral treatment within 4 wk before study — no. (%)	224 (94)	456 (94)
CD4+ count — cells/mm ³		
Mean ±SD	27±19.7	26±19.6
Median	23	21
Range	0–100	0–91
CD4+ count ≤50/mm ³ — no. (%)	211 (88)	429 (88)

^{*}According to the 1987 criteria of the Centers for Disease Control.

12-month incidence of investigator-reported colitis was 7 percent in the placebo group and 3 percent in the ganciclovir group (P = 0.003).

Only 12 percent of the study subjects randomly assigned to treatment (85 of 725) had a base-line CD4+ lymphocyte count greater than 50 per cubic millimeter. In this subgroup, prophylaxis with ganciclovir was associated with a significant reduction in the rate of development of CMV disease (relative risk, 0.24; 95 percent confidence interval, 0.07 to 0.84; P = 0.02). Similarly, ganciclovir significantly reduced the risk of CMV disease in 640 subjects with base-line CD4+ lymphocyte counts of ≤50 per cubic millimeter (relative risk, 0.55; 95 percent confidence interval, 0.38 to 0.79; P = 0.001).

Ganciclovir decreased the risk of CMV disease regardless of the concomitant use of antiretroviral agents. Ganciclovir was associated with a significant reduction in the incidence of CMV disease in the 631 subjects receiving antiretroviral therapy (relative risk, 0.57; 95 percent confidence interval, 0.39 to 0.83; P = 0.003) and in the 94 subjects not receiving antiretroviral agents (relative risk, 0.30; 95 percent confidence interval, 0.11 to 0.80; P = 0.01). The concomitant use of acyclovir also did not affect the efficacy of ganciclovir prophylaxis. The risk of CMV disease was reduced by treatment with ganciclovir both among the 468 subjects who received concomitant oral acyclovir (relative risk, 0.57; 95 percent confidence interval, 0.38 to 0.86; P = 0.007) and among the 257 subjects who did not receive acyclovir (relative risk, 0.42; 95 percent confidence interval, 0.22 to 0.81; P = 0.007).

Cultures for CMV

At base line, urine cultures were positive for CMV in 44 percent of the placebo group and 41 percent of the ganciclovir group; two months after the start of treatment, the proportions were 43 percent and 10 percent, respectively (P < 0.001) (Fig. 2). This significant difference between the study groups in the proportion of

urine cultures positive for CMV was sustained throughout treatment. A CMV-positive culture at base line was associated with an increased risk of CMV disease (relative risk, 2.5 and 1.9 for the placebo and ganciclovir groups, respectively), and prophylaxis with ganciclovir reduced the risk of CMV disease regardless of the results of the base-line urine culture. Subjects with CMV-positive base-line cultures who received placebo had a 12-month incidence of protocol-defined CMV disease of 32 percent, as compared with 17 percent for subjects with CMV-positive cultures who received ganciclovir (relative risk, 0.56; 95 percent confidence interval, 0.33 to 0.97; P = 0.04). Subjects with CMV-negative cultures at base line who received placebo had a 12-month inci-

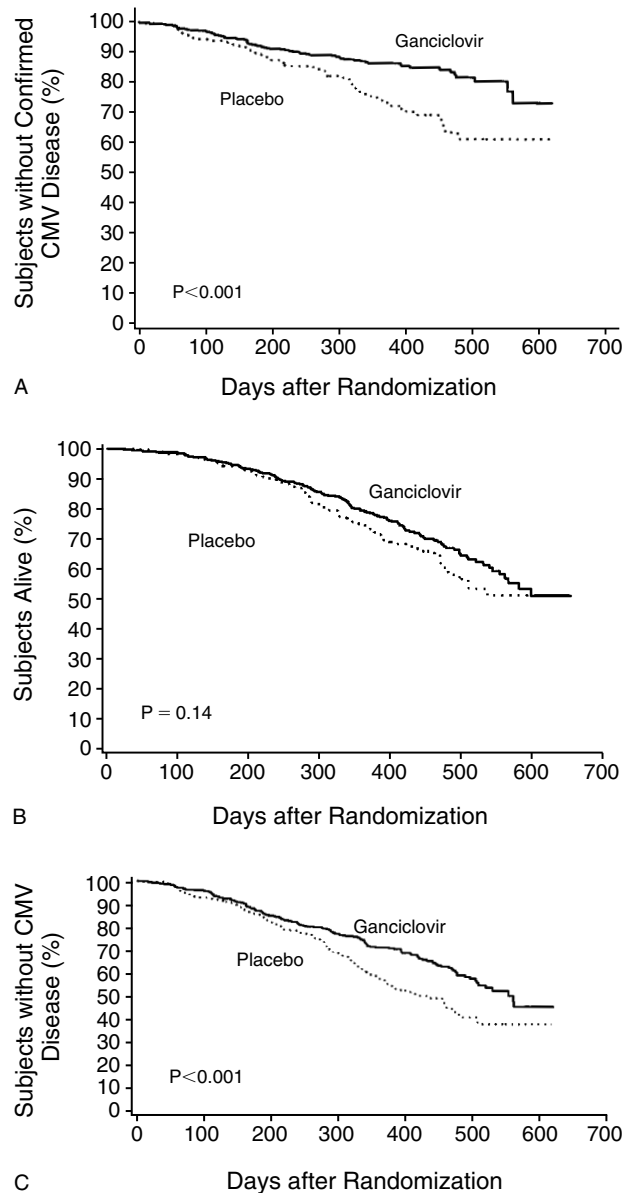


Figure 1. Kaplan-Meier Curves of Survival without Confirmed, Protocol-Defined CMV Disease (Panel A), Overall Survival (Panel B), and Survival without CMV Disease (Panel C) in the Ganciclovir Group (N = 486) and the Placebo Group (N = 239).

dence of CMV disease of 22 percent, as compared with 11 percent among ganciclovir recipients with negative base-line cultures (relative risk, 0.49; 95 percent confidence interval, 0.28 to 0.83; $P=0.007$).

Clinical Events Related to HIV

In the study, a new HIV-related event was defined as a condition of which there was no previous history and that was not present at base line. The incidence of herpes simplex virus disease was 7 percent in the placebo group and 3 percent in the ganciclovir group ($P<0.01$); that of herpes zoster, 1 percent in the placebo group and 2 percent in the ganciclovir group; and that of oral hairy leukoplakia, 8 percent in the placebo group and 6 percent in the ganciclovir group. No significant differences between the placebo and ganciclovir groups were observed in the 12-month Kaplan–Meier estimates of invasive candidiasis (7 percent in the placebo group and 8 percent in the ganciclovir group), cryptococcal infection (1 percent and 1 percent), mycobacterial infection (11 percent and 10 percent), *P. carinii* pneumonia (10 percent and 12 percent), or toxoplasmosis (2 percent and 3 percent). Also, the incidence of Kaposi's sarcoma (12 percent in the placebo group and 8 percent in the ganciclovir group), non-Hodgkin's lymphoma (2 percent and 3 percent), wasting syndrome (3 percent and 5 percent), AIDS dementia complex (4 percent and 2 percent), and progressive multifocal leukoencephalopathy (2 percent and 1 percent) did not differ significantly between the two groups. The mean CD4+ lymphocyte counts 12 months after the start of treatment were 14 cells per cubic millimeter in the placebo group and 12 cells per cubic millimeter in the ganciclovir group.

Survival and Survival Free of CMV Disease

At 12 months the Kaplan–Meier estimate of the rate of death was 26 percent in the placebo group and 21 percent in the ganciclovir group (relative risk, 0.81; 95

percent confidence interval, 0.61 to 1.07; $P=0.14$) (Fig. 1B). The predominant cause of death in both groups was progressive HIV-related disease. The relative risk of death in the ganciclovir group, as compared with the placebo group, was similar in the two strata of base-line CD4+ lymphocyte counts. Ganciclovir prophylaxis did significantly improve survival free of CMV disease (Fig. 1C). The 12-month Kaplan–Meier estimate of CMV disease or death was 43 percent in the placebo group and 29 percent in the ganciclovir group (relative risk, 0.65; 95 percent confidence interval, 0.51 to 0.84; $P<0.001$).

Adverse Events and Discontinuation of the Study Drug

Of the 725 study subjects, 446 (62 percent) discontinued the study medication during the study period — 158 (66 percent) in the placebo group and 288 (59 percent) in the ganciclovir group. Reasons for discontinuation of the study drug were the development of CMV disease (26 percent of the placebo group and 13 percent of the ganciclovir group), adverse events (16 percent and 19 percent), death (4 percent and 6 percent), withdrawal from the study (11 percent and 10 percent), administrative problems (5 percent and 5 percent), and loss to follow-up (2 percent and 3 percent).

Gastrointestinal symptoms were the most commonly reported adverse events, occurring in 74 percent of the placebo group and 77 percent of the ganciclovir group (Table 3). Severe gastrointestinal symptoms were reported in 14 percent of the placebo group and 15 percent of the ganciclovir group. Neuropathy occurred in 15 percent of the placebo group and 21 percent of the ganciclovir group ($P=0.09$) and was severe in 2 percent of each group. Severe neutropenia, defined as an absolute neutrophil count below 500 cells per cubic millimeter, occurred in 6 percent of the placebo group and 10 percent of the ganciclovir group ($P=0.1$). Severe anemia, defined as a hemoglobin concentration below

Table 2. Incidence of CMV Disease in the Study Groups at 12 and 18 Months, According to Kaplan–Meier Estimates of Protocol-Defined and Investigator-Reported Events.*

TYPE OF DISEASE	PROTOCOL-DEFINED EVENTS				RELATIVE RISK (95% CI)	P VALUE†	INVESTIGATOR-REPORTED EVENTS				RELATIVE RISK (95% CI)	P VALUE†
	PLACEBO (N = 239)		GANCICLOVIR (N = 486)				PLACEBO (N = 239)		GANCICLOVIR (N = 486)			
	12 mo	18 mo	12 mo	18 mo			12 mo	18 mo	12 mo	18 mo		
	percent						percent					
All CMV disease	26	39	14	20	0.51 (0.36–0.73)	<0.001	33	47	18	24	0.50 (0.37–0.69)	<0.001
Retinitis	24	39	12	18	0.51 (0.35–0.75)	<0.001	24	39	12	18	0.51 (0.35–0.75)	<0.001
Colitis	2	4	2	2	0.68 (0.22–2.14)	0.50	7	13	3	4	0.37 (0.18–0.74)	0.003
Esophagitis	<1	<1	1	1	0.97 (0.09–10.70)	0.98	<1	<1	1	1	1.45 (0.15–13.90)	0.75
Gastroenteritis	1	2	1	1	0.72 (0.12–4.33)	0.72	1	2	2	2	1.7 (0.35–8.19)	0.50
Hepatitis	0	0	0	0	NC	NC	1	1	0	0	0 (0–NC)	0.15
Pneumonia	0	2	<1	<1	0.44 (0.03–7.06)	0.55	3	5	1	3	0.46 (0.15–1.42)	0.16
Polyradiculopathy	0	0	0	0	NC	NC	<1	<1	1	1	0.97 (0.09–10.64)	0.98
Other CMV disease	0	0	1	1	NC	0.33	1	1	2	2	1.93 (0.41–9.11)	0.40

*"Protocol-defined events" include only CMV end points confirmed with the criteria described in the Methods section. CI denotes confidence interval, and NC not calculable.

†By the stratified log-rank test.

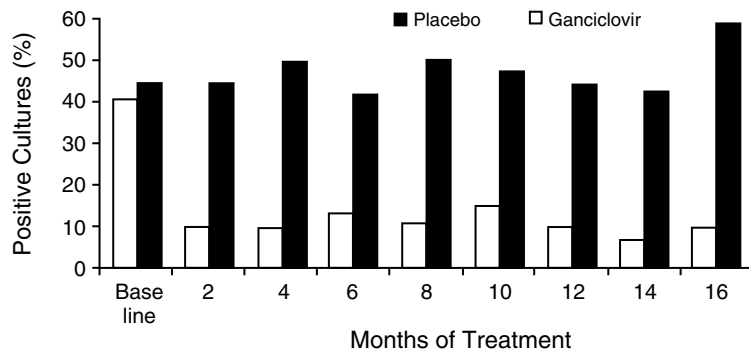


Figure 2. Prevalence of CMV-Positive Urine Cultures in the Ganciclovir and Placebo Groups.

Only subjects with cultures that could be evaluated are included. The differences between the placebo and ganciclovir groups were significant ($P < 0.001$ by the two-sided Fisher's exact test).

8 g per deciliter, was reported in 4 percent of the placebo group and 5 percent of the ganciclovir group. Granulocyte colony-stimulating factor was given to 24 percent of the ganciclovir group and 9 percent of the placebo group ($P < 0.001$). The duration of treatment per person-year was 16 days in the placebo group and 47 days in the ganciclovir group. Similarly, treatment with erythropoietin was more frequent in the ganciclovir group than in the placebo group (14 percent vs. 6 percent, $P < 0.01$). The number of days of treatment with erythropoietin per person-year of treatment with the study drug was 17 days in the placebo group and 26 days in the ganciclovir group. A maximal serum creatinine concentration of 1.5 mg per deciliter ($133 \mu\text{mol}$ per liter) or more was reached in 21 percent of the ganciclovir group and 13 percent of the placebo group ($P = 0.03$). A maximal creatinine concentration above 2.5 mg per deciliter ($221 \mu\text{mol}$ per liter) occurred in 1 percent of the ganciclovir group and 2 percent of the placebo group.

DISCUSSION

Currently, CMV is the most common serious opportunistic pathogen in persons with AIDS for which no effective prophylaxis is available. Intravenous ganciclovir administered prophylactically has successfully reduced the incidence of CMV disease after bone marrow or solid-organ transplantation.^{29,30} However, because the risk of CMV disease progressively increases as HIV disease advances, intravenous prophylaxis for persons with AIDS would require the placement of a central venous catheter for its prolonged use, an impractical procedure that would be unacceptable to most patients. Our study demonstrates that in persons with advanced AIDS, an average of 9 months of prophylaxis with oral ganciclovir decreased the rate of CMV disease by approximately 50 percent during ap-

proximately 12 months of observation. As expected, CMV retinitis was the most frequent event and the form of CMV disease most markedly affected by oral ganciclovir. However, the rate of CMV colitis may also have decreased in the subjects receiving ganciclovir. More cases of colitis were reported by investigators than met the definition in the study protocol (Table 2), and the beneficial effect of ganciclovir was more marked in the investigator-reported cases. This discrepancy may reflect the difficulty of establishing the diagnosis of many CMV diseases other than retinitis. The subjects who met the strict criteria of this study for the diagnosis of CMV disease may represent only a portion of those who actually had CMV disease.

Preliminary results of another study, Terry Bein Community Programs for Clinical Research on AIDS (CPCRA 023), have suggested that oral ganciclovir may not be effective in preventing CMV disease in persons with AIDS.³¹ However, several important differences exist between the CPCRA study and our own. Persons enrolled in the CPCRA study had a median CD4+ lymphocyte count 67 percent higher than that of the subjects in our study, and follow-up during randomized drug therapy was shorter. Most im-

Table 3. Incidence of Selected Adverse Events According to Study Group.*

EVENT	PLACEBO	GANCICLOVIR	P VALUE†
	(N = 234)	(N = 478)	
	<i>percent</i>		
Any gastrointestinal symptoms	74	77	0.46
Diarrhea	42	48	0.15
Nausea	33	30	0.39
Anorexia	16	19	0.47
Vomiting	11	14	0.20
Neuropathy	15	21	0.09
Neutropenia‡			0.001
Absolute neutrophil count, 500–749/mm ³	7	16	
Absolute neutrophil count, <500/mm ³	6	10	
Anemia‡			0.58
Hemoglobin, 8.0–9.4 g/dl	16	15	
Hemoglobin, <8.0 g/dl	4	5	
Low platelet count			0.39
25,000–49,999/mm ³	2	2	
<25,000/mm ³	0	1	
High serum creatinine§			0.01
1.5–2.4 mg/dl	11	19	
≥2.5 mg/dl	2	1	

*Only subjects who actually received the assigned study treatment are included.

†By the two-sided Fisher's exact test or the chi-square test (for laboratory data).

‡Treatment with granulocyte colony-stimulating factor or erythropoietin was more frequent in the ganciclovir group.

§To convert creatinine values to micromoles per liter, multiply by 88.4.

portant, dilated-eye examinations by an ophthalmologist were not required before entry into the CPCRA study or during the study unless visual symptoms were reported. Thus, participants in the CPCRA study could have entered the trial with unrecognized CMV retinitis or retinitis could have developed unrecognized during the study period.

Our study found a significant decline from base line in the prevalence of CMV-positive urine cultures in the ganciclovir group, as compared with the placebo group. This virologic response to oral ganciclovir strongly suggests a beneficial clinical effect. Moreover, the presence of infectious virus, as seen in urine cultures, was associated with an increased risk of subsequent CMV disease.

Severe adverse events were uncommon in the subjects who received oral ganciclovir. Gastrointestinal symptoms, although common, were not significantly more frequent in the ganciclovir group than in the placebo group. The most common adverse events in the ganciclovir group — as seen in laboratory testing — included neutropenia, anemia, and mild increases in serum creatinine concentrations. Subjects in the ganciclovir group used hematopoietic stimulating factors, including granulocyte colony-stimulating factor and erythropoietin, more often than those in the placebo group. However, the use of these growth factors was specifically encouraged in the study protocol to help subjects continue to take the study drug.

Our findings must be applied to the care of persons infected with HIV in the light of the specific characteristics of the study population. Although persons with CD4+ lymphocyte counts between 50 and 100 per cubic millimeter could have been enrolled in the study if they had had an AIDS-defining opportunistic infection, only 12 percent of study subjects were in this category. Therefore, our data came mostly from persons with CD4+ lymphocyte counts below 50 per cubic millimeter (median, 22 per cubic millimeter). Thus, CMV-positive persons with AIDS and CD4+ lymphocyte counts below 50 per cubic millimeter may be good candidates for prophylaxis with oral ganciclovir. However, ganciclovir also benefited the subgroup of subjects who had CD4+ lymphocyte counts of 51 to 100 per cubic millimeter. Although CMV-positive urine cultures were associated with a greater risk of CMV disease, CMV disease developed in some subjects in each study group even though they had persistently negative results on urine cultures. It is possible that emerging techniques for the rapid and sensitive detection of CMV^{32,33} will help to identify patients who are at highest risk for CMV disease.

Our study demonstrates that oral ganciclovir can significantly decrease the risk of CMV disease in persons with advanced AIDS. Although prophylaxis with ganciclovir was not associated with improved overall survival, survival free of CMV disease was significantly prolonged. Ganciclovir is generally well tolerated, but some patients will require hematopoietic stimulating factors for the treatment of neutropenia and anemia.

Oral ganciclovir promises to be a useful drug for prophylaxis against CMV disease in persons with AIDS.

APPENDIX

In addition to the authors, the members of the Roche Cooperative Oral Ganciclovir Study Group are L. Meixner and W.R. Freeman (University of California, San Diego); M. Giordano and M.-H. Heinemann (Cornell Medical Center, New York); D.N. Friedberg and A. McMeeking (New York University Medical Center, New York); M. Thompson (AIDS Research Consortium of Atlanta); M.H. Grieco and S. Plotyia (St. Luke's-Roosevelt Hospital, New York); W.L. Drew, J. Sayre, and D. Miner (Mt. Zion Medical Center, University of California, San Francisco); A. Stein (Community Research Initiative of South Florida, Coral Gables); P.C. Jensen (Veterans Affairs Medical Center, San Francisco); P. Kumar and J. Lavelle (Georgetown University Hospital, Washington, D.C.); C.S. Crumpacker, D.V. Ives, and M.A. Laureano (Beth Israel Hospital, Harvard Medical School, Boston); M. Braffman (Pennsylvania Hospital, Philadelphia); D. McMahon (University of Pittsburgh, Pittsburgh); C.A. Benson, D. Samano, and T. Deutsch (Rush Medical College, Chicago); C.L. Brosgart, N.A. Orcutt, and R. Sorenson (East Bay AIDS Center, Berkeley, Calif.); B. McNamara and L. Savan (Kraus-Beer Medical Group, Los Angeles); M. Guerrero and P. Miller (Harbor-UCLA Medical Center, Torrance, Calif.); and A. Shadman (Roche Pharmaceuticals, Palo Alto, Calif.).

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