Phase I Trial of Valaciclovir, the L-Valyl Ester of Acyclovir, in Patients with Advanced Human Immunodeficiency Virus Disease

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Valaciclovir, the L-valyl ester of acyclovir, is rapidly and extensively converted in humans to acyclovir after oral administration by first-pass metabolism. A phase I study was conducted in two cohorts of volunteers with advanced human immunodeficiency virus (HIV) disease (absolute CD4 lymphocyte count of <150 cells per μl) who received oral valaciclovir at dosages of 1,000 or 2,000 mg four times daily for 30 days. All patients were clinically stable without any changes in underlying HIV-related medications for ≥6 weeks prior to entry in study; these medications were continued throughout the study. Multiple-dose administration of valaciclovir showed a generally favorable safety profile. Nausea, vomiting, diarrhea, and abdominal pain each were reported in ≤31% of the patients; of these symptoms, only one episode of diarrhea was considered causally related to valaciclovir exposure. Four patients developed neutropenia (two at each dose level) which was not clinically significant. There were no renal or neurologic adverse events. Valaciclovir was rapidly absorbed and converted to acyclovir, with plasma valaciclovir levels generally undetectable or levels of ≤0.4 μg/ml. After 3 h postdosing, valaciclovir was not detectable in plasma. Acyclovir was measurable in plasma as early as 15 min following valaciclovir dosing, and plasma concentrations of acyclovir greatly exceeded those of valaciclovir. The mean values for the maximum concentration of drug in plasma, time to maximum concentration of drug in plasma, area under the concentration-time curve from 0 h to infinity, and apparent half-life of acyclovir obtained after single- and multiple-dose valaciclovir administration in HIV-infected patients were similar to those reported in normal healthy volunteers. The time to maximum concentration in serum and half-life of acyclovir after oral administration were approximately 2 and 3 h, respectively, which were similar to those reported after oral administration of acyclovir itself. The mean trough and peak acyclovir concentrations and the daily area under the concentration-time curve acyclovir values at steady state were 2.5 and 8.4 μg/ml and 120 h · μg/ml, respectively, after a dosage of 2,000 mg of valaciclovir four times daily. These values were approximately fivefold greater than those achieved with high dosages of oral acyclovir (800 mg, five times daily) and were not affected by continued use of medications necessary for management of advanced HIV disease. Thus, 2,000 mg of valaciclovir given orally four times daily should be evaluated for its potential efficacy in suppressing cytomegalovirus and other herpes group virus infections not optimally managed with current oral acyclovir therapy.

Valaciclovir (256U87) is the L-valyl ester of acyclovir as the hydrochloride salt and is rapidly converted to acyclovir after oral administration in rats, monkeys, and humans (4, 8, 27). Preclinical studies have shown that valaciclovir undergoes extensive first-pass hydrolysis to acyclovir in the liver and intestinal wall, resulting in concentrations of acyclovir in plasma greatly exceeding those of valaciclovir (4, 8). In animals, valaciclovir is well tolerated, with a safety profile similar to that reported for acyclovir (21). In healthy human volunteers, multiple oral dosages of valaciclovir (1,000 to 2,000 mg four times daily) produced plasma acyclovir concentrations ranging from three to five times greater than those obtained after high oral dosages of acyclovir (800 mg five times daily) (27). Acyclovir levels obtained after valaciclovir dosages of 1,000 to 2,000 mg four times daily also exceeded or approached those obtained following intravenous acyclovir administration (5 to 10 mg/kg of body weight every 8 h). Plasma valaciclovir concentrations were either undetectable or generally ≤0.4 μg/ml, regardless of the dose administered (27). No serious or unexpected adverse events or laboratory abnormalities were reported for healthy subjects receiving valaciclovir dosages of up to 2,000 mg four times daily for 11 days (27).

Patients with advanced human immunodeficiency virus (HIV) disease and low absolute CD4 lymphocyte counts are at high risk of developing progressive or recurrent mucocutaneous herpes simplex virus (HSV) or varicella-zoster virus (VZV) infections. The development of progressive mucocutaneous disease caused by acyclovir-resistant HSV and VZV isolates has become a problem of increasing clinical importance, which may be due, in part, to suboptimal chronic oral dosing with acyclovir (10, 15). Patients with advanced HIV disease are also at risk of developing opportunistic cytomegalovirus (CMV) end-organ disease (25). Valaciclovir, which produces substantially higher acyclovir levels in plasma than those currently achievable with oral acyclovir therapy, might be effective in preventing both the emergence of acyclovir-resis-
tant HSV or VZV disease and the occurrence of CMV disease in HIV-infected patients with low absolute CD4 counts.

The safety and pharmacokinetic data for valaciclovir obtained from phase I studies involving healthy volunteers may not be applicable to patients with advanced HIV disease, who often have clinical or subclinical malabsorption or hepatic or renal impairment, which could affect the pharmacokinetics of valaciclovir. These patients also require concomitant antiretroviral and prophylactic antimicrobial medications which may complicate the pharmacokinetic and safety profiles of valaciclovir. We therefore conducted a phase I trial to evaluate the pharmacokinetics and safety of oral dosages of 1,000 and 2,000 mg of valaciclovir four times daily for 30 days in patients with advanced HIV disease who were being treated with multiple concomitant medications necessary for the management of their disease throughout the study period.

**MATERIALS AND METHODS**

**Study medication.** Valaciclovir was administered as opaque white capsules, each containing 250 mg of valaciclovir (the anhydrous free base content) plus excipients, at a dose of 1,000 or 2,000 mg. The molecular weight of valaciclovir as the hydrochloride salt is 360.8 (or 324.34 for the free base).

Valaciclovir capsules were supplied by Burroughs Wellcome Co. (Greenville, N.C.). Each dose of the study medication was administered with a minimum of 200 mL of water.

**Study population.** Patients with a documented positive serum HIV antibody test result or clinical evidence of HIV infection with no other known cause of immunosuppression were eligible for entry if their absolute CD4 lymphocyte count was ≥150 cells per μL, body weight was ≥45 kg (≥40 kg for women), and renal function was normal (creatinine ≤2.0 mg/dL). Patients were excluded if there was active HSV, VZV, or CMV disease requiring specific antiviral therapy; history of prior acyclovir intolerance; pregnancy; serum albumin ≤2.0 g/dL; bilirubin of ≥5.0 mg/dL; creatinine of ≥2.0 mg/dL; hemoglobin of ≤9.0 g/dL; absolute neutrophil count (ANC) of ≤750 cells per μL; or severe or persistent nausea, vomiting, or diarrhea. Patients were not permitted to take any antithrombotic medication, including acyclovir and interferon, during the week prior to enrollment or during the study period.

A total of 17 volunteers (14 males and 3 females) were enrolled at two study sites: the San Francisco General Hospital (San Francisco, Calif.; 8 volunteers) and the Johns Hopkins University (Baltimore, Md.; 9 volunteers). Patients were randomly assigned to one of the two valaciclovir dosage regimens at both study sites. Nine patients received 1,000 mg of valaciclovir (cohort 1) and eight patients received 2,000 mg of valaciclovir (cohort 2) four times daily for 30 days. Both study sites enrolled a similar number of patients at each dose level.

**Clinical and laboratory evaluation.** A complete medical history and physical examination were performed within 14 days prior to enrollment and again at 7 to 10 days after completing the 30-day-study drug-dosing period. Vital signs, review of body systems, and routine hematology, serum chemistry, and urinalysis were examined weekly during the 30-day dosing period and at 7 to 10 days upon completion of the dosing period. Urine CMV cultures at study entry and after 2 and 4 weeks of administration of the study medication were obtained from patients at the San Francisco General Hospital.

**Dosing and sampling procedures.** The pharmacokinetics of acyclovir and valaciclovir following single- and multiple-dose valaciclovir administration were evaluated on days 1 and 30, respectively. Patients reported to the study site the night before day 1 and remained there throughout the next day. Patients took the first dose of valaciclovir on day 1 at about 7 a.m. after an 8-h fast, and serial blood samples were collected for up to 10 h following dosing. Patients continued to fast for another 3 h postdosing, with fluid intake ad libitum. On days 2 to 30, each patient took the study drug four times daily at approximately 7 a.m., 12 noon, 5 p.m., and 10 p.m. (i.e., at 5-, 5-, 5-, and 9-h intervals per day) on an outpatient basis. The night before day 30, patients were readmitted to the study site for full pharmacokinetic evaluation as was done on day 1 and remained at the study site until the 24-h-postdosing blood sample was collected.

Blood samples (5 mL each) were collected for measurements of concentrations of acyclovir and valaciclovir in plasma on day 1 at time zero (prior to dosing) and 0.25, 0.5, 1, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, and 10.0 h postdosing and then on day 30 at the same times as day 1 samplings but with additional samplings at 12.0, 16.0, and 24.0 h postdosing. For monitoring purposes, blood samples were obtained at 0.75 to 3.24 h morning (first) dose of immediately before the second dose on days 7, 14, and 21 of the study. Blood was collected by venipuncture into EDTA-containing tubes and held at 4°C. Plasma was separated within 1 h of collection, with aliquots frozen at −20°C or below until assayed.

**Analytical methods.** Concentrations of acyclovir and valaciclovir in plasma were determined by a previously described radioimmunoassay (26) and a high-performance liquid chromatography (HPLC) method (27), respectively. Both assay methods were validated. For analysis of plasma acyclovir concentrations, samples collected from this study were diluted 10 to 1,000 times into the concentration range of the standard curve samples (0.0007 to 0.09 μg/mL). The mononuclear antibody used in the radioimmunoassay was specific to acyclovir, with less than 5% cross-reactivity with valaciclovir or acyclovir metabolites. The intra- and interassay variabilities (percent coefficient of variation [% CV]) in the assay were less than 10% at acyclovir concentrations ranging from 0.0004 to 0.045 μg/mL. The lower limit of quantitation for acyclovir in plasma was 0.01 μg/mL prior to dilution. The HPLC analysis of valaciclovir in plasma did not require sample dilution and showed a linearity over the concentration range of 0.08 to 3.24 μg/mL. The assay was specific for valaciclovir and had intra- and interassay variabilities of less than 5% at concentrations of 0.08 to 1.62 μg/mL. The lower limit of quantitation for valaciclovir in plasma was 0.06 μg/mL.

**Pharmacokinetic and statistical analyses.** The concentration versus time data for acyclovir in plasma obtained on days 1 and 30 were analyzed by noncompartmental methods to determine the following pharmacokinetic parameters: peak drug concentration in plasma (Cmax) and its time of occurrence (Tmax), apparent half-life (T1/2), and area under the plasma concentration versus time curve from time zero to infinity (AUC0-∞). Cmax and Tmax were determined by direct inspection of the data. T1/2 was calculated as 0.693λ, where λ is the slope of the apparent linear portion of the log drug concentration in plasma versus time curve. AUC0-∞ was determined by using the trapezoidal rule up to the last time point with measurable concentration (Cmeas) plus the extrapolated area to infinity, calculated as Cmeas/λ. AUC0-∞ on day 30 was corrected for the area attributable to residual drug concentration from the previous dose (or corrected to a single-dose condition) by subtracting C0λ, where C0 is the predose concentration on day 30.

Pharmacokinetic parameter estimates for acyclovir obtained on days 1 and 30 were compared within each patient for both dosing groups by a nonparametric method, the sign rank test.
In addition, pharmacokinetic parameter estimates for acyclovir obtained from the HIV-infected patients in this study were compared with those obtained previously from normal healthy volunteers (27) by the Wilcoxon rank sums test. A P value of <0.05 from the nonparametric tests is considered to be statistically significant.

RESULTS

Patient demographics and characteristics. Demographics and baseline characteristics of the HIV-infected patients enrolled in this study are summarized in Table 1. All patients had normal liver function as shown by the aspartate transaminase and alanine transaminase levels and had normal or minimally impaired renal function as shown by the estimated creatinine clearance rate (63.1 to 115.7 ml/min/1.73 m²). The baseline characteristics were similar among the two groups of patients with regard to age, weight, height, and the advanced stage of HIV disease as indicated by the absolute CD4⁺ counts and hemoglobin values. Additionally, both cohorts had similar histories of HIV-associated conditions with regard to episodes of candidiasis, Pneumocystis carinii pneumonia, Kaposis sarcoma, oral hairy leukoplakia, HSV infection, and VZV infec-
tion (data not shown). Of note, African-Americans and women were only represented in the 1,000-mg-dose group. Five vol-
unteers reported grade I nausea or diarrhea, and one volunteer reported grade II abdominal pain prior to initiation of study medication (graded per standard National Institute of Allergy and Infectious Diseases criteria).

All patients completed the single-dose phase, and all except two patients completed the multiple-dose phase of the study. One patient in the 2,000-mg-dose group withdrew from the study prematurely because of an adverse experience (neutropenia), and the other patient, in the 1,000-mg-dose group, was withdrawn prematurely because of noncompliance. Compli-
ance with study drug administration was assessed by pill counts of returned study medication containers.

Pharmacokinetics. Valaciclovir was rapidly absorbed and converted to acyclovir, with concentrations of valaciclovir in plasma that were either nondetectable or generally <0.4 μg/ml regardless of the dose administered. After 3 h postdosing, valaciclovir was not detectable in the plasma of any patient. No pharmacokinetic analysis was performed on the plasma data of valaciclovir because of its low and transient concentrations following oral dosing.

Concentrations of acyclovir in plasma were measurable as early as the first sampling time (15 min) following oral administration of valaciclovir. Mean acyclovir concentrations over a 24-h interval at steady state fluctuated between 1.83 and 5.54 μg/ml in the 1,000-mg-dose group and between 2.50 and 8.45 μg/ml in the 2,000-mg-dose group. The mean acyclovir concentration in plasma versus time curves obtained on days 1 and 30 and during the monitoring period from both cohorts are depicted in Fig. 1. The mean (±CV) values of the pharmacokinetic parameters for acyclovir obtained after single-dose (day 1) and multiple-dose (day 30) valaciclovir administration in the HIV-infected patients are listed in Table 2. T1/2, AUC₀–₂₄, and C₀–₁₂, are different between day 1 and day 30 at either dose (P > 0.05), indicating that acyclovir kinetics were unaltered and predictable after repeated admin-
istration of valaciclovir for 30 days. The observed C₀–₂₄ values of acyclovir were higher on day 30 than those on day 1 because of slight accumulation after multiple dosing. The ratios of mean C₀–₂₄ values of acyclovir were not significantly different between day 1 and day 30 at either dose (P > 0.05). On the basis of the mean estimates of pharmacokinetic parameters for acyclovir, the daily acyclovir AUC₀–₂₄ values at steady state (AUC₀–₂₄) were determined to be 66 and 120 h·μg/ml after dosages of 1,000 and 2,000 mg of valaciclovir four times daily, respectively. For comparison, the mean (±CV) steady-state values of acyclovir pharmacokinetic param-
eters following oral dosing of valaciclovir obtained from a previous study in normal healthy volunteers (27) for the 2,000-mg dose were C₀–₂₄ of 8.49 μg/ml (20%), T₁/₂ of 2.29 h (40%), AUC₀–₁₂ of 27.37 h·μg/ml (29%), and T₁/₂ of 3.18 h (6%). The mean T₁/₂, C₀–₂₄, and AUC₀–₂₄ values of acyclovir after single and multiple doses of valaciclovir at either dose were not statistically or clinically significantly different between the HIV-infected patients and healthy normal volunteers. These findings indicate that acyclovir pharma-
cokinetics following valaciclovir administration was unaltered by the disease conditions associated with HIV infection or by

### Table 1. Summary of patients’ demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1,000 mg</th>
<th>2,000 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>9</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/3</td>
<td>8/0</td>
<td>14/3</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ZDV</td>
<td>7</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>DDI or ddC</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ZDV and ddC</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ZDV or DDI as a (blinded) study drug</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* ZDV, zidovudine; DDI, didanosine; ddC, dideoxyctydine; AST, aspartate transaminase; ALT, alanine transaminase.

* Total number of patients and median values for both groups.
which included VAOL. 38, because of prematurely multiple the tion of ing adverse infected patients. complaint (nausea had had no adverse occurring the addition, only episode (diarrhea) and diarrhea probable a single- after 1,000 (V) and 2,000 mg (V) of valaciclovir in HIV-infected patients.

One patient in the 2,000-mg-dose group was discontinued prematurely because of a finding of neutropenia. Table 4 summarizes the median value and range for the ANC and hemoglobin for each cohort at baseline, on days 7, 14, 21, and 30, and at the posttreatment (follow-up) visit. The baseline value for each individual was determined as the average of measurements taken at screening and predose on day 1. In both cohorts, the median values for hemoglobin were similar at baseline and the posttreatment visit. In cohort 1, the median ANC values were slightly lower during the posttreatment period than at baseline, whereas in cohort 2 the median ANC

![Graph showing mean concentration versus time curves of acyclovir in plasma following single and multiple (four times daily) oral administration of 1,000 (■) and 2,000 mg (V) of valaciclovir in HIV-infected patients.]

FIG. 1. Mean concentration versus time curves of acyclovir in plasma following single and multiple (four times daily) oral administration of 1,000 (■) and 2,000 mg (V) of valaciclovir in HIV-infected patients.

<table>
<thead>
<tr>
<th>Dose group and day</th>
<th>No. of patients</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0→∞&lt;/sub&gt; (h·µg/mL)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 mg 1</td>
<td>8</td>
<td>4.84 (38)</td>
<td>2.01 (36)</td>
<td>20.1 (30)</td>
<td>3.32 (31)</td>
</tr>
<tr>
<td>1,000 mg 30</td>
<td>8</td>
<td>5.54 (29)</td>
<td>2.04 (52)</td>
<td>16.42 (19)</td>
<td>3.14 (11)</td>
</tr>
<tr>
<td>2,000 mg 1</td>
<td>7</td>
<td>6.69 (19)</td>
<td>2.51 (41)</td>
<td>30.42 (27)</td>
<td>3.07 (16)</td>
</tr>
<tr>
<td>2,000 mg 30</td>
<td>7</td>
<td>8.45 (24)</td>
<td>2.00 (37)</td>
<td>30.06 (26)</td>
<td>3.56 (7)</td>
</tr>
</tbody>
</table>

* Values in parentheses are % CV.

* AUC values on day 30 are corrected to a single-dose condition.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000-mg-dose group</td>
<td>2,000-mg-dose group</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>Elevated total bilirubin</td>
<td>1</td>
</tr>
<tr>
<td>Elevated ALT and/or AST*</td>
<td>1</td>
</tr>
</tbody>
</table>

* ALT, alanine transaminase; AST, aspartate transaminase.
values were slightly higher at the posttreatment visit. As shown in Table 5, four patients developed grade 3 or 4 neutropenia (ANC, <750 or <500 cells per μL) per standard National Institute of Allergy and Infectious Diseases criteria. One individual had a baseline ANC of <1,000 cells per μL and all four patients had an increase in ANC after valaciclovir was discontinued (at the follow-up exam [Table 5]). In addition, at 16 days after discontinuation of valaciclovir, the ANC in one patient (no. 201) reached 1,600 cells per μL. This patient was rechallenged with 2,000 mg of valaciclovir four times daily for 7 days without reduction of ANC.

CMV virology. At San Francisco General Hospital, one of eight (12.5%) patients at study entry and week 2 and none of the eight (0%) patients at week 4 had positive urine cultures for CMV.

Concomitant medications. All patients were being treated with some medication for prophylaxis against P. carinii pneumonia. The use of concomitant medications for HIV disease was similar in both cohorts. All but two patients were taking antiretroviral medications prior to study entry. As shown in Table 1, seven patients in cohort 1 and three patients in cohort 2 were taking zidovudine, and one patient in cohort 1 and three patients in cohort 2 were taking either didanosine or dideoxycytosine. One patient was on combination therapy of zidovudine and dideoxycytosine. An additional patient was on zidovudine or didanosine as a study drug in a blinded clinical trial.

DISCUSSION

In patients with advanced HIV disease, the kinetics of acyclovir disposition after multiple doses of 1,000 or 2,000 mg of valaciclovir (four times daily) was unchanged compared with that after single-dose administration. Estimates of the acyclovir pharmacokinetic parameters (Cmax, fmax, AUC0→∞, and T1/2) obtained for the HIV-infected patients were similar to those reported in a phase 1 valaciclovir study of normal healthy volunteers. These results suggest that the pharmacokinetics of acyclovir following multiple oral administration of valaciclovir is unaltered in patients with advanced HIV disease who also received multiple concomitant medications.

The steady-state peak and trough acyclovir concentrations and daily acyclovir AUC values obtained after administration of 1,000 and 2,000 mg of valaciclovir four times daily were approximately three to five times greater than those observed previously after high oral doses of acyclovir (800 mg five times daily) and were comparable to those observed after intravenous doses of acyclovir (5 to 10 mg/kg every 8 h) in patients with normal renal function (3, 7). In addition, the intersubject variability in concentrations of acyclovir in plasma following administration of valaciclovir was less than that after administration of acyclovir itself (CV for AUCₜₐₛₘₛₐₖ <30% versus 40%) (27). The increased bioavailability of acyclovir after oral administration of valaciclovir may offer a therapeutic advantage by improving efficacy and dosing convenience and extending the range of viral infections amenable to oral therapy.

In the present study, the steady-state acyclovir Cₚₚₛₙ and AUCₚₘₐₓ values achieved with valaciclovir administration in HIV-infected patients are comparable to those obtained in transplant patients who were effectively protected against CMV disease with intravenous acyclovir (for bone marrow transplant patients) or high doses of oral acyclovir (for renal transplant patients) (2, 9, 11, 18, 20). Thus, 2,000 mg of valaciclovir administered four times daily may be effective in preventing opportunistic CMV disease and other herpesvirus infections in HIV-infected patients. Because up to 30% of patients with AIDS develop CMV end organ disease (12, 14, 16, 22), we are now conducting a multicenter, prospective, actively controlled study to evaluate the prophylactic efficacy of valaciclovir (2,000 mg four times daily) in HIV-infected patients with fewer than 100 CD4 lymphocytes per μL. The rationale for this study is also supported by the results of a recent prospective, uncontrolled trial in which high doses of intravenous acyclovir had some beneficial effect as a suppressive therapy for AIDS-related CMV retinitis after ganciclovir induction (24).

In our phase I trial, too few subjects were secreting CMV in urine to draw any conclusion about valaciclovir efficacy in inhibiting CMV replication in vivo.

While no dose-related adverse events were observed in this phase I trial, nausea, vomiting, diarrhea, and abdominal pain each were reported in approximately one-third of the patients during the 30-day period of valaciclovir exposure. Since gastrointestinal symptoms, particularly diarrhea, have been re-
ported to occur in two-thirds of, or more, patients with AIDS (1, 13, 17, 23), it is difficult in this study to attribute such symptoms specifically to valaciclovir exposure without a placebo control unless causality can be established by methods such as drug rechallenge. In only one volunteer who reported diarrhea was a causal association between gastrointestinal symptoms and valaciclovir exposure considered to be probable. Although all patients had an ANC of ≥750 cells per μl at entry in this trial, neutropenia with an ANC of <500 cells per μl occurred in three (19%) individuals (two in the 1,000-mg-dose group and one in the 2,000-mg-dose group), all of whom recovered after valaciclovir was discontinued (Table 5). Of note, one of these three individuals was concomitantly receiving zidovudine. In addition, one patient who was rechallenged with 2,000 mg of valaciclovir for 7 days did not have a decreased ANC. Previous studies of high doses of oral and intravenous acyclovir in immunocompromised patients, including those with advanced HIV disease, have not reported myelosuppression as an adverse experience (2, 5, 6, 11, 20). In addition, acyclovir is not toxic to bone marrow progenitor cells in vitro (19). However, it is known that patients with advanced HIV disease frequently become neutropenic, because of a variety of etiologies including the common use of myelosuppressive drugs and other AIDS-related opportunistic infections and malignancies as well as a possible direct effect of HIV on myeloid precursors (28). An actively controlled trial of valaciclovir in advanced HIV disease, currently being conducted, should determine if the neutropenia observed in this phase I trial was due to an effect of high doses of valaciclovir or acyclovir exposure, concomitant medications, or other factors related to HIV disease.

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REFERENCES

