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A Randomized, Controlled Trial of Foscarnet in the Treatment of Cytomegalovirus Retinitis in Patients with AIDS

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■ *Objective:* To evaluate foscarnet sodium in treating cytomegalovirus retinitis in patients with AIDS.

■ *Patients:* Twenty-four previously untreated persons with AIDS and cytomegalovirus retinitis who were at low risk for loss of their visual acuity.

■ *Intervention:* Patients were randomly assigned to receive either no therapy (delayed treatment, control group) or immediate treatment with intravenous foscarnet at a dose of 60 mg/kg body weight three times a day for 3 weeks (induction regimen) followed by a maintenance regimen of 90 mg/kg once a day.

■ *Measurements:* Patients were examined weekly until they reached the primary clinical end point, defined as progression of their retinitis border by 750 μm or the development of a new retinal lesion due to cytomegalovirus. Progression was evaluated using retinal photographs by masked readers. Secondary evaluations included changes in visual acuity, cytomegalovirus shedding in the blood and urine, serum levels of human immunodeficiency virus type 1 (HIV-1) p24 antigen, and total CD4 T lymphocyte counts.

■ *Results:* The mean time to progression of retinitis was 3.2 weeks in the control group ($n = 11$) compared with 13.3 weeks in the treatment group ($n = 13$) ($P < 0.001$). Nine of 13 patients in the treatment group had positive blood cultures for cytomegalovirus at entry and all nine cleared their blood of cytomegalovirus by the end of the induction period ($P = 0.004$) compared with one of six patients in the control group. No reductions in p24 levels were seen in the control patients compared with a reduction of more than 50% in p24 levels for all four patients on treatment for whom follow-up levels were available. The main adverse effects of foscarnet treatment were seizures (2 of 13 patients), hypomagnesemia (9 of 13), hypocalcemia (11 of 13), and elevations in serum creatinine above 176.8 μmol/L (2.0 mg/dL) (3 of 13). The control patients received an average of 0.2 units of blood per week compared with an average of 0.6 units of blood per week for the patients on treatment.

■ *Conclusions:* The administration of foscarnet decreases the rate of progression of cytomegalovirus retinitis in persons with AIDS. Its judicious use is likely to prevent loss of vision in these patients. In this study, however, there was little change in visual acuity in patients in either the immediate or delayed treatment group because only patients with non-sight-threatening disease were selected.

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Cytomegalovirus infection, reactivated from the latent state, is a common opportunistic infection and a leading cause of death in patients with the acquired immunodeficiency syndrome (AIDS) (1, 2). Reactivation of cytomegalovirus is a relatively late manifestation of AIDS, generally occurring in patients with fewer than 0.100×10^9 CD4 cells/L (3). It may present in various clinical forms, including retinitis, colitis, pneumonitis, esophagitis, and encephalitis (4).

Cytomegalovirus retinitis occurs in 7% to 20% of patients with AIDS. It is the most common cause of visual impairment in these patients, accounting for at least 70% of all intraocular infections in patients with AIDS (5, 6). Various therapeutic agents have been used to treat cytomegalovirus retinitis. One of these, 9-(1,3)-dihydroxy-2-propoxymethylguanine (DHPG, ganciclovir, or Cytovene, Syntex Laboratories, Palo Alto, California), was licensed by the Food and Drug Administration in June 1989 for use in treating this disease.

Data from a series of uncontrolled trials have shown that this drug is effective in delaying progression of retinitis in approximately 80% to 90% of patients during a 2- to 3-week course of intravenous therapy (3, 7-10). Unfortunately, despite daily maintenance therapy with ganciclovir, cytomegalovirus retinitis eventually progresses (median time to progression, approximately 15 weeks) (11). Another problem associated with ganciclovir therapy is a profound neutropenia that precludes concomitant zidovudine therapy and that necessitates premature withdrawal of ganciclovir in 82% of patients taking both drugs (12). Because of this inability to administer zidovudine and ganciclovir concomitantly, patients with cytomegalovirus retinitis often have to choose between loss of vision and progression of their human immunodeficiency virus (HIV) infection.

Trisodium phosphonoformate (foscarnet; Astra Pharmaceutical Products, Westborough, Massachusetts) is a pyrophosphate analog that inhibits various viral DNA polymerases, including the reverse transcriptase of HIV-1 (13-15). It is virustatic against all classes of herpes viruses including cytomegalovirus (16). In the last several years, the drug has shown promise in the treatment of cytomegalovirus retinitis in a series of uncontrolled studies (17-20). In addition, the use of foscarnet therapy in patients with AIDS has been reported to be associated with declines in HIV-1 culture positivity and in the circulating levels of the HIV-1 core antigen p24 (21-24). Foscarnet appears to have considerably less bone marrow toxicity than that seen with ganciclovir, suggesting that simultaneous therapy with zidovudine and foscarnet can be tolerated. The purpose of our study was to evaluate the efficacy of foscarnet for the treatment of cytomegalovirus retinitis in patients with AIDS.

A major problem in the development of therapeutic agents for cytomegalovirus retinitis in patients with AIDS has been the difficulty in designing appropriately controlled trials. The standard placebo-controlled trial design is not appropriate for the evaluation of a disease process that permanently destroys vision when an agent for which there is strong anecdotal evidence of efficacy is being studied. For this reason, we used a controlled trial comparing immediate with delayed therapy and chose patients with previously untreated peripheral lesion retinitis in whom progression of disease could be documented without risk for significant visual loss. This design, together with the use of masked readers at a fundus photography reading center who assessed the progression of retinitis by examining retinal photographs, permitted us to carry out a controlled trial with minimal bias and minimal risk to the patient.

Patients and Methods

Patients between 18 and 60 years of age with HIV infection and with cytomegalovirus retinitis that was not immediately sight threatening were eligible for this study. Patients with appropriate lesions were referred by internists and ophthalmologists throughout the United States to the National Institutes of Health (NIH) for screening. The diagnosis of cytomegalovirus retinitis was based on the presence of characteristic progressive, white, fluffy or granular retinal infiltrates, with or without associated hemorrhage. The presence of an area of atrophic retina surrounded by an area of active retinitis was also used as a diagnostic criterion for cytomegalovirus retinitis. Lesions were defined as not immediately sight threatening if they were located at least 1500 μm from the margin of the optic disc and 3000 μm from the center of the fovea or if they had already involved the optic disc or fovea or both sufficiently to reduce visual acuity to 20/400 or less. Ophthalmologic eligibility criteria were determined independently by two ophthalmologists.

Additional entry criteria included no previous therapy with foscarnet or ganciclovir, serum creatinine level less than 176.8 μmol/L (2.0 mg/dL), absolute neutrophil count greater than 0.50×10^9 cells/L (500 cells/mm^3), platelet count greater than 25×10^9 cells/L (25 000/mm^3), and a Karnofsky score of at least 60. Concomitant therapy with zidovudine or dideoxyinosine was permitted. Systemic acyclovir therapy was not permitted. All patients received 300 mg of pentamidine administered monthly as an aerosol as prophylactic treatment against *Pneumocystis carinii* pneumonia. The study protocol was approved by the clinical research subpanel of the National Institute of Allergy and Infectious Diseases.

Treatment Regimens

After signing an informed consent and designating a durable power of attorney, eligible patients were randomly assigned to receive either immediate or delayed therapy with foscarnet. Patients assigned to immediate therapy were admitted to the Warren Grant Magnuson Clinical Center, NIH. After a Hickman catheter was placed, patients received a total of 3 weeks of intravenous foscarnet at a dose of 60 mg/kg body weight every 8 hours administered in 0.9% sodium chloride over 1 hour at a concentration of 12 mg/mL (induction therapy). In an effort to minimize nephrotoxicity, patients received continuous intravenous hydration (3 to 4 L/d) throughout the induction phase. If therapy had to be interrupted for any reason, once it was resumed, it was continued until the patient had received a total of 21 days of induction therapy. After the induction regimen, patients were discharged from the hospital and received single daily 2-hour infusions of foscarnet as maintenance therapy at a dose of 90 mg/kg diluted to a total volume of 500 mL with 0.9% sodium chloride infusion. During maintenance therapy, patients were hydrated with 0.5 to 1.0 L of 0.45 sodium chloride before receiving each dose of foscarnet (25).

Patients were evaluated weekly with ophthalmologic examinations; complete blood count and differential; serum electrolytes, including Ca^{++} and Mg^{++}; serum creatinine; aspartate aminotransferase; alanine aminotransferase; alkaline phosphatase; lactic dehydrogenase; and uric acid. The dose of foscarnet was adjusted during therapy based on calculated creatinine clearance as noted in Table 1. When patients reached a study end point, they were eligible to continue foscarnet at the discretion of the investigators and their referring physician.

Patients who were assigned to delayed therapy were not hospitalized but were monitored weekly as if they were on therapy. In the interval from study entry to study end point, these patients received no therapy for cytomegalovirus and thus served as an untreated control group. When they reached

Table 1. Adjustment of Maintenance Foscarnet Dosing

Creatinine Clearance*	Foscarnet Dose
mL/s·kg (*mL/min·kg*)	*mg/kg·d*
> 0.023 (1.4)	90
0.020 to 0.023 (1.2 to 1.4)	78
0.017 to 0.020 (1.0 to 1.2)	75
0.013 to 0.017 (0.8 to 1.0)	71
0.010 to 0.013 (0.6 to 0.8)	63
0.07 to 0.010 (0.4 to 0.6)	57

* Creatinine clearance was calculated as (140 − age)/(serum creatinine × 72) for men; and (140 − [age × 0.85])/(serum creatinine × 72) for women.

Table 2. Baseline Patient Characteristics*

Characteristic	Immediate Treatment (n = 13)	Control (n = 11)
Age, *y*	34.8 ± 4.43	42.3 ± 7.17
Hemoglobin, *g/L*	95 ± 13.6	108 ± 9.3
Leukocyte count, × 10^9/*L*	2.923 ± 2.385	2.100 ± 0.840
Absolute neutrophils, 10^9/*L*	1.434 ± 0.755	1.264 ± 0.645
CD4 lymphocytes, 10^9/*L*	0.010 ± 0.010	0.044 ± 0.032
p24 antigen,† *pg/mL*, (*n*)	352 ± 228 (5)	131 ± 114 (9)
Karnofsky score	78 ± 9.0	73 ± 11.9
Fraction of patients with an opportunistic infection other than cytomegalovirus, *n/n*	12/13	6/11
Time from diagnosis of AIDS to study entry, *mo*	15.4 ± 12.8	7.2 ± 6.2
Time from diagnosis of cytomegalovirus retinitis to study entry, *mo*	3.9 ± 3.4	3.3 ± 5.0

* Where appropriate, data are presented as the mean ± SD.
† Calculated only for those patients with levels greater than 30 pg/mL.

a study end point, they were eligible to receive treatment with foscarnet on a schedule identical to that administered to the patients randomized to immediate therapy.

Study End Points

The number of weeks to progression of retinitis was the primary study end point. Progression of retinitis was defined as the movement of a retinal lesion by at least 750 μm across a 750-μm front into previously normal retina or the development of a new lesion at least 1/16 of the disc area in size. Progression was defined by comparison with photographs taken at the end of the first week of study and was determined by masked readers at the photographic reading center at the University of Wisconsin. We decided to use the week-1 photographs as the starting point for comparison to allow for the fact that patients with cytomegalovirus retinitis treated with ganciclovir may show progressive disease before a therapeutic effect is seen. Secondary end points included changes in visual acuity, changes in cytomegalovirus shedding, changes in p24 antigen levels, and changes in total CD4 T-lymphocyte counts.

Ophthalmologic Evaluations

Ophthalmologic examinations were done weekly. Best corrected visual acuity was measured under standard conditions using the Early Treatment for Diabetic Retinopathy Study (ETDRS) eye chart. Photographs of the retina were taken using a 60 deg Canon fundus camera (Canon CF-60U, Canon, Tokyo, Japan) and Kodachrome ASA 64 film (Eastman Kodak, Rochester, New York). Nine standard photographic fields were used to document the retina posterior to the equator, with the central, superior, and inferior photographs being stereoscopic. Masked observers assessed the photographs by retro-illuminating transparencies on a light box with examination through a Donaldson stereoscopic viewer (Model PS-4A, Luminos Photocorp, New York, New York) (magnification, × 5). Relevant fields were traced to create retinal drawings using a microfilm reader (Dokumator, Aus Jena, Jena, Federal Republic of Germany) without reference to previous photographs or drawings. Lesion borders were compared with those at baseline (week 1 of study) by overlaying the retinal borders.

Laboratory Evaluations

Samples of urine and blood were cultured for cytomegalovirus at study entry, at the end of the induction phase of treatment, and when the patient reached an ophthalmologic end point. Cultures were done by inoculating 0.2 mL of urine, or 0.2 mL of the buffy coat from 10 mL of blood onto human embryonic lung (MRC-5) and observing them for 5 weeks for the presence of cytopathic effects due to cytomegalovirus as previously described (26). Lymphocyte subsets were determined using monoclonal antibodies to CD3 (OK-T3, Ortho Diagnostics, Raritan, New Jersey), CD4 and CD8 (Leu-3a and Leu-2, Becton-Dickinson, Sunnyvale, California) conjugated to fluorescein-isothiocyanate with analysis on a FACS-II analyzer (Becton-Dickinson) by previously described procedures (27). Serum levels of HIV-1 p24 antigen were determined using the Abbott kit (Abbott Laboratories, Chicago, Illinois), according to the manufacturer's specifications on batched, frozen sera.

Statistical Analysis

Using an assumption of an 80% treatment effect and a 10% spontaneous remission rate, a sample size of 10 patients per group was determined to be adequate to show a difference. The alpha and beta chosen for these calculations were 0.05 and 0.20, respectively. The data for the primary end point (days to progression) were examined using a Kaplan-Meier analysis with statistical analysis by the Mantel-Cox *t*-test. Patient baseline data were analyzed using the Student *t*-test or, in the case of history of previous opportunistic infection, the Fisher exact test. All *P* values are two-tailed.

Results

A total of 24 patients were enrolled in this trial. Thirteen patients were randomized to immediate therapy and 11 patients were randomized to the control group (delayed therapy). The baseline characteristics of these patients are given in Table 2. Patients randomized to immediate therapy appeared to have slightly more advanced disease in that they had slightly lower total CD4 counts (0.010 × 10^9 cells compared with 0.044 × 10^9 cells/L for the control group, $P = 0.001$), were more likely to have had an additional AIDS-defining opportunistic infection other than cytomegalovirus before entry (12 of 13 compared with 6 of 11) and had been diagnosed with AIDS for a longer period (15.4 months compared with 7.2 months, $P = 0.06$). In addition, they were somewhat younger than the patients in the control group (34.8 years compared with 42.3 years, $P = 0.005$).

Efficacy

The time to study end point is shown in Figure 1. For patients randomized to delayed therapy, the mean time to study end point was 3.2 weeks (range, 1 to 6 weeks).

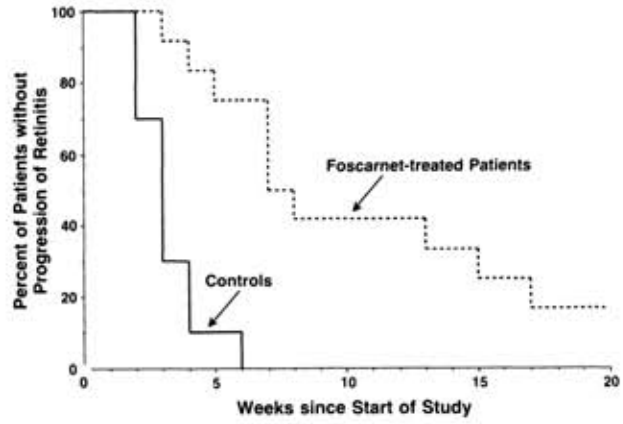

Figure 1. Kaplan-Meier plot. Fraction of patients with progression of retinitis as a function of time.

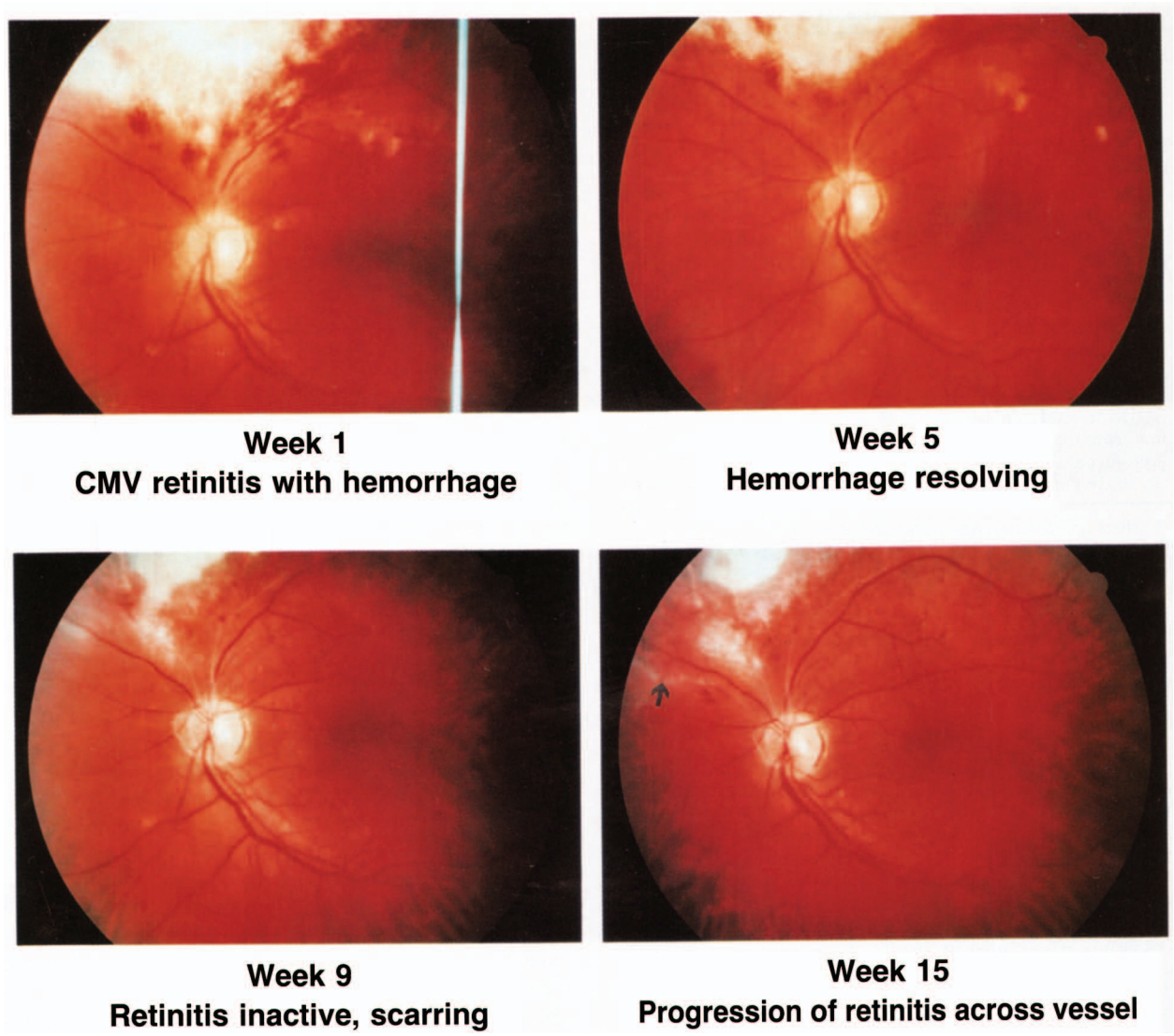

Figure 2. Representative example of retinal changes for a patient on immediate therapy. Retinal photographs at entry (*top left*), at 5 weeks (*top right*), at 9 weeks (*bottom left*), and at 15 weeks (*bottom right*), at which time progression (→) was noted.

In contrast, for patients randomized to immediate therapy, the mean time to end point was 13.3 weeks (range, 3 to more than 52 weeks, $P < 0.001$). When the study was terminated in July 1990, only one patient, a patient in the immediate treatment group, had not yet reached an end point. This patient had yet to show evidence of progression of retinitis at 52 weeks.

Representative examples of the types of retinal changes seen are shown in Figures 2 and 3. In all but one patient, the study end point was photographic documentation of progression of retinitis. In this patient, who was randomized to the immediate treatment group, supervening medical problems, predominantly due to systemic cryptococcosis, precluded him from returning to the NIH after 19 weeks of follow-up. At 19 weeks there was no evidence of progression of retinitis. For purposes of data analysis his data were included as a week-20 progression. Two patients (one from each group) were excluded from analysis. The first of these, randomized to the immediate treatment group, was lost to follow-up after 1 week because he developed cryptococcal meningitis. The second patient, randomized to the delayed therapy group, developed sight-threatening retinitis between study entry and week 1 and was placed on foscarnet therapy with subsequent arrest of the progression of his retinitis. Inclusion of both these patients in the data analysis would not have changed the statistical significance of these findings.

Minimal changes in visual acuity were noted during this trial. Data were evaluated independently for each eye (Table 3). The mean visual acuity in these patients at the start of study was 20/25. As expected, vision did not improve by more than one line in any patient in either group. The visual acuity of one eye of one patient in the immediate treatment group declined from 20/40 to less than 20/200. In addition, one patient in each group had one eye that lost one line of vision.

At the time of study entry, 15 of 24 patients had positive blood cultures for cytomegalovirus. Blood cultures were positive in 9 of 13 patients randomized to immediate therapy and in 6 of 11 patients randomized to delayed therapy. All nine patients with positive blood cultures for cytomegalovirus who were randomized to immediate therapy had negative cultures for cytomega-

lovirus by the end of induction ($P = 0.004$). None of the four patients with negative blood cultures who were randomized to immediate therapy became blood-culture positive. In contrast, only one of the six patients with a positive blood culture for cytomegalovirus who were randomized to delayed therapy showed clearing of their blood before the study end point, whereas one of the five patients with a negative blood culture who were randomized to delayed therapy became blood-culture positive.

All 24 patients had positive urine cultures for cytomegalovirus at the time of study entry. Six of the 13 patients randomized to immediate therapy showed clearing of their viruria whereas none of the 11 patients in the control group had a negative urine culture at the time of study end point ($P = 0.03$).

Treatment with foscarnet was associated with a decline in circulating levels of HIV-1 p24 antigen (Figure 4). All four patients randomized to immediate treatment who had detectable levels of p24 antigen before therapy and who had follow-up levels available had declines in p24 antigen levels from a mean of 407 pg/mL to 80 pg/mL at the end of induction therapy. These declines were generally transient, with levels increasing in three of the four patients in the first 3 months of maintenance therapy. In contrast, the five patients with detectable levels of p24 who were randomized to the delayed arm and who had sequential determinations of p24 antigen levels had no changes in p24 levels until a study end point had been reached and foscarnet therapy was initiated. At that time, similar to the findings for the patients randomized to immediate therapy, p24 antigen levels declined considerably from a mean of 164 pg/mL to a mean of 9 pg/mL.

In general, patients with cytomegalovirus retinitis have total CD4 counts of less than 0.100×10^9/L, and the patients in this study (Table 2), all had CD4 counts under 0.100×10^9/L at study entry. No substantive changes were seen in total CD4 counts or percent of

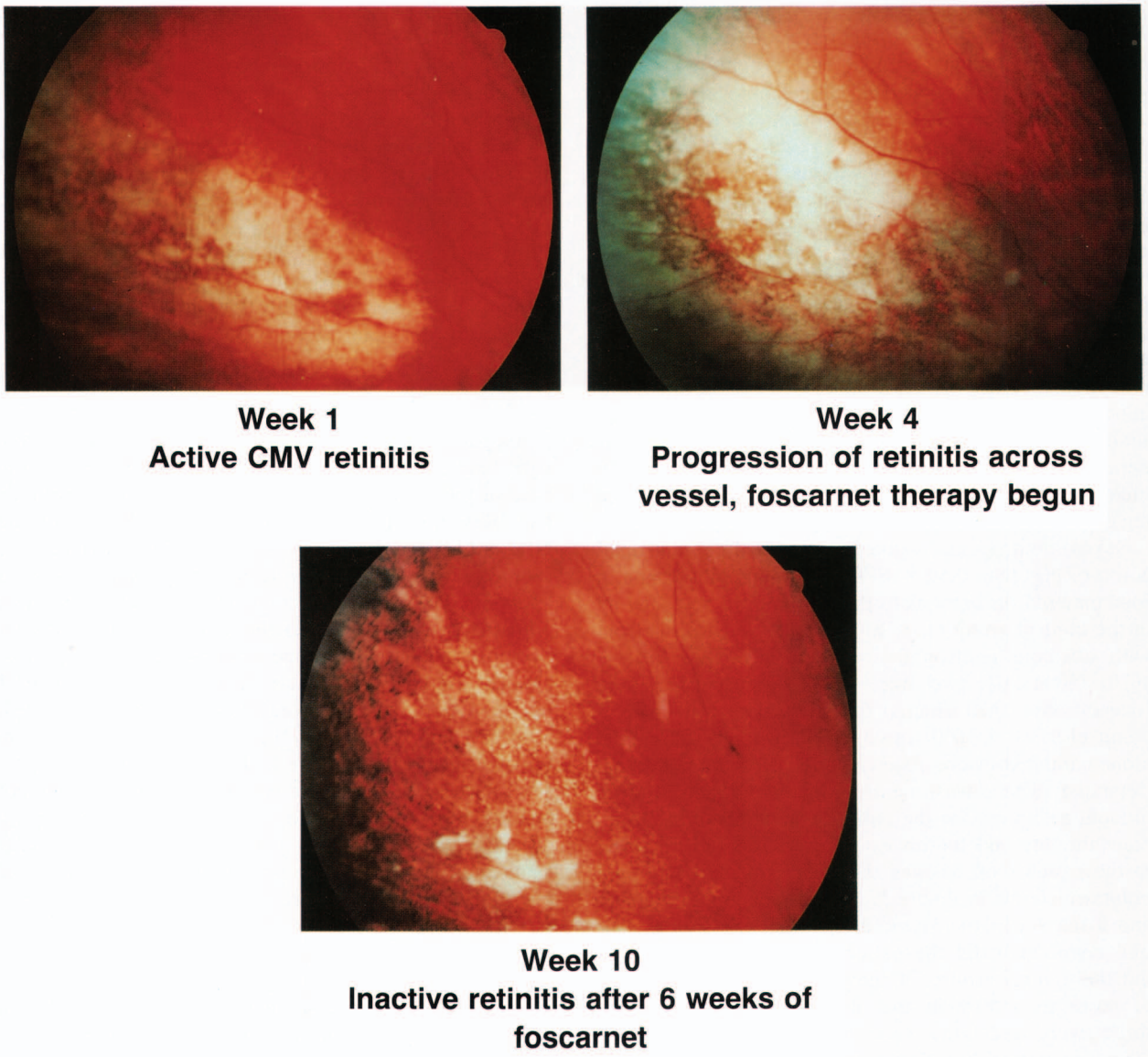

Figure 3. Representative example of retinal changes for a patient on delayed therapy. Retinal photographs at entry (*top left*), at 4 weeks (*top right*), at which time progression was noted and foscarnet therapy begun, and at 10 weeks (*bottom*), 6 weeks after foscarnet therapy was begun.

Table 3. Change in Vision from Study Entry until Study End Point

Acuity Range	Number of Eyes within Each Acuity Range			
	Immediate Treatment		Delayed Treatment	
	Before Study	At Study End Point	Before Study	At Study End Point
20/20 to 20/30, *n/n*	22/26	22/26	18/22	17/22
20/40 to 20/60, *n/n*	3/26	2/26	3/22	4/22
20/80 to 20/200, *n/n*	0/26	0/22	0/22	0/22
< 20/200, *n/n*	1/26	2/26	1/22	1/22

circulating T cells bearing the CD4 marker during therapy with foscarnet, although the mean CD4 count for the treatment group increased from $0.010 \pm 0.010 \times 10^9$/L to $0.035 \pm 0.060 \times 10^9$/L at study end point.

Toxicities

Serum electrolyte abnormalities, predominantly hypocalcemia, hypomagnesemia, and hypophosphatemia, were the most common side effects noted during foscarnet therapy (Table 4). Magnesium replacement that ranged from 2 to 24 mmol/d was required in 7 of the 13 patients induced at NIH. Elevations in serum creatinine occurred in three patients during induction, with the highest serum creatinine level being 459.7 μmol/L (5.2 mg/dL), which occurred in a patient who was also taking amphotericin B. After withdrawal of both drugs, the patient's serum creatinine level returned to normal. He was restarted on foscarnet, and his cryptococcal disease was treated with fluconazole without additional renal problems. In the other two patients, peak serum creatinine levels of 300.6 μmol/L (3.4 mg/dL) and 185.6 μmol/L (2.1 mg/dL) were recorded. Both of these patients were managed with dose reductions after which their creatinine levels decreased to 176.8 μmol/L (2.0 mg/dL) and 106.1 μmol/L (1.2 mg/dL), respectively.

Severe neutropenia, defined as an absolute neutrophil count of less than 0.50×10^9/L ($500/mm^3$), developed in four patients on immediate therapy and in two patients in the control group (*see* Table 4). Of these six patients with absolute neutrophil counts of less than 0.50×10^9/L ($500/mm^3$), two were receiving foscarnet alone (one of whom had entered the study with a neutrophil count of 0.360×10^9/L), two were receiving zidovudine alone, and two were receiving both foscarnet and zidovudine. The lowest neutrophil count (nadir) during induction therapy for the patients randomized to immediate therapy and the lowest neutrophil count recorded in the patients on delayed therapy before reaching end point are shown in Figure 5. The patients on zidovudine and foscarnet had substantially greater drops in neutrophil count than did the patients on foscarnet alone or did the control group. Of the four patients with a drop of more than 50% in the absolute neutrophil count, three were receiving concomitant zidovudine. Data from one patient are not included in Figure 5. He entered the study on granulocyte-macrophage colony-stimulating factor (GM-CSF) with an absolute neutrophil count of 2.328×10^9/L. When GM-CSF was withdrawn and foscarnet was begun, his neutrophil count declined to 0.480×10^9/L.

Six of the 12 patients randomized to immediate therapy were also receiving zidovudine at the time foscarnet was started, and one more patient was begun on zidovudine after foscarnet was started. As noted above, three of these patients had drops of more than 50% in neutrophil count during induction therapy with foscarnet (*see* Figure 5). One patient on both agents developed cholestatic jaundice that resolved after both drugs were withdrawn. Only one patient, on the delayed arm, was receiving dideoxyinosine. Fifty percent of the patients induced at the NIH had nausea. In two patients, both randomized to the delayed arm, it was necessary to discontinue foscarnet because of intractable nausea. Control patients required an average of 0.2 units of blood per week compared with an average of 0.6 units of blood per week for the patients on treatment. No additional toxicities were noted when these two drugs were administered concomitantly.

Two patients who were randomized to immediate therapy developed seizures during the study. One of these patients had central nervous system toxoplasmosis and the other, based on a positive serum cryptococcal antigen test and a history of cryptococcal meningitis, was receiving therapy for systemic cryptococcosis. Two patients in the delayed therapy group and one patient in the immediate group had idiopathic seizure disorders. None had a seizure during the time from study entry to study end point. One had a seizure after progression of retinitis and treatment with foscarnet. Serum Ca^{++} and Mg^{++} levels at the time of the seizures were not determined.

Long-term Follow-up

As part of this study, 24 patients received therapy with foscarnet either as immediate therapy or, in the case of the control group, when progression of retinitis had been documented. Patients were followed at the NIH until they reached a study end point, at which time care was resumed by the referring physicians. Frequent telephone contacts and consultations were continued with the patients and referring physicians until the patients died. The median time from diagnosis of cytomegalovirus retinitis until death has been longer than 12 months. At the time of study termination in July 1990, four patients (three from the control group, one from the treatment group) have had major reductions in vision, associated with a retinal detachment. One patient has lost visual acuity in one eye as a result of cytomegalovirus progression. No patients have had clinically significant visual loss because foscarnet failed to control the spread of active retinitis.

Discussion

Our study has clearly shown that foscarnet has a beneficial effect in the treatment of cytomegalovirus retinitis in a controlled trial of patients with HIV-1 infection. This benefit was seen as a delay in time to progression of retinitis, a decrease in cytomegalovirus shedding in blood and urine, declines in circulating lev-

els of p24 antigen, and modest increases in total CD4 T-lymphocyte counts. We believe that the strict primary end point for this study, photographic documentation of advancement of retinitis, is a good clinical surrogate for subsequent development of blindness. Although it has not been validated, it seems reasonable that any therapy shown capable of slowing progression of retinitis into a previously uninvolved area of the retina should also slow the progression of retinitis to the point of loss of significant vision or blindness. Because the photographs were read by a trained observer who was masked as to the treatment status of the patient, we believe that these data were assessed in an unbiased manner.

The differences in the mean times to progression of retinitis for the two groups, 3.2 weeks for the control group compared with 13.3 weeks for the treatment group, is the minimal benefit one can expect to see from therapy with foscarnet. Although retinitis progressed despite foscarnet therapy and significant relapses did occur on the maintenance regimen chosen, patients were successfully re-induced with a second course of induction therapy or by an increase in the maintenance dose. This high success rate may be due in part to the fact that the most patients enrolled in this trial had minimal, peripheral-lesion retinitis coupled with the fact that we used a somewhat higher maintenance dose (90 mg/kg per day) than had been used in most previous studies (17-20).

Given the small size of this trial, baseline differences between the two treatment groups were not surprising. The patients randomized to immediate treatment might be expected, by several variables, to have a poorer overall prognosis. Their mean CD4 count was lower, they had had more previous opportunistic infections and, on average, had been diagnosed with AIDS 6 months earlier than had the patients in the control group. The variables that favored the immediate treatment group were the greater number of patients who were p24 antigen positive and a slightly higher mean neutrophil count. In the treatment group, only 5 of 13 patients were p24 antigen positive compared with 9 of 11 patients in the control group.

The most direct and efficient way to determine the potential efficacy of an experimental treatment is through the use of a controlled clinical trial, using the best known treatment for the condition as a control or, when no such treatment exists, a placebo control. In designing this trial, we faced several obstacles. At the time this trial was initiated there was no licensed treatment for cytomegalovirus retinitis; however, there was a considerable amount of data from several well done, uncontrolled trials that strongly suggested that ganciclovir was an effective agent (3, 7-11). The idea for a delayed-therapy controlled trial, using patients with non-sight-threatening retinitis, came from our desire to demonstrate efficacy in as rigorous a fashion as possible. We hoped this would hasten the licensure of the agent, while at the same time allowing us to conduct our research without compromising patient care and safety.

It is virtually impossible to make accurate comparisons of these data to the historical data on patients with untreated cytomegalovirus retinitis or even to patients with cytomegalovirus retinitis treated with ganciclovir. Since the time of the earliest ganciclovir studies, much has changed in the management of patients with HIV infection, including the use of specific antiretroviral therapy and the incorporation of prophylactic regimens to protect patients from *Pneumocystis carinii* pneumonia. The limited long-term follow-up data generated by this study suggest that, as an anticytomegalovirus agent, foscarnet is comparable to ganciclovir. When coupled with the fact that foscarnet itself has direct antiretroviral activity and can usually be given concomitantly with zidovudine, it can be argued that it may be an important alternative to ganciclovir for the treatment of patients with AIDS-related cytomegalovirus retinitis. Controlled trials are currently underway to address this question directly. At present, both foscarnet and ganciclovir must be given as daily intravenous infusions, generally through central catheters, which increases the inconvenience to the patient as well as the morbidity of treatment. In addition, both therapies are associated with considerable toxicity: profound neutropenia in the case of ganciclovir; and nephrotoxicity, electrolyte abnormalities, nausea, and possible lowering of the seizure threshold in the case of foscarnet. Thus, there is a pressing need to develop better regimens for the treat-

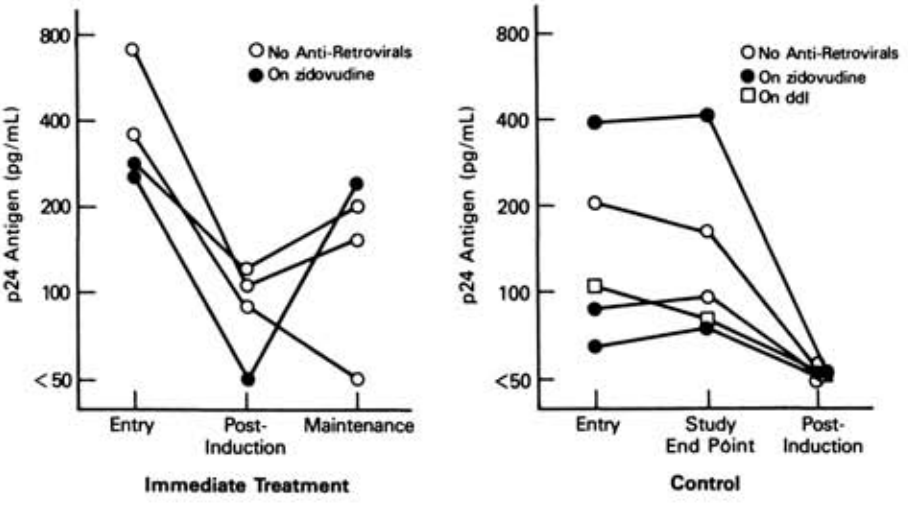

Figure 4. Changes in serum p24 antigen levels as a function of foscarnet therapy. The mean interval between entry and post-induction for the patients on immediate treatment (*left*) was 3 weeks (range, 3 to 5 weeks). Maintenance values were measured approximately 3 months after induction. The mean interval between entry and study end point for patients in the delayed treatment group (*right*) was 3 weeks (range, 2 to 8 weeks). Post-induction values were measured 3 weeks after the study end point for all patients. ddI = dideoxyinosine.

Table 4. Adverse Effects of Foscarnet Therapy

Adverse Effect	Immediate Therapy	Delayed Therapy
Creatinine > 176.8 μmol/L (2.0 mg/dL), *n/n*	3/13	0/11
Magnesium < 0.494 mmol/L (1.2 mg/dL), *n/n*	9/13	1/11
Calcium < 0.75 mmol/L (3.0 mg/dL), *n/n*	11/13	3/11
Phosphate < 0.71 mmol/L (2.2 mg/dL), *n/n*	8/13	3/11
Absolute neutrophil count, *n/n*		
< 1.0×10^9/L ($1000/mm^3$)	7/13	7/11
< 0.50×10^9/L ($500/mm^3$)*	4/13	2/11
Seizure, *n/n*	2/13	0/11
Transfusion requirement, *units*		
Total	86	6
Units/patient · wk	0.6	0.2

* Includes one patient with an absolute neutrophil count of less than 0.50×10^9/L before entry.

ment of this common life-threatening complication of AIDS. Given the synergistic effect of these two agents on cytomegalovirus replication in vitro, one possible strategy is to explore combination therapy of these two drugs at reduced dose levels (28, 29).

A unique feature of treating AIDS-associated cytomegalovirus retinitis with foscarnet is that the agent has demonstrated activity in vitro against HIV-1, both alone and in synergistic combination with zidovudine (14, 15, 30). In this trial, every patient with a positive HIV-1 p24 antigen level before foscarnet therapy, including those patients receiving zidovudine or dideoxyinosine, had a substantial reduction in p24 antigen level after foscarnet therapy was begun. In some cases, these reductions persisted; in others, they were transient. In this regard, these in-vitro data are comparable to those generated by other studies (22-24). Although the clinical significance of this laboratory surrogate has yet to be validated, when coupled with the observation that these declines in p24 antigen level were associated with modest increases in total CD4 T-lymphocyte counts, these data support the notion that treatment with foscarnet may provide significant antiretroviral effect as well as a delay in the progression of cytomegalovirus retinitis.

The toxicities of foscarnet noted in this study were similar to those reported by others (17-20). The most serious toxicities we noted were nephrotoxicity, manifested by elevations in serum creatinine and renal wasting of magnesium and calcium; mild bone marrow suppression; and lowering of the seizure threshold. Administration of foscarnet is known to be associated with a reversible nephropathy manifested by tubular necrosis and associated with electrolyte abnormalities. We attempted to decrease the incidence of renal disease, reported to be as high as 66% in some series, by vigorous hydration with saline before infusion of the drug (25). Despite this, we still had a 23% incidence of creatinine elevations above 176.8 μmol/L (2.0 mg/dL) and significant hypomagnesemia in 9 of 13 patients in the treatment group. The most serious renal toxicity was seen in a patient receiving concomitant amphotericin B for a history of cryptococcosis. Thus, this combination should be used with caution and with careful attention to changes in renal function. Foscarnet alone had a minimal effect on the absolute neutrophil count. However, for the six patients who were receiving zidovudine when foscarnet therapy was initiated, three had a decline of more than 50% in the neutrophil count, one of whom had a neutrophil count of less than 0.500×10^9/L. Thus, although the combination of foscarnet and zidovudine seems to be better tolerated than the combination of ganciclovir and zidovudine (12), patients on this combination require careful hematologic monitoring. It remains to be seen whether or not this foscarnet/zidovudine-induced neutropenia can be reversed by GM-CSF, as has been the case with ganciclovir-induced neutropenia (31). In addition to causing a mild neutropenia when given with zidovudine, patients receiving foscarnet also had a higher transfusion requirement (0.6 units/patient per week) than the patients in the control group (0.2 units/patient per week), but some of the transfusion requirements may have been due to the need for increased safety and pharmacokinetic monitoring during treatment. The propensity for the development of anemia in patients receiving foscarnet is well known (19) and is another possible complication of therapy with this agent. Perhaps the most disconcerting problem noted during this trial was the development of seizures in three patients receiving foscarnet; two on the immediate-therapy arm and one on the delayed-therapy arm after the initiation of open treatment. Although patients with HIV infection have various central nervous system problems that may predispose them to seizures, the potential propensity for foscarnet to lower the seizure threshold, through mechanisms not yet understood, indicate that it should be used cautiously in patients with a history of a seizure disorder.

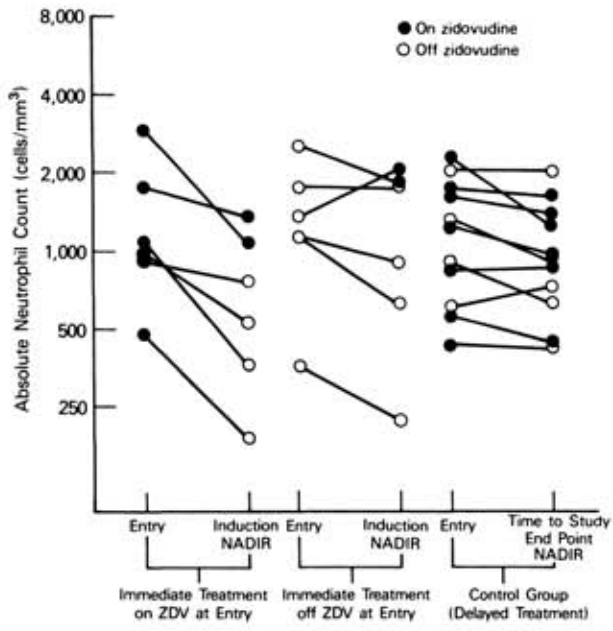

Figure 5. Changes in absolute neutrophil counts for patients on foscarnet and for control patients. Patients are split into three groups: those who were randomized to immediate therapy and were on zidovudine (*ZDV*), those who were randomized to immediate therapy and who were not on zidovudine, and those who were randomized to delayed therapy. For the last group, all data points represent times during which patients were not receiving foscarnet; the mean interval between entry and study end point was 3 weeks (range, 2 to 8 weeks).

As the magnitude of the AIDS problem increases, more patients will need therapies to treat the complications of long-standing immunosuppression. A concerted effort is needed to develop better treatments for the opportunistic infections and neoplasms that occur in these patients. Syndromes due to reactivation of cytomegalovirus will almost certainly continue to be a prominent problem. Foscarnet has a potential role in preventing the progression of cytomegalovirus retinitis and therefore in improving the quality of life for patients with AIDS.

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