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# Foscarnet Treatment of Cytomegalovirus Retinitis in Patients with the Acquired Immunodeficiency Syndrome

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**Ten patients with acquired immunodeficiency syndrome with newly diagnosed cytomegalovirus (CMV) retinitis were treated with an induction regimen of intravenous foscarnet, 60 mg/kg of body weight, administered as a 2-h infusion and repeated every 8 h for 14 days. At the end of induction, 9 of 10 patients had stabilized (no new retinal lesions and stable old lesions [7 patients]) or improved (decreased retinal opacification [2 patients]). All eight patients with CMV in urine or blood upon entry into the study had negative urine and blood cultures at the end of induction. After induction therapy, seven patients continued maintenance foscarnet therapy, 60 mg/kg as a single daily infusion, 5 days/week. In six patients, retinal lesions increased in size after 2 to 32 weeks of maintenance therapy. One was inevaluable because a retinal detachment developed. Only 9 of 42 blood and urine cultures obtained during maintenance foscarnet therapy yielded CMV, compared with 7 of 14 obtained prior to the initiation of foscarnet induction therapy ($P = 0.04$). Foscarnet toxicity was mild and infrequent: elevation in serum creatinine by 0.5 to 1.3 mg/dl over the base line (two patients), muscle twitching (three patients), hemoglobin decrease by 1 mg/dl (two patients), nausea (two patients), absolute neutrophil count decrease by 50% (one patient), rise in serum phosphorus to >5.5 mg/dl (four patients), and proteinuria (two patients). Intermittently administered intravenous foscarnet appears to be an effective, relatively nontoxic therapy for CMV retinitis. Additional studies to determine the optimal dosage for maintenance therapy are needed, as are comparative trials with ganciclovir.**

Cytomegalovirus (CMV) retinitis is a sight-threatening opportunistic viral infection that occurs in about 5% of patients with the acquired immunodeficiency syndrome (AIDS) (6a). Investigations with intravenous ganciclovir, a nucleoside analog with in vitro activity toward CMV (9, 13), have suggested that treatment with this drug halts progression of CMV retinitis (5, 6a, 8). However, myelosuppression is a frequent adverse effect of ganciclovir therapy, and dose-limiting neutropenia occurs in approximately one-third of patients treated chronically with this drug (4, 5, 6a, 8).

Foscarnet (trisodium phosphonoformate) is a pyrophosphate analog that also has in vitro activity toward CMV and the human immunodeficiency virus (1, 12). In published reports of its use for serious CMV disease, foscarnet therapy has been administered only by continuous intravenous infusion over periods of 2 to 3 weeks or longer (7, 10, 11, 14). Such regimens appear to be effective for CMV disease but have resulted in azotemia in 29 to 50% of patients treated (7, 10, 14).

On the basis of pharmacokinetic modeling, it was predicted that intravenous foscarnet therapy administered by intermittent infusion would have similar efficacy and possibly less nephrotoxicity than continuous intravenous foscarnet therapy. We now report data from 10 patients treated with intermittently administered intravenous foscarnet for AIDS-associated CMV retinitis.

## MATERIALS AND METHODS

**Patients.** Patients were enrolled in this study if they met the criteria of the Centers for Disease Control, Atlanta, Ga., for AIDS (3) and had CMV retinitis identified by its characteristic ophthalmoscopic appearance and verified by fundus photography. CMV retinitis was diagnosed if there were characteristic retinal opacities (often in a perivascular distribution and often with associated hemorrhage) with no other likely explanation for the retinal findings (i.e., laboratory, clinical, or retinal findings suggestive of central nervous toxoplasmosis or panophthalmitis caused by herpes simplex virus or varicella-zoster virus). Patients were excluded if their Karnofsky performance score was <60, their serum creatinine was >2.0 mg/dl, or their total neutrophil count was <500 cells per μl, or if they had previously been treated with ganciclovir or foscarnet or required concurrent therapy with nephrotoxic medication. Concurrent treatment with acyclovir or zidovudine was not permitted during the initial 14 days of foscarnet therapy (induction).

**Foscarnet therapy.** Foscarnet was provided by Astra Clinical Research Associates, Hopkinton, Mass., in glass bottles containing 500 ml of foscarnet solution (24 mg/ml, pH 7.4). At this concentration, the drug was administered only via a central venous catheter. For administration via a peripheral vein, foscarnet was diluted, in glass only, to 12 mg/ml with 5% glucose solution. Patients were initially hospitalized for induction therapy with 60 mg of foscarnet per kg of body weight, administered by infusion pump over a 2-h period and repeated every 8 h for 14 days. Since foscarnet is eliminated solely by renal excretion, serum creatinine was measured daily during induction, and the dosage was adjusted daily for patients with an estimated creatinine clearance of <1.6 mg/ml per kg (Table 1). Patients who tolerated the induction regimen with stabilization or improvement of retinitis continued to receive foscarnet in an outpatient maintenance regimen of 60 mg/kg administered over a 2-h period and repeated daily, 5 days/week. During maintenance therapy, serum creatinine was measured weekly, and the foscarnet dosage was adjusted weekly for patients with an estimated creatinine clearance of <1.4 mg/ml per kg (Table 1).

**Response to therapy.** The extent of retinitis was assessed

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TABLE 1. Foscarnet dosing algorithm

| Therapy | Creatinine clearance (ml/min per kg) | Foscarnet dose (mg/kg)[a] |
|---|---|---|
| Induction | ≥1.60 | 60 |
| | 1.50–1.59 | 56.5 |
| | 1.40–1.49 | 53 |
| | 1.30–1.39 | 49.4 |
| | 1.20–1.29 | 45.9 |
| | 1.10–1.19 | 42.4 |
| | 1.00–1.09 | 38.9 |
| | 0.90–0.99 | 35.5 |
| | 0.80–0.89 | 31.8 |
| | 0.70–0.79 | 28.3 |
| | 0.60–0.69 | 24.8 |
| | <0.60 | NG |
| Maintenance | ≥1.40 | 60 |
| | 1.20–1.39 | 52 |
| | 1.00–1.99 | 50 |
| | 0.80–0.99 | 47 |
| | 0.60–0.79 | 42 |
| | <0.60 | NG |

[a] Administered every 8 h for induction therapy and every 24 h for maintenance therapy. NG, Not given.

by serial indirect ophthalmologic exams, retinal photographs, and best-corrected visual acuity measurements. At each visit, retinal lesions were drawn on standard retinal maps with the sectors formed by the intersection of clock hours with the ora serrata, the equator, and the posterior vascular arcade. Progression of retinitis was deemed to have occurred when a lesion entered a new sector or crossed a major vessel, a lesion increased by a disk diameter or more in size, or a new lesion greater than one disk diameter in size appeared. Retinitis stabilization was defined as a lack of progression, and improvement was defined as the decreased opacification of retinal exudates.

**Viral culture technique.** Virologic response to therapy was assessed by serial cultures of urine and washed buffy coat specimens inoculated into human foreskin fibroblast and human embryonic lung cell lines. After adsorption for 1.5 h, the specimen was decanted and fresh medium (Eagle minimal essential medium with 2% fetal calf serum) was added. The presence of CMV was detected by typical cytopathic effects and was confirmed by reaction with fluorescein-conjugated CMV-specific monoclonal antibodies (Syva Corp., Bethesda, Md.) and by lack of reaction with fluorescein-conjugated polyclonal adenovirus antisera (MA Bioproducts). All cultures were observed for at least 30 days before being discarded as negative.

Add-back experiments showed that residual foscarnet in urine or blood did not inhibit the detection of CMV. Fibroblast cultures were inoculated with urine samples containing 3 or 20 PFU of CMV, with or without foscarnet (5,000 μg/ml, the highest concentration observed in urine in our pharmacokinetic studies). Cytopathology was observed in the cultures inoculated with drug-free urine at 8 to 10 days (3 PFU) and 6 to 7 days (20 PFU), versus 17 to 20 days (3 PFU) and 13 to 21 days (20 PFU) in the cultures inoculated with urine containing foscarnet.

**Toxicity evaluation.** Drug safety was evaluated by daily clinical assessments and blood chemistry tests, twice-weekly complete blood counts and urinalyses, and weekly electrocardiograms during induction and by weekly clinical assessments, blood chemistry tests, complete blood counts, and urinalyses during maintenance therapy.

TABLE 2. Characteristics of 10 CMV retinitis patients prior to foscarnet therapy

| Characteristic[a] | No. or median | Range |
|---|---|---|
| Age (yr) | 36 | 25–43 |
| Karnofsky performance score | 70 | 60–90 |
| Prior AIDS diagnosis (no. of patients) | 9 | |
| AIDS-CMV retinitis interval (mo)[b] | 11 | 1–19 |
| Prior PCP diagnosis (no. of patients) | 7 | |
| PCP-CMV interval (mo)[b] | 12 | 4–19 |
| Hemoglobin (g/dl) | 11.2 | 6.7–12.2 |
| Absolute neutrophil count (cells/μl) | 2,070 | 670–4,190 |
| $CD4^+$ lymphocyte count (cells/μl) | 19 | 1–48 |

[a] Abbreviation: PCP, *Pneumocystis carinii* pneumonia.
[b] Interval between index diagnosis of AIDS or PCP and development of CMV retinitis.

## RESULTS

Ten patients received induction foscarnet therapy (nine patients received the full 14-day induction course, and one received only 10 days of induction therapy). The median and range of values for important base-line patient characteristics are summarized in Table 2. Five of the ten patients (patients 2, 3, 8, 9, and 10) were receiving zidovudine at a reduced dose (300 to 600 mg/day) when CMV retinitis was diagnosed. Three patients (patients 1, 5, and 6) had never received zidovudine, and two patients (patients 4 and 7) had received this drug but it was discontinued 3 to 4 weeks prior to diagnosis of retinitis. Four patients (patients 1, 4, 6, and 10) were receiving acyclovir (400 to 1,000 mg/day) for therapy or chemosuppression of mucocutaneous herpes simplex virus infection when CMV retinitis was diagnosed.

**Foscarnet efficacy.** At the end of induction foscarnet therapy, 9 of the 10 patients had stable (7 patients) or improved (2 patients) retinitis and 1 had progression of retinitis (increase in size of the initial retinal lesion) (Fig. 1). After completing induction, seven patients continued to receive the maintenance foscarnet regimen for a median 6 weeks (range, 3 to 37 weeks) (Fig. 1). One of these patients (patient 3) was inevaluable because retinal detachment occurred after the first week of maintenance therapy. In the remaining six patients, retinitis progressed after 2 to 32 weeks of maintenance therapy, with a median time to retinitis progression of 24.5 days after the initiation of maintenance foscarnet therapy. Nine of the ten patients had a corrected visual acuity of 20/30 or better in one eye at the time they last received foscarnet. We observed no correlation between either prior zidovudine or acyclovir therapy, base-line indicators of immune status, or human immunodeficiency virus disease stage and time to retinitis progression during foscarnet therapy.

Eight of the ten patients had CMV isolated from urine alone (seven patients) or urine and blood (one patient) prior to foscarnet therapy. Seven of these eight patients completed a 14-day course of induction foscarnet therapy, and all seven had negative urine and blood viral cultures at the end of induction. For the seven patients who continued maintenance foscarnet therapy, only 9 (21%) of 42 blood and urine cultures obtained during maintenance therapy yielded CMV, compared with 7 (50%) of 14 cultures obtained prior to initiating foscarnet induction ($P = 0.04$, Fisher exact test).

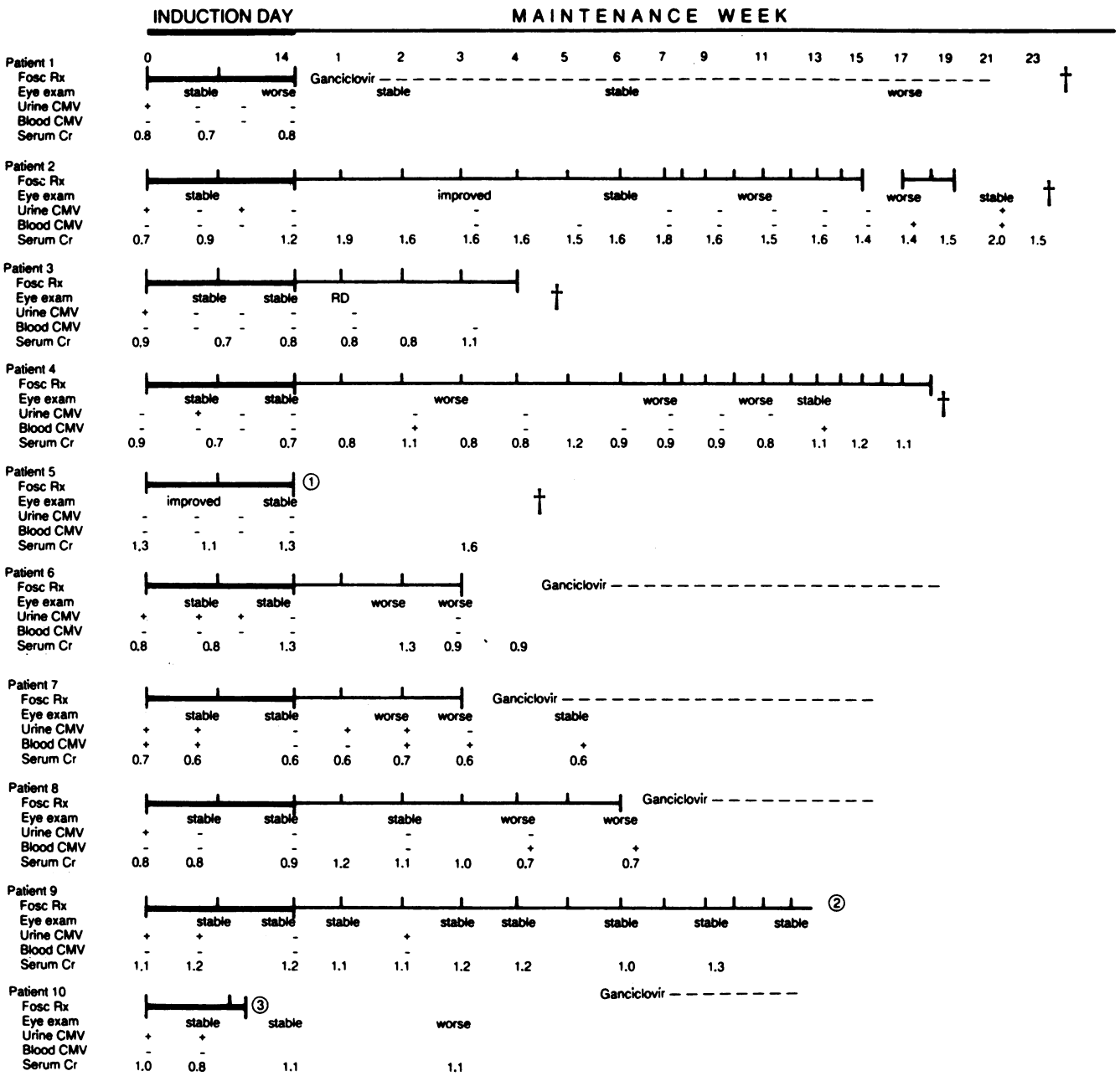


FIG. 1. Results of foscarnet therapy for CMV retinitis. Abbreviations: RD, retinal detachment; Cr, serum creatinine (in milligrams per deciliter); urine CMV, urine CMV culture; blood CMV, blood CMV culture; Rx, therapy. Symbols: +, positive culture for CMV; −, negative culture for CMV; †, patient died. ①, Patient refused further therapy. ②, Patient continues to receive maintenance foscarnet therapy. Retinitis progression first occurred during week 32 of maintenance therapy. Monthly urine and blood CMV cultures were negative from weeks 8 through 26. However, CMV was isolated from both urine and blood on week 30, 2 weeks before retinitis progression was observed. ③, Patient was withdrawn from study because of frequent premature ventricular contractions (see Results).

For the entire group of patients, 9 (45%) of 20 cultures obtained prior to initiating foscarnet therapy yielded CMV, compared with 0 of 18 cultures obtained at the end of induction therapy ($P = 0.001$) and 9 (21%) of 42 cultures obtained during maintenance foscarnet therapy ($P = 0.03$) (Fig. 1). Of note, for four patients progression of retinitis was contemporaneous with reisolation of CMV from blood (patients 4, 7, 8, and 9; Fig. 1).

**Foscarnet toxicity.** During induction foscarnet therapy, 2 of the 10 patients (patients 2 and 6) had increases of 0.5 mg/dl in serum creatinine from the base-line value (Fig. 1). Following induction therapy, the serum creatinine normalized to the base-line value in all patients except for one (patient 2; Fig. 1), whose creatinine remained elevated by 0.8 to 0.9 mg/dl over the base-line value during 19 weeks of maintenance therapy and at 4 weeks after discontinuing foscarnet therapy. Also, 2 of the 10 patients (patients 5 and 9) developed proteinuria by urine dipstick during foscarnet therapy. Patient 5 developed 3+ proteinuria (approximately 500 mg/dl) at the end of foscarnet induction. This patient had just completed a 1.5-g course of amphotericin B for cryptococcal meningitis 1 week prior to initiating foscarnet ther-

apy. He refused further treatment or evaluation and died 1 month later. Patient 9 developed stable 1+ proteinuria (approximately 30 mg/dl) during maintenance foscarnet therapy.

One patient (patient 10; Fig. 1) had foscarnet therapy discontinued on day 10 of induction therapy because of frequent, asymptomatic, premature ventricular contractions. The patient also was receiving albuterol and ciprofloxacin for *Pseudomonas aeruginosa* bronchitis. All three drugs were discontinued, and the premature ventricular contractions resolved.

The absolute neutrophil count increased by 20 to 300% during foscarnet therapy in the five patients who had discontinued zidovudine therapy during the 7 days before beginning foscarnet. Among the five patients who had never received zidovudine or who had discontinued the drug at least 3 weeks before initiating foscarnet, three had small changes (<20%) in absolute neutrophil count during foscarnet therapy, and for two the absolute neutrophil count decreased to 75% (patient 6) and 50% (patient 7) of the pre-foscarnet value. All patients maintained an absolute neutrophil count of above 800 cells per μl during foscarnet therapy.

Intermittent subjective muscle twitching without objective myoclonus occurred in three patients (patients 2, 3, and 8). Hemoglobin decreased by 1 g/dl from the base line in two patients (patients 4 and 6). Nausea with occasional vomiting was associated with maintenance foscarnet therapy in two patients. However, both these patients had similar symptoms prior to initiating foscarnet induction therapy and had resolution of nausea during foscarnet induction therapy.

Abnormalities of phosphorus and calcium concentrations in serum not accompanied by symptoms occurred during induction foscarnet therapy in 9 of 10 patients (Fig. 2). All changes in serum calcium and phosphorus values normalized after foscarnet induction was completed, even among patients who continued to receive a maintenance foscarnet regimen. The most frequent abnormality was hyperphosphatemia, which occurred at some point during induction in 9 of the 10 patients. During week 2 of foscarnet induction therapy, the mean serum phosphorus concentration was 4.4 mg/dl, compared with 3.6 mg/dl before therapy was initiated ($P = 0.066$, two-sample $t$ test). Four of the patients had marked hyperphosphatemia (serum phosphorus, >5.5 mg/dl) during week 2 of foscarnet induction therapy. Serum parathyroid hormone levels were measured in the first six patients before, during, and after foscarnet induction. The concentration of parathyroid hormone in serum increased during foscarnet therapy in all six patients from a mean 29.2 pg eq/ml (picogram equivalents, referring to a synthetic peptide standard) before therapy to 38.8 pg eq/ml after 2 to 3 weeks of foscarnet therapy ($P = 0.03$, one-sample $t$ test) (Fig. 2). Among three patients with marked foscarnet-associated hyperphosphatemia, the parathyroid concentration in serum increased by 7 to 21 pg eq/ml during therapy, and serum phosphorus values later normalized without phosphate-binding antacid therapy (data not shown). Among three patients with minor or no changes in serum phosphorus during therapy, the parathyroid concentration in serum increased by only 3 to 5 pg eq/ml.

We observed no correlation between either prior zidovudine or acyclovir therapy, base-line indicators of immune status, or human immunodeficiency virus disease stage and subsequent toxicity associated with foscarnet therapy.

Of note, one patient (patient 9) has received concurrent zidovudine (300 to 600 mg/day) and maintenance foscarnet (60 mg/kg, 5 days/week) for 34 weeks without hematologic toxicity.

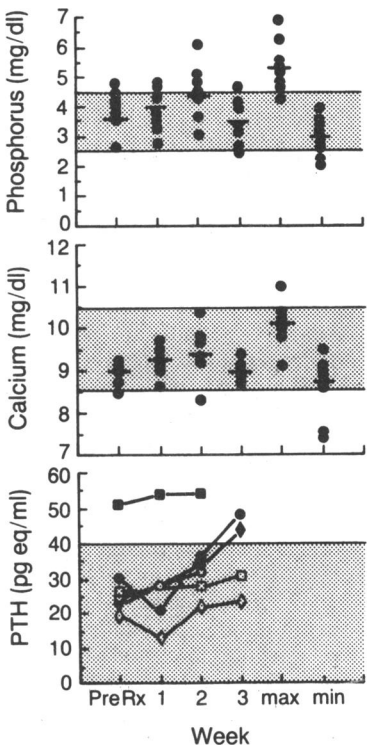


FIG. 2. Results of phosphorus, calcium, and parathyroid hormone (PTH) concentrations in sera of patients treated with intermittently administered intravenous foscarnet. Phosphorus and calcium levels in serum are shown for all 10 patients before initiating foscarnet therapy (Pre Rx), during weeks 1 and 2 of induction foscarnet therapy (median value for each patient is displayed), and 1 week after completing foscarnet induction (week 3). The maximum (max) and minimum (min) values recorded during foscarnet induction therapy are also shown. The mean values for the group are indicated by the bars. Normal values are indicated by the shaded areas. Concentrations of parathyroid hormone in serum are shown for patients 1 to 6 before initiation foscarnet therapy (Pre Rx), at the end of weeks 1 and 2 of foscarnet induction therapy (weeks 1 and 2), and 1 week after completing foscarnet induction (week 3).

## DISCUSSION

Induction foscarnet therapy administered by intermittent intravenous infusion stabilized or improved CMV retinitis in 9 of 10 patients with AIDS. The efficacy of foscarnet seen in this study, as well as in one Phase 1 study of foscarnet administered by continuous intravenous infusion (14), was equivalent to that reported with 2-week intermittent intravenous ganciclovir regimens (5, 6a, 8). The intermittent infusion regimen could be self-administered at home, and unlike ganciclovir, foscarnet had no myelosuppressive toxicity.

As with ganciclovir (4, 6a, 8), the clinical efficacy of foscarnet therapy was associated with a definite antiviral effect. Nearly all patients stopped shedding virus during induction therapy, and the proportion of cultures yielding CMV during maintenance foscarnet therapy was significantly lower than in cultures obtained before induction therapy began. These results are comparable to our recent experience with ganciclovir therapy (6a). Among 27 patients with CMV retinitis treated with ganciclovir at San Francisco General Hospital, 70% of blood or urine cultures obtained

prior to induction yielded CMV, compared with 19% of cultures obtained at the end of ganciclovir induction ($P < 0.001$) and 9% of cultures obtained during maintenance ganciclovir therapy ($P < 0.001$) (6a). Among the 10 patients treated with foscarnet, 45% of all cultures obtained prior to induction yielded CMV (Fig. 1), compared with none of those obtained at the end of foscarnet induction ($P = 0.001$) and 21% obtained during maintenance foscarnet therapy ($P = 0.03$). Of note, during maintenance therapy, three patients had funduscopically documented progression of retinitis concurrent with reisolation of CMV from blood cultures that previously had been negative. This close temporal association between control of retinitis and antiviral effect suggests that foscarnet halts retinal damage by inhibiting CMV replication. This association has not been noted with ganciclovir (6a).

In previous studies of continuously infused foscarnet, nephrotoxicity has been the most frequent dose-limiting adverse effect. Walmsley et al. reported that of 13 AIDS patients with CMV retinitis given continuous intravenous foscarnet (230 mg/kg per day [a larger dose than used in the present study] for 14 days), in 6 (46%) serum creatinine increased to 2 to 3.5 times the base-line value (14). Nephrotoxicity was severe enough to require drug discontinuation in three patients. Klintmalm et al. noted a rise in serum creatinine to 1.5 times the base line in three (50%) of six renal and bone marrow transplant patients given continuous intravenous foscarnet, 78 to 171 mg/kg per day for 4 to 21 days (7), and Ringden et al. reported increased serum creatinine (not quantified) in 10 (29%) of 34 renal and bone marrow transplant patients given foscarnet (115 mg/kg per day) for a median 14 to 16 days (10). With an intermittent intravenous regimen of 180 mg/kg per day for 14 days, we observed minimal increases in serum creatinine in only 2 (20%) of 10 patients treated. Hence, nephrotoxic reactions associated with our intermittent intravenous regimen appeared to be less frequent and less severe than reported with continuous-infusion regimens. This difference in toxicity may have been due to the difference in pharmacokinetics between intermittent and continuous intravenous drug administration (e.g., lower trough levels with intermittent administration) or to the frequent and precise monitoring of renal function and dosage adjustment employed in our study.

Other adverse effects attributed to foscarnet were neither frequent nor severe in this study. Although hyperphosphatemia occurred at some point during induction therapy in 90% of the patients we treated, it was not associated with morbidity. Abnormalities in calcium and phosphorus concentrations in serum have been observed previously in some individual patients given foscarnet (A. Larsson, Astra Lakemedal, unpublished data), but a consistent trend toward hyperphosphatemia has not been reported. Hyperphosphatemia could be caused by foscarnet deposition in bone (A. Larsson, unpublished data), resulting in the release of bone phosphorus stores, or by foscarnet inhibiting sodium and phosphate cotransport by renal epithelium (15). In our study, hyperphosphatemia was always followed by a rise in parathyroid hormone, ultimately resulting in normalization of both calcium and phosphorus levels in serum, even when foscarnet maintenance therapy was continued for up to 19 weeks. Since the median survival of AIDS patients with CMV retinitis is about 6 months (6a), long-term toxicity caused by secondary hyperparathyroidism or foscarnet bone deposition would be detected rarely in this patient population.

AIDS patients with CMV retinitis require long-term, if not lifetime, antiviral therapy to prevent progression of CMV retinitis, because these drugs do not eliminate latent CMV infection, and the defect in cell-mediated immunity that permits the reactivation of latent CMV infection is progressive rather than reversible. In noncomparative studies of ganciclovir therapy, relapse or progression of CMV retinitis has invariably followed discontinuation of antiviral therapy (4, 5, 8). The most objective criterion for judging the efficacy of an antiviral maintenance regimen in AIDS-associated CMV retinitis may be the length of time to the first funduscopic evidence of retinitis progression. We have reported the results of a prospective study in which AIDS patients with peripheral CMV retinitis received a standard ganciclovir induction regimen followed by randomization to receive either immediate ganciclovir maintenance therapy or to have further ganciclovir therapy deferred until funduscopic evidence of progression of retinitis occurred (6). With biweekly ophthalmologic monitoring, the median time to progression of retinitis was 42 days for patients receiving immediate ganciclovir maintenance versus 16 days for patients who had maintenance therapy deferred (6). In an uncontrolled trial, the median time to progression of retinitis was 105 days for 32 AIDS patients who received 25 to 35 mg/kg per week versus 47 days for 20 AIDS patients given no ganciclovir maintenance therapy (2).

After foscarnet induction therapy, most of our patients continued to receive maintenance foscarnet, 60 mg/kg, 5 days/week. Six patients were evaluable for the time to retinitis progression on maintenance foscarnet therapy. The median time to progression in the six patients treated with foscarnet was 24.5 days, compared with 42 days for historical controls treated with ganciclovir at our institution (6a). Four patients had progression of retinitis documented within 2 to 4 weeks after initiating the foscarnet maintenance regimen (a result similar to that seen in untreated patients), while two patients went 11 or more weeks on maintenance foscarnet therapy without progression (a better result than the average reported with ganciclovir maintenance therapy). Since minimal drug toxicity was observed with the 5-day/week maintenance foscarnet regimen, either a 7-day/week maintenance regimen or an increase in the total weekly maintenance dose or both might improve the efficacy of maintenance foscarnet therapy without serious toxicity.

Foscarnet therapy suppresses replication of CMV and controls CMV retinitis with minimal toxicity when given via intermittent intravenous infusions. Dose-limiting myelosuppression specifically was not observed. This drug also has an antiretroviral effect (12). Continued study of foscarnet therapy for CMV retinitis with higher maintenance dosing regimens is warranted, and comparative trials with ganciclovir should be planned.

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