ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1998, p. 2240–2244 Vol. 42, No. 9
0066-4804/98/$04.00+0

Incidence of Foscarnet Resistance and Cidofovir Resistance in Patients Treated for Cytomegalovirus Retinitis

DOUGLAS A. JABS,[1,2]* CHERYL ENGER,[3] MICHAEL FORMAN,[4] AND J. P. DUNN[1] FOR THE CYTOMEGALOVIRUS RETINITIS AND VIRAL RESISTANCE STUDY GROUP

Departments of Ophthalmology,[1] Oncology,[3] Pathology,[4] and Medicine,[2] The Johns Hopkins University School of Medicine, Baltimore, Maryland

Received 8 December 1997/Returned for modification 1 April 1998/Accepted 19 June 1998

Cytomegalovirus (CMV) retinitis is a common opportunistic infection in patients with AIDS. With long-term therapy for CMV retinitis, resistant CMV may develop. In a prospective study of 122 patients with CMV retinitis, 2.4 and 0.8% of patients had foscarnet-resistant blood culture isolates (50% inhibitory concentration [IC_{50}], >400 μM) and urine culture isolates, respectively, at diagnosis of CMV retinitis prior to treatment, whereas 4.1 and 6.6% had cidofovir-resistant (IC_{50}, >2 μM) blood and urine culture isolates, respectively. Patients were treated according to best medical judgement. Of 44 foscarnet-treated patients, 26% had a resistant blood or urine culture isolate by 6 months of treatment and 37% had a resistant isolate by 9 months; of 13 cidofovir-treated patients, 29% had a resistant blood or urine culture isolate by 3 months of therapy. The probabilities of developing foscarnet resistance while on foscarnet and developing cidofovir resistance while on cidofovir were not significantly different from that for developing ganciclovir resistance while on ganciclovir (odds ratios, 1.87 [$P = 0.19$] and 2.28 [$P = 0.15$], respectively).

Cytomegalovirus (CMV) retinitis is the most common intraocular infection in patients with AIDS and has been reported to affect approximately 30% of patients with AIDS (9, 10, 12). Left untreated, CMV retinitis is a progressive disease, which spreads throughout the retina, causing total retinal destruction and blindness (12). As of November 1997, three drugs were approved by the United States Food and Drug Administration for the treatment of CMV retinitis: ganciclovir, foscarnet, and cidofovir. All are effective, but none eliminates virus from the retina, and chronic suppressive therapy is required (10, 15, 17). The use of chronic suppressive antiviral therapy is associated with the development of resistant virus (5, 7, 13), and resistant CMV is associated with a poor response to therapy (7, 13, 14). The Cytomegalovirus Retinitis and Viral Resistance Study (8, 11, 13) is a prospective study of CMV resistance to antiviral agents. Herein we report results on the incidence of resistance to foscarnet and to cidofovir.

MATERIALS AND METHODS

The Cytomegalovirus Retinitis and Viral Resistance Study is a prospective observational study of consecutive, CMV drug-naive patients at The Johns Hopkins Medical Institutions undergoing antiviral drug therapy for CMV retinitis from 1993 to 1997. The CMV drug and drug dose chosen for initial therapy were determined by the clinical personnel based upon best medical judgement and without knowledge of patients' baseline results. Enrolled patients were untreated for CMV retinitis. Prior to initiation of therapy, patients underwent an eye examination, measurement of $CD4^+$ T-cell count, and cultures of blood and urine for CMV. Patients returned for follow-up examinations monthly. Cultures of blood and urine were repeated at 1 and 3 months after enrollment and every 3 months thereafter and when clinically evident progression of the retinitis occurred. All positive culture isolates were submitted for sensitivity testing. The study was approved by The Johns Hopkins Medical Institutions Joint Committee for Clinical Investigation, and written informed consent was obtained from all patients enrolled in this study.

Blood and urine samples for CMV culture were processed in tubes of MRC-5, WI-38, and MRHF fibroblasts. Tubes were read daily for CMV-specific cytopathic effect, and CMV was confirmed by fluorescence microscopy. All uncontaminated cultures were held for 6 weeks before being recorded as negative. All positive cultures were tested for susceptibility to foscarnet and cidofovir, regardless of the patient's treatment. Susceptibility testing was performed with the Hybriwix Probe System/CMV Antiviral Susceptibility Test kit (Diagnostic Hybrids, Inc., Athens, Ohio) (4). Confluent human foreskin fibroblasts in 24-well plates were infected with CMV at 1,000 PFU per well. After 90 min of absorption, minimal essential medium containing 10% fetal bovine serum with the anti-CMV drug to be tested was added. Foscarnet was added at concentrations of 0, 100, 200, 300, 400, and 500 μM, and cidofovir was added at concentrations of 0, 0.2, 0.4, 0.8, 1.6, and 3.2 μg/ml; if necessary, higher concentrations were used. After 5 to 7 days, media were removed, lysis solution was added, and the Hybriwix probes were inserted into the wells. Hybriwix probes were batch hybridized with an ^{125}I-radiolabeled DNA probe specific for CMV. The processed Hybriwix probes were counted in a gamma counter, and the mean radioactivity for each concentration of the drug was determined (11, 13). The concentration of drug which resulted in a 50% reduction in DNA hybridization versus the no-drug control established the 50% inhibitory concentration (IC_{50}) against that CMV isolate. For foscarnet, isolates were considered sensitive if the IC_{50} was ≤400 μM and resistant if the IC_{50} was >400 μM (6, 11), and for cidofovir, isolates were considered sensitive if the IC_{50} was ≤2.0 μM (0.6 μg/ml) and resistant if the IC_{50} was >2.0 μM (2). For quality control purposes, a subset of isolates, obtained both at the diagnosis of CMV retinitis and during follow-up, underwent susceptibility testing with both the Hybriwix assay and the plaque reduction assay (8, 11).

Patients were treated according to best medical judgement. The induction dose of foscarnet was 90 mg/kg of body weight twice daily intravenously for 2 weeks, followed by maintenance therapy at 90 to 120 mg/kg once daily, and cidofovir induction was 5 mg/kg once weekly for 2 weeks, followed by maintenance therapy at 3 or 5 mg/kg once weekly.

Kaplan-Meier analysis was done to estimate the resistance-free time. The log rank test was used to compare resistance-free times between groups of patients. Cox proportional hazards regression analysis was done to estimate hazard ratios.

RESULTS

This report includes data on patients enrolled from November 1993 through 31 December 1996 with follow-up through 28 February 1997. The patient population was generally young (median age, 39 years) and predominantly male (77.0%) and had severe immunodeficiency (median $CD4^+$ T-cell count, 9 cells/μl). Risk groups for human immunodeficiency virus infection were as follows: men having sex with men, 53.3%; injection drug use, 19.7%; heterosexual transmission, 22.1%; and other, 4.9%. Of the 122 patients, 121 received treatment; one patient enrolled in the study but did not return for follow-up. For these 121 patients, initial therapy was intravenous

* Corresponding author. Mailing address: The Wilmer Ophthalmological Institute, Suite 700, 550 N. Broadway, Baltimore, MD 21205. Phone: (410) 955-1966. Fax: (410) 955-0629. E-mail: dajabs@welchlink.welch.jhu.edu.

TABLE 1. Life table analysis of percentage of patients developing foscarnet resistance

IC_{50} and culture source (n = 44)	% of patients for time on therapy (mo)			
	3	6	9	12
>400 μM				
Blood	6	22	31	31
Urine	3	3	14	14
Blood or urine	9	26	37	37
>500 μM				
Blood	3	17	18	18
Urine	0	0	11	11
Blood or urine	3	17	19	19

ganciclovir induction and maintenance therapy (67.8%), intravenous foscarnet induction and maintenance (18.6%), ganciclovir implant and oral ganciclovir (5.9%), and intravenous cidofovir (7.6%). Throughout the study, 44 patients received foscarnet and 13 patients received cidofovir at some time.

Baseline blood cultures were positive in 60.7% of patients, and urine cultures were positive in 59.0% of patients; overall, 79.5% of patients had either a positive blood or a positive urine culture at diagnosis of CMV retinitis. The proportions of foscarnet-treated patients with a positive blood or urine culture while on foscarnet were as follows: after 1 to 3 months of therapy, 31.4% (blood, 22.9%; urine, 23.1%); 4 to 6 months, 25.0% (blood, 25.0%; urine, 0%); and 7 to 9 months, 33.3% (blood, 33.3%; urine, 12.5%). The proportions of cidofovir-treated patients with a positive blood or urine culture while on cidofovir were as follows: after 1 to 3 months of therapy, 62.5% (blood, 62.5%; urine, 37.5%), and 4 to 6 months, 50.0% (blood, 50%; urine, 0%).

Seventy-one blood culture isolates and 65 urine culture isolates from patients prior to treatment underwent foscarnet susceptibility testing, and 62 blood culture and 53 urine culture isolates underwent cidofovir susceptibility testing. The mean pretreatment IC_{50} of foscarnet was 210 μM, and the 95th percentile IC_{50} was 387 μM. The mean pretreatment IC_{50} of cidofovir was 0.94 μM, and the 95th percentile IC_{50} was 2.5 μM. Eighty-five isolates from either blood or urine obtained at either diagnosis or follow-up underwent foscarnet susceptibility testing with both the Hybriwix assay and the plaque reduction assay. The mean foscarnet IC_{50}s ± standard deviations for the two assays were 254 ± 152 and 258 ± 217 μM, respectively. Sixty-three isolates underwent cidofovir susceptibility testing by both techniques. The mean cidofovir IC_{50}s ± standard deviations were 1.10 ± 0.86 and 2.05 ± 1.51 μM for the Hybriwix and plaque reduction assays, respectively. Based upon these results, we elected to use the previously determined thresholds for classifying an isolate as foscarnet resistant (400 μM) or cidofovir resistant (2.0 μM) (2, 6, 11). Three patients (2.4%) had a foscarnet-resistant blood culture isolate at the time of diagnosis of CMV retinitis, and one patient (0.8%) had a foscarnet-resistant urine culture CMV isolate. Five patients (4.1%) had a cidofovir-resistant blood culture isolate, and eight patients (6.6%) had a cidofovir-resistant urine culture isolate at the time of diagnosis of CMV retinitis.

Life table analysis results of the percentage of patients with foscarnet-resistant isolates during follow-up are presented in Table 1. For foscarnet-treated patients, 37% of patients treated for 9 months developed at least one foscarnet-resistant isolate from either blood or urine (Fig. 1). Among patients who developed a foscarnet-resistant isolate, the peak IC_{50} ranged from 439 to 873 μM with a median IC_{50} of 646 μM and a mean IC_{50} of 636 μM. Only one patient remained on cidofovir after 6 months. Among cidofovir-treated patients, 29% of patients treated for 3 months developed at least one cidofovir-resistant isolate from either blood or urine (Table 2 and Fig. 2). Among

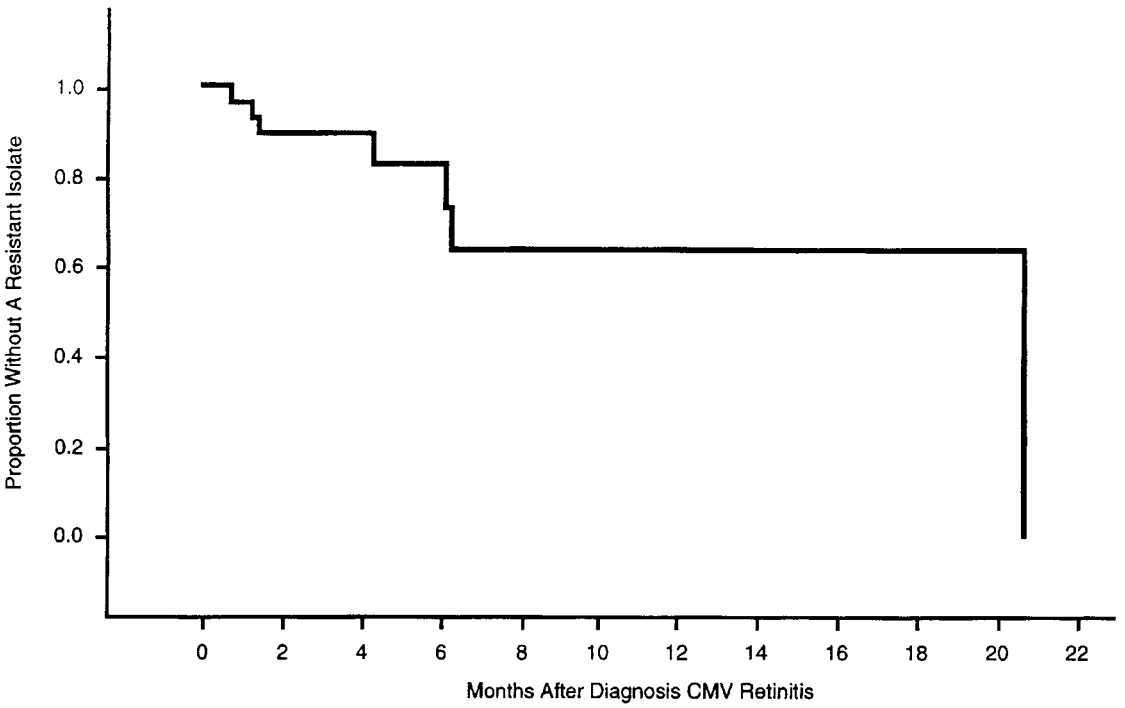

FIG. 1. Proportion of foscarnet-treated patients without a foscarnet-resistant isolate.

TABLE 2. Life table analysis of percentage of patients developing cidofovir resistance

IC_{50} and culture source (n = 13)	% of patients for time on therapy (mo)			
	3	6	9	12
>2 μM				
Blood	20	20	20	100[a]
Urine	8	8	8	8
Blood or urine	29	29	29	100
>2.5 μM				
Blood	20	20	20	20
Urine	0	0	0	0
Blood or urine	20	20	20	20

[a] Only one patient remained on cidofovir beyond 6 months.

patients who developed a cidofovir-resistant isolate, the peak IC_{50} (from either blood or urine) ranged from 2.9 to 5.5 μM.

The probability of developing ganciclovir resistance in either blood or urine while on ganciclovir among the cohort was 7% at 3 months, 12% at 6 months, and 27% at 9 months of therapy (13). The relative risk for developing a foscarnet-resistant isolate among foscarnet-treated patients compared to that for developing a ganciclovir-resistant isolate among ganciclovir-treated patients (Table 3) was 1.62 for blood cultures (95% confidence interval [CI] = 0.59 to 4.40; P = 0.35), 1.50 for urine cultures (95% CI = 0.27 to 8.28; P = 0.64), and 1.87 for either blood or urine cultures (95% CI = 0.73 to 4.78; P = 0.19). The relative risk for developing a cidofovir-resistant isolate among cidofovir-treated patients compared to that for developing a ganciclovir-resistant isolate among ganciclovir-treated patients was 3.44 for blood cultures (95% CI = 0.88 to 13.41; P = 0.08), 1.09 for urine cultures (95% CI = 0.13 to 8.88; P = 0.94), and 2.28 for either blood or urine cultures (95% CI = 0.75 to 6.97; P = 0.15).

TABLE 3. Relative risk of resistance to foscarnet or cidofovir while undergoing treatment with foscarnet or cidofovir, respectively, versus risk of resistance to ganciclovir while on ganciclovir

Drug	Isolate source	Relative risk	95% CI
Foscarnet	Blood	1.62	0.59–4.40
	Urine	1.50	0.27–8.28
	Blood or urine	1.87	0.73–4.78
Cidofovir	Blood	3.44	0.88–13.41
	Urine	1.09	0.13–8.88
	Blood or urine	2.28	0.75–6.95

All but two of the patients who developed foscarnet resistance were sensitive to ganciclovir and to cidofovir. One patient was resistant to ganciclovir (IC_{50} = 13.68 μM), but he had been treated with ganciclovir previously. The other patient's CMV was sensitive to ganciclovir but resistant to cidofovir (IC_{50} = 2.72 μM). All of the patients who developed cidofovir resistance were sensitive to foscarnet; one patient was found to be moderately ganciclovir resistant (IC_{50} = 8.20 μM).

DISCUSSION

The Cytomegalovirus Retinitis and Viral Resistance Study is a prospective epidemiologic study of the development of resistance in patients with AIDS treated for CMV retinitis. We previously reported that a ganciclovir-resistant isolate could be identified in 27% of patients treated with ganciclovir for 9 months (13) and that identification of a resistant isolate was associated with adverse outcomes, such as dissemination to the other eye (13) and rapid progression of the retinitis (7).

Because a large number of specimens needed to be processed, we elected to use the Hybriwix DNA hybridization assay. For foscarnet susceptibility testing, the DNA hybridiza-

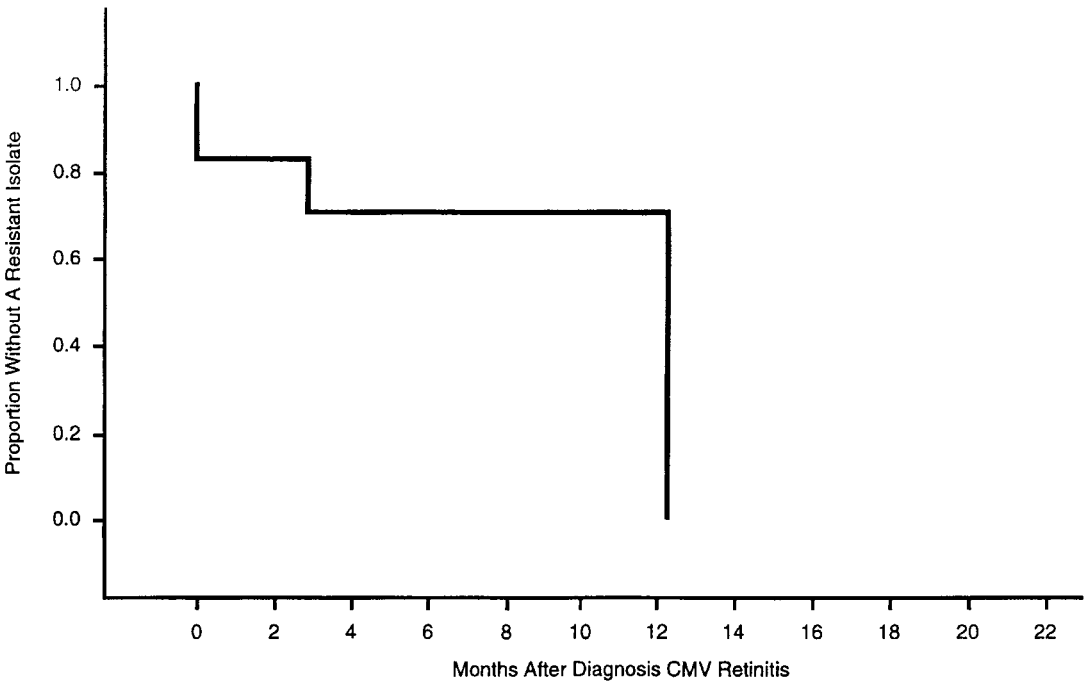

FIG. 2. Proportion of cidofovir-treated patients without a cidofovir-resistant isolate.

tion assay gave an IC_{50} similar to that of the plaque reduction assay, and the statistical approach suggested by Drew et al. (6) for determining the upper limit of foscarnet sensitivity from pretreatment isolates suggested that the threshold of 400 μM was appropriate. For cidofovir susceptibility testing, the DNA hybridization assay tended to give a lower IC_{50} than did the plaque reduction assay. However, the statistical analysis of pretreatment isolates suggested that an IC_{50} of 2.5 μM might be more appropriate for classifying cidofovir resistance. Because these two data sets suggested different adjustments to the previously proposed 2 μM threshold for classifying an isolate as cidofovir resistant, we elected to use the 2 μM threshold and also to report the data with the higher 2.5 μM threshold.

The frequencies of a foscarnet-resistant isolate or a cidofovir-resistant isolate at the time of diagnosis of CMV retinitis were low, a result consistent with the previous work from our group and others (2, 6, 11). However, with prolonged therapy use, there was an increasing proportion of patients who developed a resistant isolate: 37% of patients treated with foscarnet for 9 months had a foscarnet-resistant isolate, and 29% of patients treated with cidofovir for 3 months had a cidofovir-resistant isolate.

A good correlation has been reported between the resistant phenotype for ganciclovir, defined by an IC_{50}, and detection of genetic mutations in the CMV UL97 and UL54 genes (3, 16). The correlation between phenotypic detection of resistance, defined by an IC_{50}, and genetic mutations conferring resistance has been less well studied and less well determined for foscarnet and cidofovir. Although the 400 μM threshold has been used as the IC_{50} for identifying a foscarnet-resistant isolate (6), we also analyzed our data with a higher threshold, 500 μM. Even with this higher threshold, 19% of patients had a foscarnet-resistant isolate by 9 months of therapy. Similarly, we analyzed the incidence of cidofovir resistance with a higher, 2.5 μM threshold. With this threshold, 20% of patients developed a cidofovir-resistant isolate. There have been some preliminary data from genetic analyses suggesting that the 2 μM threshold may be too conservative (1a) and that one as high as 4 μM may be more appropriate. No patient developed an isolate with an IC_{50} of >4 μM cidofovir while on cidofovir, but one patient developed a rising IC_{50} on cidofovir which peaked at 5.5 μM after discontinuing cidofovir.

We compared the probability of developing a foscarnet-resistant isolate on foscarnet and of developing a cidofovir-resistant isolate on cidofovir to that of developing a ganciclovir-resistant isolate while on ganciclovir. These probabilities appeared to be no less than that of developing a ganciclovir-resistant isolate, and our data suggested that they may be greater. However, the *P* values for this difference did not achieve statistical significance, possibly because of the number of patients on foscarnet and cidofovir. Caution must be used in interpreting these comparisons because our study was a prospective epidemiologic one and not a controlled clinical trial; other, unidentified factors might influence the development of resistance. However, our previous work could not detect other factors which increased the likelihood of developing ganciclovir resistance (13). Therefore, our data suggest that foscarnet resistance and cidofovir resistance are at least no less likely than ganciclovir resistance when patients are treated for comparable time periods.

The Study of Ocular Complications of AIDS (SOCA) Research Group reported that they could not detect cases of foscarnet resistance, possibly due to the fact that foscarnet-resistant isolates were at a growth disadvantage in culture (18). In contrast to the SOCA Research Group, we were able to detect foscarnet resistance. It is possible that methodological differences contributed to the different results. In our study, foscarnet resistance testing was done promptly upon positively identified cultures, rather than on banked frozen specimens, as was done in the SOCA study (18). If foscarnet resistance confers a growth disadvantage, regrowth of cultures from banked specimens may be problematic, and the identification of foscarnet resistance may be more difficult.

One limitation of this study is that resistance could be detected only in patients with positive cultures; it is possible that patients could harbor resistant virus which could not be detected by our methodology. Foscarnet resistance and presumably cidofovir resistance occur due to mutations in the CMV DNA polymerase gene (1), but these mutations have not been as well characterized as have those for ganciclovir in the UL97 gene. Data on mutations were not available in our study.

In conclusion, our data suggest that, among patients with prolonged treatment with either foscarnet or cidofovir, foscarnet and cidofovir resistance each occur in approximately one-third of patients and that foscarnet and cidofovir resistance may develop at rates similar to those of ganciclovir resistance.

APPENDIX

The Cytomegalovirus Retinitis and Viral Resistance Study Group consists of the following individuals at the following institutions: Clinical Center, Johns Hopkins University School of Medicine, Baltimore, Md., Douglas A. Jabs (principal investigator), John G. Bartlett, Stephen G. Bolton, J. P. Dunn, John H. Kempen, Susan M. LaSalvia, Laura G. Neisser, Earline Nanan, and Richard D. Semba; Data Center, Johns Hopkins University School of Medicine, Cheryl Enger, Shirley Quaskey, and Judy Southall (former members, Melissa Chapin and Rhonda Blasdel); Flow Cytometry Laboratory, Johns Hopkins University School of Hygiene and Public Health, Joseph B. Margolick (director) and Elvia Ramirez; Fundus Photograph Reading Center, University of Wisconsin, Madison, Matthew D. Davis (director), Larry Hubbard, Judy Brickbauer, and Linda Kastorff; and Virology Laboratory, Johns Hopkins University School of Medicine, Patricia Charache, Michael Forman, and Tamieca Hamlin (former member, Alicja Rylka).

ACKNOWLEDGMENTS

This study was supported by grant EY 10268 from the National Eye Institute, National Institutes of Health, and by an unrestricted grant from Research to Prevent Blindness. D.A.J. is the recipient of a Research to Prevent Blindness Lew R. Wasserman Merit Award.

REFERENCES

1. **Baldanti, F., M. R. Underwood, S. C. Stanat, K. K. Biron, S. Chou, A. Sarasini, E. Silini, and G. Gerna.** 1996. Single amino acid changes in the DNA polymerase confer foscarnet resistance and slow-growth phenotype, while mutations in the UL97-encoded phosphotransferase confer ganciclovir resistance in three double-resistant human cytomegalovirus strains recovered from patients with AIDS. J. Virol. **70:**1390–1395.

1a. **Cherrington, J.** Personal communication.

2. **Cherrington, J. M., R. Miner, M. J. Hitchcock, J. P. Lalezari, and W. L. Drew.** 1996. Susceptibility of human cytomegalovirus to cidofovir is unchanged after limited in vivo exposure to various regimens of drug. J. Infect. Dis. **173:**987–992.

3. **Chou, S., S. Guentzel, K. R. Michels, R. C. Miner, and W. L. Drew.** 1995. Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. J. Infect. Dis. **172:**239–242.

4. **Dankner, W. M., D. Scholl, S. C. Stanat, M. Martin, R. L. Sonke, and S. A. Spector.** 1990. Rapid antiviral DNA-DNA hybridization assay for human cytomegalovirus. J. Virol. Methods **28:**293–298.

5. **Drew, W. L., R. C. Miner, D. F. Busch, S. E. Follansbee, J. Gullett, S. G. Mehalko, S. M. Gordon, W. F. Owen, Jr., T. R. Matthews, W. C. Buhles, and B. DeArmond.** 1991. Prevalence of resistance in patients receiving ganciclovir for serious cytomegalovirus infection. J. Infect. Dis. **163:**716–719.

6. **Drew, W. L., R. C. Miner, and E. Saleh.** 1993. Antiviral susceptibility of cytomegalovirus: criteria for detecting resistance to antivirals. Clin. Diagn. Virol. **1:**179–185.

7. **Dunn, J. P., M. W. MacCumber, M. S. Forman, P. Charache, L. Apuzzo, and**

D. A. Jabs. 1995. Viral sensitivity testing in patients with cytomegalovirus retinitis clinically resistant to foscarnet or ganciclovir. Am. J. Ophthalmol. **119:**587–596.
8. **Enger, C., D. A. Jabs, J. P. Dunn, M. S. Forman, N. M. Bressler, J. B. Margolick, P. Charache, and the CRVR Research Group.** 1997. Viral resistance and CMV retinitis: design and methods of a prospective study. Ophthalmic Epidemiol. **4:**41–48.
9. **Hoover, D. R., Y. Peng, A. Saah, R. Semba, R. R. Detels, C. R. Rinaldo, Jr., and J. P. Phair.** 1996. Occurrence of cytomegalovirus retinitis after human immunodeficiency virus immunosuppression. Arch. Ophthalmol. **114:**821–827.
10. **Jabs, D. A.** 1995. Ocular manifestations of HIV infection. Trans. Am. Ophthalmol. Soc. **93:**623–683.
11. **Jabs, D. A., J. P. Dunn, C. Enger, M. Forman, N. Bressler, and P. Charache for the Cytomegalovirus Retinitis and Viral Resistance Study Group.** 1996. Cytomegalovirus retinitis and viral resistance: prevalence of resistance at diagnosis, 1994. Arch. Ophthalmol. **114:**809–814.
12. **Jabs, D. A., C. Enger, and J. G. Bartlett.** 1989. Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch. Ophthalmol. **107:**75–80.
13. **Jabs, D. A., C. Enger, J. P. Dunn, and M. Forman for the Cytomegalovirus Retinitis and Viral Resistance Study Group.** 1998. Cytomegalovirus resistance and viral resistance. 4. Ganciclovir resistance. J. Infect. Dis. **177:**770–773.
14. **Leport, C., S. Puget, J. M. Pepin, S. Levy, C. Perronne, F. Brun-Vezinet, and J. L. Vilde.** 1993. Cytomegalovirus resistant to foscarnet: clinicovirologic correlation in a patient with human immunodeficiency virus. J. Infect. Dis. **168:**1329–1330. (Letter.)
15. **Palestine, A. G., M. A. Polis, M. D. De Smet, B. F. Baird, J. Falloon, J. A. Kovacs, R. T. Davey, J. J. Zurlo, K. M. Zunich, M. Davis, L. Hubbard, R. Brothers, F. L. Ferris, E. Chew, J. L. Davis, B. I. Rubin, S. D. Mellow, J. A. Metcalf, J. Manischewitz, J. R. Minor, R. B. Nussenblatt, H. Masur, and H. C. Lane.** 1991. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. Ann. Intern. Med. **115:**665–673.
16. **Smith, I. L., J. M. Cherrington, R. E. Jiles, M. D. Fuller, W. R. Freeman, and S. A. Spector.** 1997. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. J. Infect. Dis. **176:**69–77.
17. **Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group.** 1994. Foscarnet-ganciclovir cytomegalovirus retinitis trial. 4. Visual outcomes. Ophthalmology **101:**1250–1261.
18. **Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group.** 1997. Cytomegalovirus (CMV) culture results, drug resistance, and clinical outcome in patients with AIDS and CMV retinitis treated with foscarnet or ganciclovir. J. Infect. Dis. **176:**50–58.