

## CONCISE COMMUNICATIONS

## Randomized Phase I Trial of Two Different Combination Foscarnet and Ganciclovir Chronic Maintenance Therapy Regimens for AIDS Patients with Cytomegalovirus Retinitis: AIDS Clinical Trials Group Protocol 151

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AIDS patients with newly diagnosed cytomegalovirus (CMV) retinitis who had just completed a 14-day course of ganciclovir induction therapy were randomly assigned to an alternating or concurrent combination regimen of chronic ganciclovir-foscarnet therapy for CMV retinitis. Each regimen used lower weekly cumulative doses of each drug than standard monotherapy maintenance treatment regimens. Dose-limiting toxicity attributable to foscarnet occurred in only 2 (7%) of 29 evaluable patients, and no patients experienced dose-limiting nephrotoxicity. Although absolute neutrophil counts  $<500$  cells/ $\mu$ L occurred in 11 (38%) of 29 patients, all who subsequently used adjunctive granulocyte colony-stimulating factor had severe neutropenia prevented. Severe toxicity of any type and neutropenia, in particular, occurred significantly more frequently in patients assigned to the concurrent treatment regimen. CMV was isolated from none of 21 patients who had urine cultured and from only 1 of 24 who had blood cultured while being treated during the study (median evaluation, 12 weeks). This suggests that combination therapy provides better *in vivo* antiviral activity in suppressing CMV replication than previously reported with monotherapy regimens.

Cytomegalovirus (CMV) retinitis is a sight-threatening opportunistic infection that affects ~20% of patients with advanced human immunodeficiency virus disease [1, 2]. Foscarnet and ganciclovir are currently available to treat this condition [3, 4]. Standard therapy is a 2-week intensive induction regimen with either drug, followed by long-term, daily, intravenous maintenance therapy with the same agent. In the one large randomized trial in which foscarnet and ganciclovir were compared for the initial treatment of AIDS-

related CMV retinitis, the two agents were equally efficacious in controlling progression of retinal necrosis [5]. However, retinitis progression occurred relatively early (median, 2 months) with either drug regimen, and drug toxicity was common, especially with foscarnet [5].

*In vitro* data from several laboratories have demonstrated that, when combined, foscarnet and ganciclovir have an additive or synergistic inhibitory effect on CMV replication [6, 7]. The two drugs also have very different toxicity profiles: Myelosuppression and renal and metabolic abnormalities are the most common respective ganciclovir- and foscarnet-associated adverse effects [5]. On the basis of these observations, a strategy that combined ganciclovir and foscarnet in a chronic maintenance regimen for CMV retinitis, using lower cumulative weekly doses of each drug than in standard monotherapy maintenance treatment, could be hypothesized to reduce drug toxicity while maintaining or improving treatment efficacy.

Here we report the results of a randomized phase I trial designed to examine the tolerance and antiviral activity of two combination regimens of chronic ganciclovir-foscarnet maintenance therapy for CMV retinitis.

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Informed consent was obtained from all patients following guidelines for human experimentation of the US Department of Health and Human Services and the institutional review boards of the participating institutions.

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## Methods

Subjects were patients  $\geq 13$  years old with newly diagnosed CMV retinitis who had just completed a course of ganciclovir induction therapy (5 mg/kg intravenous [iv] infusion every 12 h for 14 days) within 7 days of enrollment. Patients were randomized in a 1:1 ratio without stratification to one of two regimens. Regimen 1 comprised concurrent daily combination therapy with ganciclovir (3.75 mg/kg as a 1-h intravenous infusion daily) followed immediately by foscarnet (60 mg/kg iv as a 1-h infusion daily). The second regimen was ganciclovir (6.0 mg/kg as a 1-h infusion every other day) with foscarnet (120 mg/kg) given as a 2-h infusion, coadministered with 1 L of normal saline, every other day, on days when ganciclovir was not administered.

For both regimens, dosing for ganciclovir was reduced by 50% and 75% for estimated creatinine clearances  $< 1.0$  or  $0.6$  mL/min/kg, respectively. Similarly, foscarnet dosing was reduced by 13%, 17%, 22%, 30%, or 37% for estimated creatinine clearances of  $< 1.4$ ,  $1.2$ ,  $1.0$ ,  $0.8$  or  $0.6$  mL/min/kg.

**Evaluation of toxicity and efficacy.** The primary end point of this trial was dose-limiting toxicity. Secondary end points were antiviral efficacy, ophthalmologic efficacy, and survival. Patients were followed for  $\leq 52$  weeks while receiving study drugs but were withdrawn from the study if they experienced serious toxicity or retinitis progression. The latter were defined as a new retinal lesion in a previously uninvolved area of either eye or advancement of the border of any preexisting posterior (to the equator) lesion by  $\geq 750$   $\mu\text{m}$  or of any preexisting anterior (to the equator) lesion into a new clock-hour sector of the retina.

At entry, patients were monitored for laboratory evidence and clinical findings of toxicity and for fundoscopic evidence of retinitis progression (by dilated indirect ophthalmologic examination). Thereafter, they were monitored at least every 2 weeks for the first 12 weeks and then at least monthly.

**Virologic evaluation.** CMV cultures of urine and blood were obtained at study entry and at weeks 4, 8, 12, 24, 36, and 52 during the study. Cultures were done locally according to suggested guidelines. There was no system of standardized virologic quality assurance or control. Blood cultures were done by allowing heparinized blood to settle at room temperature until the buffy coat could be pipetted and transferred to another tube for washing. A resuspended cell pellet was then inoculated into cell culture. For CMV urine cultures, urine specimens were treated with antibiotic mix and phenol red solution, then neutralized with sodium hydroxide (and centrifuged if still turbid) before inoculation. Cell culture medium consisted of human foreskin fibroblast or embryonic lung cells and was examined for  $\leq 6$  weeks for evidence of cytopathic effect typical of CMV. Positive results were confirmed by polyclonal or monoclonal CMV antigen-specific antibodies. At one site (University of Southern California), a shell vial technique was used.

**Statistical analysis.** Treatment assignment groups were compared by Wilcoxon's and Fisher's exact tests for continuous and categorical baseline characteristics and outcome variables. Time to retinitis progression or death was calculated by the product limit method, and median times were compared by the log rank test.

## Results

**Patient characteristics.** Thirty-two patients were enrolled (16 were randomized to each treatment group) between April 1991 and November 1992. Of these, 29 (13 assigned to concurrent and 16 to alternating regimens) were evaluable. Three patients were excluded from further analysis: 2 never received the study drug and 1 was found not to have CMV retinitis. Of the evaluable patients, 93% were male and 79% were Caucasian. Mean age was 40 years. Demographic and baseline clinical characteristics generally did not differ significantly between treatment assignment groups. However, there was a trend toward more women, Hispanics, and injection drug users in the group receiving the alternating regimen, and mean serum creatinine was significantly lower in those receiving alternating drugs. Of note, there was also a trend toward more patients in the alternating treatment arm receiving some form of dideoxynucleoside therapy while participating in the study (13 of 16 vs. 7 of 13).

**Toxicity.** The mean time that patients received assigned study medication was 20 weeks. Dose-limiting toxicity resulted in 3 patients being withdrawn from the study: 2 assigned to the concurrent arm (absolute neutrophil count  $< 500$  cells/ $\mu\text{L}$  attributed to ganciclovir, penile ulcer attributed to foscarnet) and 1 assigned to the alternating treatment arm (absolute neutrophil count  $< 500$  cells/ $\mu\text{L}$  attributed to ganciclovir). In addition, 1 patient assigned to the alternating arm voluntarily withdrew because of symptoms of mild malaise (grade 2 by standard criteria of the National Institute of Allergy and Infectious Diseases [NIAID]) attributed to foscarnet. Nine other patients had absolute neutrophil counts  $< 500$  cells/ $\mu\text{L}$ . All continued receiving study drug, and 5 were given adjunctive granulocyte colony-stimulating factor (G-CSF) therapy, which effectively prevented any further dose-limiting neutropenia.

The number of patients who had serious toxicities (grades 3 or 4, standard NIAID criteria) are listed in table 1 by general toxicity category and by specific toxicity. Of note, there was significantly more grade 4 toxicity of any type and, in particular, more hematologic toxicity in patients assigned to the concurrent regimen. Specifically, both grade 3 and 4 neutropenia (absolute neutrophil counts  $< 750$  and  $< 500$  cells/ $\mu\text{L}$ , respectively) occurred significantly more frequently in patients assigned to the concurrent arm (10 and 8 patients had grades 3 and 4 neutropenia, respectively) than to the alternating arm (5 and 3 patients, respectively;  $P = .025$  for the grade 3 comparison,  $P = .027$  for the grade 4 comparison, 2-tailed Fisher's exact test). This difference in toxicity was observed even though more patients in the alternating arm received concomitant myelosuppressive zidovudine or trimethoprim-sulfamethoxazole therapy while participating in the study.

**Virologic efficacy.** Results of CMV urine and blood cultures during the study are summarized in table 2. Prior to

**Table 1.** Number of toxicities occurring while patients were on study protocol.

Patients with	Protocol		Total	P
	Alternating	Concurrent		
Any toxicity				
Grade 3	11	11	22	.41
Grade 4	8	12	20	.02
Grade 3 hematology	9	11	20	.13
Grade 4 hematology	5	9	14	.07
Grade 3 chemistry*	4	3	7	1.0
Grade 4 chemistry†	3	3	6	1.0
Any signs or symptoms				
Grade 3‡	2	3	5	.63
Grade 4‡	0	1	1	.45
Hematologic toxicities (grade 3/grade 4)				
Neutropenia	5/3	10/8	15/11	
Anemia	3/2	1/1	4/3	
Decreased platelets	2/0	0/0	2/0	

\* Increased liver function test values, increased creatinine, hypophosphatemia, hyponatremia, hypocalcemia.

† Increased liver function test values, hypocalcemia.

‡ Delirium, confusion, diarrhea, fever.

§ Penile ulcer.

receiving ganciclovir induction, 84.6% of patients who had urine or blood tested had at least one positive CMV culture. At the end of ganciclovir induction treatment, prior to randomization to study drug regimens, 31.8% of patients who had urine cultured and only 8% of those who had blood cultured were positive for CMV. There were no significant differences between treatment arms for the proportions of patients with positive cultures (table 2).

Cultures were monitored for a median of 12 weeks during study treatment, and CMV was isolated from none of 21

patients who had urine cultured and from 1 of 24 who had blood cultured. The 1 patient with a positive culture was in the concurrent treatment arm and had received a 2-week course of ganciclovir induction therapy 3 months before randomization when CMV pneumonitis was diagnosed. CMV was isolated from blood at week 8 of the study; however the isolate could not be regrown for susceptibility testing. Among 16 patients who received study treatment for ≥12 weeks, none had positive cultures.

**Other outcomes.** Neither median time to retinitis progression (32 vs. 16 weeks in the alternating vs. concurrent arms,  $P = .52$ ) nor time to death (52 weeks in both arms,  $P = .82$ ) differed significantly between assigned treatment arms. Median Karnofsky performance score was 80 at baseline and remained 80 through week 24 of the study. There were no significant differences in Karnofsky score changes between treatment assignment groups during the study period.

**Discussion**

Chronic foscarnet maintenance therapy was better tolerated in this trial than in previously reported studies of long-term foscarnet therapy for CMV retinitis. Only 2 (7%) of 29 patients experienced dose-limiting foscarnet adverse effects in this trial compared with 20% in the largest randomized trial that compared ganciclovir and foscarnet monotherapies (Studies of Ocular Complications of AIDS [SOCA] Foscarnet-Ganciclovir CMV Retinitis Trial [FGCRT]) [5] and 15% in a multicenter dose-ranging trial of chronic foscarnet maintenance therapy [8]. A randomized trial comparing combination to standard foscarnet monotherapy would be required to prove the hypothesis that the combination regimen results in less foscarnet-related serious toxicity than standard foscarnet monotherapy. However, this is a reasonable hypothesis since the standard foscarnet induction phase of therapy (1260 mg/

**Table 2.** Number of CMV cultures obtained before and at end of ganciclovir induction therapy and during combination foscarnet-ganciclovir maintenance therapy.

CMV cultures, patients with	Urine cultures			Blood cultures			Blood or urine cultures		
	Alternating	Concurrent	Total	Alternating	Concurrent	Total	Alternating	Concurrent	Total
Before ganciclovir induction									
Any positive	9	10	19	3	2	5	12	10	22
Negative	0	0	0	3	5	8	2	2	4
Missing	7	3	10	10	6	16	2	1	3
At randomization									
Any positive	3	4	7	1	1	2	4	5	9
Negative	7	8	15	13	10	23	11	8	19
Missing	6	1	7	2	2	4	1	0	1
While on study drug									
Any positive	0	0	0	0	1	1	0	1	1
negative	10	11	21	13	10	23	13	10	23
Missing	6	2	8	3	2	5	3	2	5
Median no. of weeks obtained	10	12	12	8	12	12	10	12	12
Obtained ≥12 weeks	8	8	16	7	7	14	8	8	16

kg/week, as used in the SOCA FGCR) was eliminated in the current trial, and standard weekly cumulative foscarnet maintenance dosing (630 mg/kg/week) was 50% higher than the maintenance dose used in the current trial [5]. Of particular interest, dose-limiting nephrotoxicity, which is the most common serious adverse effect of foscarnet, was not observed in any of the 29 evaluable patients. In contrast, serum creatinine values  $\geq 2.5$  mg/dL occurred in 13% of patients assigned to foscarnet in the SOCA FGCR (Jabs DA, personal communication).

On the other hand, severe neutropenia (absolute neutrophil count  $< 500$  cells/ $\mu$ L) occurred more frequently with combination therapy in the current trial (38% of patients) compared with rates of 16%–34% previously reported with standard ganciclovir monotherapy, administered at higher weekly doses than in our trial [9] (Jabs DA, personal communication). Again, a randomized comparative trial with a control standard ganciclovir monotherapy arm would be required to prove a significant difference. Nevertheless, the observed greater incidence of neutropenia in this trial than reported in previous ganciclovir trials might be related to acute pharmacokinetic or pharmacodynamic interactions of ganciclovir with foscarnet. Also, severe neutropenia was significantly more common with the concurrent than alternating regimen (62% vs. 19%). This may have been due in part to the slightly higher cumulative weekly dose of ganciclovir in the concurrent than the alternating arm (26.25 vs. 21.0 mg/kg/week), although more patients receiving alternating than concurrent therapy also received myelosuppressive medications, such as zidovudine or trimethoprim-sulfamethoxazole.

An impressive antiviral effect of combination therapy in suppressing CMV replication was observed in this trial. No patients had positive CMV urine cultures and only 1 (4.2%) of 24 had any positive culture while receiving therapy. Among 16 patients receiving therapy for  $\geq 12$  weeks, none had positive cultures. Drew et al. [10] reported that 38% of patients receiving chronic ganciclovir therapy excreted CMV in urine and that 7.6% excreted ganciclovir-resistant CMV after 3 months of standard ganciclovir monotherapy. In the SOCA FGCR, urine cultures were positive in 6%–15% of patients and blood cultures were positive in 13%–24% of patients who had single samples obtained 3 months after initial standard ganciclovir or foscarnet monotherapy (Jabs DA, personal communication). Virologic results of the current trial suggest that combination ganciclovir-foscarnet dosing (administered at lower cumulative weekly doses of each agent than given with either standard monotherapy regimen) may have greater antiviral efficacy than either standard monotherapy regimen alone.

The small sample size and lack of retinal photographs for independent analysis prevent a definitive evaluation of efficacy with regard to retinitis progression in the current trial. However, the 16- to 32-week median time to retinitis progression (based on judgements of examining ophthalmologists

and comparisons of serial retinal drawings) compares favorably to the 8- to 24-week median time to progression reported using the same methodology in previous studies involving ganciclovir or foscarnet monotherapy [8, 11].

In summary, the treatment strategy of ganciclovir induction followed immediately by combination ganciclovir-foscarnet maintenance treatment was well tolerated. Although severe neutropenia occurred more frequently than previously reported with ganciclovir monotherapy, it was easily controlled with adjunctive G-CSF therapy in all patients who received this additional intervention. The promising tolerance and antiviral activity of combination drug treatment warrant future randomized trials comparing combination with standard single-drug maintenance therapy. Given the shorter weekly infusion time, lesser toxicity, and trend toward better efficacy observed with the alternating combination regimen, this regimen would appear to be the more optimal of the two.

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#### Appendix

At the University of California, San Francisco (UCSF), antibiotic medium was gentamicin (50  $\mu$ g/mL) and amphotericin B (1.25  $\mu$ g/mL), the cell culture medium was Eagle MEM with Earl's salt solution and phenol red (10 mg/L), and the anti-CMV antibody was Bartel's CMV reagent (Baxter Diagnostics, Issaquah, WA), a monoclonal direct fluorescent antibody that targets CMV nuclear and cytoplasmic antigens.

At the University of Washington, the antibiotic medium was gentamicin (100  $\mu$ g/mL), penicillin (1000 units/mL), amphotericin B (5.5  $\mu$ g/mL), and polymyxin B (100 units/mL). The cell culture medium was Eagle MEM with 5% fetal calf serum, penicillin (5000 units/mL), streptomycin (5000  $\mu$ g/mL), L-glutamine (200 mM, 10 mL/L), tricine buffer (1 M, 10 mL/L), and sodium bicarbonate (8.8%, 15 mL/L). The anti-CMV antibody was an in-house preparation described in [12].

At Memorial Sloan Kettering Cancer Center, the same antibiotics and culture medium were used as at UCSF. The anti-CMV antibody was a mouse monoclonal antibody directed against immediate early nuclear protein of human CMV (Du Pont, Wilmington, DE).

At the University of North Carolina, the antibiotic medium was a buffered salt solution containing 0.5% gelatin, penicillin (1000 units/mL), streptomycin (100  $\mu$ g/mL), and amphotericin B (20  $\mu$ g/mL). The culture medium was the same as used at UCSF. The anti-CMV antibody was a monoclonal antibody from Ortho Diagnostics (Raritan, NJ).



At the University of Southern California, a shell vial technique was used with MRC-5 cells in conjunction with an indirect immunofluorescence assay to detect CMV in blood or urine. The antibiotic medium was gentamicin (50  $\mu\text{g}/\text{mL}$ ), the cell culture medium was Medium 199 with phenol red plus 2% fetal calf serum (BioWhittaker, Walkersville, MD), and the anti-CMV antibody was a monoclonal antibody targeting CMV nuclear and cytoplasmic antigen (Light Diagnostics CMV Indirect Immunofluorescence Assay, Temecula, CA).

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