Foscarnet Decreases Human Immunodeficiency Virus RNA

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Foscarnet inhibits human immunodeficiency virus (HIV) replication in vitro and decreases p24 antigenemia in patients with cytomegalovirus (CMV) retinitis. To evaluate the effect of foscarnet on HIV replication, HIV RNA was quantitated in 17 patients before and during foscarnet therapy. Fifteen patients had CMV retinitis, 1 had CMV encephalitis, and 1 had intractable zoster. A decrease in HIV RNA was observed in 16 of 17 patients. Before the introduction of foscarnet, mean HIV RNA was 5.82 ± 0.24 log RNA/mL and, after a median of 13 days of therapy, mean HIV RNA was 5.30 ± 0.27 log RNA/mL ($P < .001$). Among patients with detectable p24 antigen at baseline, a significant decrease was observed ($P = .017$). This decrease in HIV RNA demonstrates that foscarnet is a potent antiretroviral drug.

Foscarnet (sodium salt of phosphonoformic acid) is, in vitro, a noncompetitive inhibitor of human immunodeficiency virus (HIV) reverse transcriptase and decreases HIV replication [1, 2]. In AIDS patients treated with foscarnet for cytomegalovirus (CMV) retinitis, a decrease in p24 antigenemia was observed, suggesting an inhibition of HIV replication in vivo [3, 4]. In a large randomized study comparing foscarnet with ganciclovir for the treatment of CMV retinitis, the effect on retinitis was similar, but patients treated with foscarnet survived longer, leading to speculation that foscarnet's anti-HIV effect might be of clinical importance [5]. In view of these data, we quantitated HIV viremia before and during foscarnet therapy to assess the effect of foscarnet on HIV load.

Patients and Methods

Study population. AIDS patients with CMV disease whose physicians decided to use foscarnet were enrolled retrospectively and prospectively. Among patients enrolled prospectively, viremia was measured using serum samples collected on day 0 (before starting foscarnet) and after 10 days of treatment. Patients were enrolled retrospectively if frozen serum samples were available between −10 and 0 days and between 10 and 30 days after the initiation of foscarnet.

Quantitation of HIV RNA, p24 antigen, and $CD4^+$ cell counts. Blood was collected without anticoagulant, centrifuged twice for 5 min at 1500 *g*, aliquoted, and stored at −75°C, all within 2 h. Total RNA from 50 μL of serum was extracted using an automated system (Autogen 540; Autogen Instrument, Beverly, MA). RNA purification was based on the single-step method of acid guanidinium thiocyanate–phenol–chloroform extraction [6].

Circulating HIV RNA was quantitated in relation to an external standard, as previously described [7, 8]. Briefly, total RNA recovered from 50 μL of serum was reverse transcribed, and a 238-bp sequence of a conserved region of the *pol* gene was amplified by polymerase chain reaction. The intra- and interassay variations were 11% and 25%, respectively (data not shown). To eliminate interassay variation, samples from the same patient were assayed in the same experiment. Viremia was expressed as logarithm of HIV RNA copies per milliliter of serum.

$CD4^+$ cell counts were determined by flow cytometry (Coulter EPICS IV; Instrumente Gesellschaft, Basel, Switzerland) using fluoresceinated DAKO-T3, DAKO-T8, and R-phycoerythrin DAKO-CD4 (Dako, Glostrup, Denmark). p24 antigen levels were measured in duplicate using batch testing (HIVAG-1; Abbott Laboratories, Abbott Park, IL).

Results

Seventeen patients were enrolled in this study: 7 retrospectively and 10 prospectively between January and October 1994. Fifteen patients had CMV retinitis (4 relapsed during maintenance therapy with ganciclovir), 1 had CMV encephalitis, and 1 had intractable disseminated zoster. The median $CD4^+$ cell count was 24/mm^3 (range, 1–202), and all patients were diagnosed with AIDS before the introduction of foscarnet. Eight patients had been receiving antiretroviral treatment for >4 weeks at the time of CMV disease; 6 were receiving didanosine and 2 were receiving zidovudine. For 2 patients, didanosine was stopped the day foscarnet was introduced, whereas the others continued to receive didanosine or zidovudine at identical dosages (table 1). For the 9 remaining patients, antiretroviral therapy was stopped for at least 10 weeks. Sixteen patients received 9.0–13.5 g/day of foscarnet, depending on body weight; 1 patient received 6 g/day because of renal failure.

A decrease in HIV RNA was observed during foscarnet therapy in all but 1 patient (table 1). At baseline, the mean (±SE) HIV RNA was 5.82 ± 0.24 log RNA/mL. After a median of 13 days of therapy, the mean HIV RNA level was 5.30 ± 0.27 log RNA/mL. A statistically significant mean de-

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Table 1. Quantitation of human immunodeficiency virus (HIV) RNA and p24 antigen in 17 patients before and during foscarnet therapy.

Patients	Concomitant antiretroviral*	Baseline $CD4^+$ cells/mm^3	Log HIV RNA/mL		p24 antigen (ng/L)	
			Before foscarnet†	After foscarnet‡	Before foscarnet†	After foscarnet†
1	No	40	5.47	4.67	52	Neg
2	ddI	79	6.58	5.67	284	188
3	No§	19	5.97	5.89	Neg	12
4	ddI	1	3.86	3.45	7	Neg
5	No§	45	4.00	3.64	172	72
6	ddI	6	4.61	4.35	Neg	Neg
7	No	36	6.23	6.04	63	26
8	No	2	4.61	3.85	5	13
9	No	1	6.54	6.32	14	4
10	No	89	5.82	5.04	36	9
11	No	24	6.48	6.88	6	8
12	No	30	6.59	6.22	Neg	Neg
13	ddI	2	6.74	6.46	5	15
14	No	79	6.80	6.32	139	13
15	AZT	4	5.66	4.17	33	11
16	AZT	202	6.40	4.87	5731	386
17	No	2	6.61	6.21	Neg	Neg

NOTE. All patients had cytomegalovirus (CMV) retinitis, except patients 14 (disseminated zoster) and 15 (CMV encephalitis). ddI, didanosine; AZT, zidovudine; neg, negative.

* In 6 patients, antiretroviral treatment with nucleoside analogues was continued during foscarnet therapy.

† 0–10 days before foscarnet.

‡ After 10 days of foscarnet.

§ Received ddI until start of foscarnet.

crease of 0.53 ± 0.12 log RNA/mL was observed during therapy (paired *t* test, $P < .001$). A decrease in HIV RNA of >0.7 log (>80%) was seen in 6 of 17 patients and a decrease of >0.3 log (>50%) in 11 patients. One patient had an increase in HIV RNA.

Of 13 patients who were p24 antigen–positive at baseline (range, 5–5531 ng/L), 10 had decreased levels (range, −34% to −100%) during therapy (table 1) that were statistically significant (Wilcoxon paired test, $P = .017$). Of the 4 patients who were p24 antigen–negative at baseline, 3 remained negative and 1 became positive.

Median survival after the diagnosis of CMV disease or zoster was 5 months (range, 1–13).

Discussion

Ganciclovir and foscarnet are equally efficacious for the treatment of CMV retinitis [5, 9, 10]. However, foscarnet has the potential advantage of also inhibiting HIV replication. Foscarnet decreases p24 antigen levels [3, 4], but no data on the impact of foscarnet therapy on HIV viremia are available. Our results show that foscarnet has a measurable effect on HIV RNA in patients with CMV disease. The decrease of HIV RNA observed in our 17 patients is significant and comparable to that observed with other antiretroviral drugs [7, 8, 11, 12]. Moreover, this effect was observed in patients previously treated for several years with nucleoside analogues. In vitro data suggest that the inhibition of HIV replication by foscarnet and zidovudine is synergistic [1, 2]. In our study, it is interesting that the 2 patients receiving zidovudine during foscarnet treatment had the largest decrease in HIV viremia (−1.49 and −1.53 log RNA/mL).

As reported previously [3, 4], we also observed a decrease in p24 antigen level. However, p24 antigen was not detectable at baseline in all patients. Moreover, in 3 patients with low p24 antigenemia (<15 ng/L), a weak elevation in p24 antigen level was observed, which did not correlate with the substantial decrease seen in HIV RNA. Slight variations of p24 antigenemia might be the result of variations in the production of anti-p24 antibodies over time. In this context, our results highlight the advantages of measuring HIV RNA, which is detectable in all patients and is a more accurate marker of HIV replication.

The median survival reported in our study was 5 months, which is lower than that in some prospective therapeutic studies [5]. However, we recruited patients regardless of clinical situation, associated comorbidities, or prognosis. Most of our patients had a history of multiple AIDS-defining events, and some had other active opportunistic infections, thus explaining the high mortality.

For patients with CMV retinitis, foscarnet's activity against HIV is an appealing side effect, perhaps resulting in increased

survival [5]. Unfortunately, the drug needs to be administered intravenously and has numerous dose-dependent adverse effects. It is unlikely, therefore, that high doses will ever be used against HIV in patients without CMV disease or intractable herpes. The effects on HIV of lower doses and possible synergy with other antiretrovirals are interesting subjects for further studies.

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