An Investigation of the Steady-State Pharmacokinetics of Oral Valacyclovir in Immunocompromised Children

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Valacyclovir was administered to 28 immunocompromised children (ages 5–12 years) to obtain preliminary pharmacokinetic and safety information. Patients were randomized to valacyclovir regimens of 250 mg (9.4–13.3 mg/kg) or 500 mg (13.9–27.0 mg/kg) twice daily or 500 mg (13.2–21.7 mg/kg) 3 times a day. Acyclovir pharmacokinetics were evaluated at steady state. Valacyclovir was rapidly absorbed and converted to acyclovir. Mean (±SD) acyclovir peak concentrations from 250 mg and 500 mg valacyclovir were 4.11 ± 1.41 and 5.19 ± 1.96 μg/mL, respectively. Corresponding single dose area-under-curve values were 12.14 ± 6.60 and 14.49 ± 4.69h × μg/mL. By using historical data for intravenous acyclovir as reference, the overall estimate of acyclovir bioavailability from valacyclovir was 48%, 2- to 4-fold greater than for oral acyclovir. In general, adverse events were not attributable to valacyclovir and were consistent with disease-related expectations and concomitant therapies. Dosage options for using valacyclovir in children are discussed.

Herpesvirus infections are very common but can be severe and even life threatening in immunocompromised persons [1]. Oral acyclovir is safe and effective for the management of herpes simplex virus (HSV) [2, 3] and varicella-zoster virus (VZV) infections [4–7] and has been used for prophylaxis against cytomegalovirus infection in organ transplant recipients [8, 9]. However, its low oral bioavailability (~10%–20%) coupled with its rapid elimination necessitates frequent dosing (up to 5 times/day) [3, 10, 11]. Intravenous infusion of acyclovir provides increased acyclovir exposure and allows the treatment of more severe or the complicated infections seen in immunocompromised persons [10].

The pharmacokinetics of acyclovir was studied in children with normal renal function for age and who were at risk of HSV or VZV infections [12, 13]. After intravenous administration, pharmacokinetic characteristics in those aged ⩾1 year appeared similar to those of adults. The average plasma elimination half-life was 2.5 h, and there was little or no evidence of drug accumulation on repeat dosing. Acyclovir clearance among children aged 2–12 years averaged (±SD) 360 ± 120 mL/min/1.73m^2 and did not differ appreciably across the age range; this value is comparable with that reported for adults (327 ± 80 mL/min/1.73m^2) [12]. In children aged 6 months to 7 years given oral acyclovir suspension, the average acyclovir bioavailability following a weight-normalized dose of 25 mg/kg was about 11% [13]. This estimate is similar to that for adults receiving high oral doses of 800 mg [12].

Valacyclovir is an oral prodrug of acyclovir that can produce systemic acyclovir exposures similar to those observed after intravenous acyclovir infusion in both immunocompetent and immunocompromised subjects [14–17]. Estimates of average acyclovir bioavailability from oral valacyclovir in different adult populations are 54%–70%. Current clinical experience with valacyclovir in children is extremely limited [18–20], but clinicians have wide interest in its use in children because of its potential to achieve higher systemic acyclovir concentrations than are possible with oral acyclovir, the possibility of less frequent dosing regimens for HSV treatment and prophylaxis, and because the need for intravenous acyclovir administration could

The study was approved by an ethics committee or institutional review board appropriate for each participating study center and was conducted in accordance with the Declaration of Helsinki of June 1964, as revised in 1996. Each patient's parent or guardian gave written informed consent before the start of the study.

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be minimized, potentially allowing the convalescent child to be treated at home.

The purpose of this pilot study was to provide preliminary steady-state pharmacokinetic and safety information for acyclovir after oral valacyclovir administration to immunocompromised children. The 250- and 500-mg doses of valacyclovir administered 2 or 3 times a day in this study correspond to doses (milligram/square meter/day) similar to those from approved regimens for prophylaxis or treatment of HSV infection in immunocompromised adults (500 or 1000 mg twice/day, respectively) or for VZV treatment in immunocompetent adults (1000 mg 3 times/day).

Materials and Methods

Patient selection. Children aged 5–12 years with a body surface area (BSA) of 0.6–1.25 m^2 were eligible for study participation if they were hospitalized, immunocompromised as a result of disease or its treatment (e.g., cancer chemotherapy, human immunodeficiency virus infection [HIV], or organ transplant recipient), considered at risk for HSV or VZV infection, required antiviral therapy, and were able to take oral medication. Patients were excluded if they had creatinine clearance <80 mL/min/1.73m^2 BSA, acute or unstable heart failure, impaired liver function (aspartate transaminase or alanine transaminase >5 times the upper limit of normal), malabsorption syndrome (vomiting, mucositis, or other gastrointestinal dysfunction that could affect drug absorption), a history of hypersensitivity to acyclovir or valacyclovir, or participated in a clinical trial with a new chemical entity within 2 weeks of screening. Other reasons for exclusion were concurrent therapy with probenecid, theophylline, mycophenolate mofetil, or systemic acyclovir.

Study design and procedures. This was an open-label, randomized, parallel group, multicenter study conducted at six sites in France, Switzerland, and Belgium. At prestudy screening, the patients' characteristics were recorded, a brief medical history was obtained, and other evaluations for study eligibility were performed, including physical examination, 12-lead electrocardiogram, hematologic assessment, clinical chemistries, and urinalysis. When feasible, creatinine clearance was estimated from a 24-h urine collection; otherwise it was calculated from body height and serum creatinine according to the method of Schwartz et al. [21]. A blood sample was also obtained to monitor for any thrombotic microangiopathy (TMA)-like symptoms. TMA was suspected in a child with microangiopathic hemolytic anemia (schistocytosis and anemia) and thrombocytopenia and either renal abnormality (serum creatinine assessment and urinalysis) or neurologic abnormality and fever.

Patients were randomized (day 0) by use of a computer-generated randomization schedule into 1 of 4 groups (nominally 6 patients per group) according to BSA. Those with BSA of 0.6–0.89 m^2 were randomized to either 250 mg (group 1) or 500 mg (group 2) of valacyclovir every 12 h; those with BSA of 0.9–1.25 m^2 were randomized to either 500 mg every 12 h (group 3) or 500 mg of valacyclovir every 8 h (group 4). Valacyclovir was administered for a minimum of 5 doses. Pharmacokinetic sampling was done after the first dose on day 3 (i.e., after 5 doses for subjects on twice daily regimens or after 7 doses for subjects on the 3 times/day regimen).

Valacyclovir was administered as 250-mg tablets (supplied by GlaxoSmithKline, UK) swallowed with either 5–10 mL of syrup BP (66.7% sucrose in water), immediately followed by an additional 100 mL of syrup BP, or swallowed with a comparable volume of water or juice. Valtrex tablets were taken with syrup BP, if possible, to aid in swallowing. Each dose was consumed within a 5-min interval. Due to its interference with the valacyclovir assay, patients were not permitted to consume any artificial sweetener containing aspartame from days 0 to 4. Patients refrained from consuming caffeine-containing foods or beverages from midnight on day 2 until 12 h after administration of the morning dose on day 3. Unless considered to interfere with adequate nutrition and hydration for the individual, patients fasted from midnight on day 2 until 2 h after the morning dose on day 3 and did not drink any fluids for a 2-h period after the day-3 dose.

Sample collection and analysis. In association with the morning dose on day 3, 2-mL blood samples were taken via a cannula inserted into a forearm vein or via an already existing cannula or central venous catheter just before drug administration and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after dosing. For all samples, a small volume of blood was aspirated and discarded prior to collection for drug concentration assays. The plasma was separated and stored frozen at −40°C prior to analysis of valacyclovir and acyclovir concentrations by previously validated methods. Acyclovir was analyzed by scintillation proximity RIA [22] and valacyclovir was assayed by high-performance liquid chromatography with UV detection [15]. Samples were diluted into the validated calibration ranges of 1.4–90 ng/mL (6.2–400 nM) for acyclovir and 80–3243 ng/mL (0.25–9.99 μM) for valacyclovir. Accuracy (% bias) and precision (% coefficient of variation) were calculated by using interpolated concentrations of quality control samples at 3 concentration levels. Accuracy and precision were less than or equal to ±6.8% and 15%, respectively, for acyclovir assays and were less than or equal to ±4.6% and 12%, respectively, for valacyclovir assays. The lower limits of quantitation were 14 ng/mL for acyclovir and 80 ng/mL for valacyclovir.

Pharmacokinetic analyses. Plasma concentration time data were analyzed by standard noncompartmental pharmacokinetic methods with use of WinNonlin Pro software (v3.0; Pharsight). The observed peak concentration (C_{max}) and the time to reach peak concentration (T_{max}) were taken directly from the observed concentration time profiles. The elimination rate constant (λ) was obtained from regression of data in the terminal log linear portion of the concentration time profile for each subject and the plasma elimination half-life ($T_{1/2}$) was calculated as $T_{1/2} = \ln 2/\lambda$. The area under the plasma concentration time curve ($AUC_{0-\tau}$) over a steady-state dosing interval of duration τ (where $\tau = 8$ or 12 h) was calculated by using log linear trapezoidal approximation. For acyclovir, apparent oral clearance (CL/F) was calculated as dose/$AUC_{0-\infty}$ and apparent volume of distribution (Vz/F) was determined as (CL/F)/λ. Since acyclovir constitutes 69.4% of valacyclovir, in estimation of acyclovir CL/F, the value for "dose" was taken to be equal to 0.694 times the valacyclovir dose, reflecting the maximum amount of acyclovir systemically available upon complete absorption and deesterification of the prodrug to acyclovir.

Statistical analyses. Statistical analysis to obtain information on dose proportionality and to assess pharmacokinetic differences related to age or body size was conducted by comparing results between selected cohorts. Group 1 (250 mg twice a day; BSA 0.6–0.89 m^2) and group 2 (500 mg twice a day; BSA 0.6–0.89 m^2) were compared for dose proportionality and groups 2 and 3 (500 mg twice a day; BSA 0.9–1.25 m^2) were compared for potential effects of age and/or body size on pharmacokinetics. For the dose proportionality comparison between groups 1 and 2, values for C_{max}, trough acyclovir concentration (C_{min}), and $AUC_{0-\infty}$ from the 250-mg dose were first normalized to a 500-mg dose. Groups 3 and 4 were also evaluated for pharmacokinetic differences between 500 mg at 2 and 3 times a day dosing. Log transformed C_{max}, $AUC_{0-\infty}$, and $T_{1/2}$ were analyzed separately by use of analysis of variance. Comparative estimates between groups were based on the ratio of the geometric least square means (LS_{mean}) with the associated 90% confidence interval (90% CI) (Statistical Analysis Systems, SAS Institute).

Safety assessments. In addition to laboratory evaluations at prestudy screening, blood samples were taken on day 4 for serum creatinine analysis for TMA and 14 days after study completion for final assessment of hematology, plasma biochemistry, TMA-related analysis, and urinalysis. Adverse events were monitored from the start of dosing until poststudy follow-up. All adverse events were categorized by severity (mild, moderate, or severe), seriousness, and the physician's considered relationship to study drug. Safety data and laboratory evaluations were assessed without inferential analysis.

Results

Patients. In total, 28 immunocompromised children aged 5–12 years were enrolled in the study and received at least 1 dose of study drug. However, only 24 subjects had evaluable pharmacokinetic data for analysis (see below). Table 1 summarizes the characteristics at enrollment of these 24 subjects. Most children (13 of 24) were immunocompromised due to leukemia, 3 were liver transplant recipients, 1 was a bone marrow transplant (BMT) recipient, 2 were infected with HIV, and 1 each were diagnosed with rhabdomyosarcoma, Ewing's sarcoma, anaplastic lymphoma, histiocytosis-X, and Wiskott-Aldrich syndrome. The pharmacokinetic population consisted of 16 boys and 8 girls and all presented with normal renal function as characterized by estimated creatinine clearance.

Two subjects withdrew prematurely from the study and 2 were excluded from the pharmacokinetic analysis. Two subjects received drug only on the first day of dosing. One of these subjects, an 8-year-old BMT recipient, was withdrawn from the study due to vomiting thought to be associated with increasing intestinal graft-versus-host disease. Oral medication was no longer considered advisable and she was treated with intravenous acyclovir. The other child, a 5-year-old liver transplant patient, withdrew after 2 doses because of difficulty swallowing study drug tablets. Two other children received the minimum number of doses according to the protocol prior to pharmacokinetic sampling, but either no samples were collected (a 6-year-old girl with acute lymphoblastic leukemia in group 2) or data were excluded from analysis (an 11-year-old girl BMT patient in group 4). The latter subject vomited after the morning dose on day 3 and shortly thereafter received a second dose. Data for this subject were excluded from the pharmacokinetic analysis because of the uncertainty of ingested dose amount just prior to and during pharmacokinetic sampling.

Valacyclovir and acyclovir pharmacokinetics. Valacyclovir was rapidly absorbed and converted to acyclovir. Plasma concentrations of the unchanged prodrug were below the lower limit of quantitation (0.08 μg/mL) for all subjects within 4 h after dosing. Measurable valacyclovir concentrations were not available for estimation of elimination rate, half-life or $AUC_{0-\infty}$. Nine subjects (4 of 8 in group 1, 1 of 5 in each of groups 2 and 3, and 3 of 6 in group 4) had no quantifiable valacyclovir concentrations at any time point. Plasma valacyclovir concentrations were <0.5 μg/mL at all sampling times. Mean ($\pm$SD) peak valacyclovir concentrations were 0.09 ± 0.12, 0.20 ± 0.17, 0.26 ± 0.17, and 0.13 ± 0.19 μg/mL for groups 1–4, respectively. The corresponding postdose sampling times for subjects with measurable concentrations were 1.00, 1.75, 1.13, and 1.50 h, respectively.

Table 2 lists pharmacokinetic parameter estimates for acyclovir after multiple dose valacyclovir administration. The mean ($\pm$SD) values for C_{max} were 4.11 ± 1.41, 5.17 ± 2.13, 5.12 ± 2.12, and 5.27 ± 2.08 μg/mL for groups 1–4, respec-

Table 1. Summary characteristics at screening for children included in pharmacokinetic analyses.

Group, valacyclovir regimen	Diagnosis	Age, years median (range)	Boys/ girls	Weight, kg median (range)	Height, cm median (range)	BSA, m^2 median (range)	CL_{cr}, mL/min median (range)
Group 1 ($n = 8$), 250 mg (2×/day)	ALL, LT, 3 each; RMS, HIV, 1 each	6.5 (5–9)	4/4	21.7 (18.8–26.5)	119.5 (101–125)	0.81 (0.66–0.88)	114 (101–139)
Group 2 ($n = 5$) 500 mg (2×/day)	ALL, 3; AnL, H-X, 1 each	5.0 (5–8)	4/1	22.0 (18.5–25.0)	114 (110–121)	0.77 (0.70–0.84)	130 (120–155)
Group 3 ($n = 5$), 500 mg (2×/day)	ALL, 3; BMT, HIV, 1 each	11 (11–11)	4/1	30.0 (26.0–36.0)	144 (128–153)	1.03 (0.90–1.16)	118 (107–127)
Group 4 ($n = 6$), 500 mg (3×/day)	ALL, 3; AML, ES, WAS, 1 each	11 (8–12)	4/2	30.5 (23.0–38.0)	139 (122–145)	1.05 (0.82–1.12)	121 (101–189)

NOTE. ALL, acute lymphoblastic leukemia; AML, acute megaloblastic leukemia; AnL, anaplastic lymphoma; BMT, bone marrow transplant; BSA, body surface area; CL_{cr}, estimated creatinine clearance; ES, Ewing's sarcoma; HIV, human immunodeficiency virus infection; H-X, histiocytosis-X; LT, liver transplant; RMS, rhabdomyosarcoma; WAS, Wiskott-Aldrich syndrome.

Table 2. Summary pharmacokinetic parameters for acyclovir from valacyclovir administration.

	Body surface area 0.6–0.9 m^2				Body surface area 0.9–1.25 m^2			
	Group 1 (n = 8), 250 mg 2×/day		Group 2 (n = 5), 500 mg 2×/day		Group 3 (n = 5), 500 mg 2×/day		Group 4 (n = 6), 500 mg 3×/day	
Parameter	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Mean ± SD	Median (range)
C_{max} (μg/mL)	4.11 ± 1.41	3.95 (1.98–6.73)	5.17 ± 2.13	6.23 (2.19–7.13)	5.12 ± 2.12	4.67 (2.82–7.55)	5.27 ± 2.08	5.89 (2.43–7.21)
T_{max} (h)	2.19 ± 0.75	2.00 (1.00–3.00)	2.57 ± 0.76	3.00 (1.50–3.28)	1.41 ± 0.39	1.50 (1.00–1.98)	2.62 ± 0.48	2.90 (2.00–3.00)
$AUC_{0-\tau}$ (h × μg/mL)	12.14 ± 6.60	10.14 (7.82–28.11)	15.35 ± 4.62	15.84 (9.03–21.70)	13.26 ± 4.56	14.00 (8.29–18.31)	14.80 ± 5.47	14.37 (7.28–21.30)
$T_{1/2}$ (h)	2.11 ± 0.35	2.06 (1.72–2.71)	2.00 ± 0.37	1.95 (1.66–2.54)	2.51 ± 0.28	2.48 (2.14–2.79)	2.34 ± 0.40	2.23 (1.96–2.99)
CL/F, mL/min	275 ± 82	285 (103–370)	409 ± 141	365 (267–640)	485 ± 179	413 (316–698)	448 ± 195	408 (271–794)
mL/min/m^2	349 ± 92	382 (154–456)	536 ± 174	508 (346–821)	478 ± 193	401 (315–775)	430 ± 149	387 (299–709)
mL/min/kg	12.5 ± 3.3	13.5 (5.5–16.4)	19.0 ± 5.7	18.8 (12.1–27.8)	16.1 ± 6.7	13.8 (9.9–26.8)	14.6 ± 5.1	12.8 (11.4–24.8)
Vz/F, L	48.7 ± 13.7	48.6 (24.1–69.5)	69.7 ± 21.6	61.5 (50.6–93.7)	105.1 ± 37.5	99.2 (58.4–150.0)	87.8 ± 33.2	75.5 (61.3–147.8)
L/m^2	61.8 ± 14.3	60.4 (36.0–85.8)	90.7 ± 23.5	87.9 (65.7–117.8)	103.5 ± 40.8	96.3 (62.1–166.6)	85.0 ± 25.1	76.1 (62.6–131.9)
L/kg	2.21 ± 0.55	2.12 (1.28–3.08)	3.21 ± 0.70	3.25 (2.30–3.99)	3.49 ± 1.43	3.31 (2.21–5.77)	2.90 ± 0.89	2.70 (2.16–4.62)

NOTE. $AUC_{0-\tau}$, area under concentration-time curve over a steady state dosing interval of duration τ; CL/F, apparent oral clearance; C_{max}, peak concentration; $T_{1/2}$, elimination half-life; T_{max}, time to peak concentration; Vz/F, apparent volume of distribution.

tively. Estimates for $AUC_{0-\tau}$ over one steady-state dosing interval, theoretically equal to AUC from time zero to infinity (i.e., $AUC_{0-\infty}$) after a single dose, were 12.14 ± 6.60, 15.35 ± 4.62, 13.26 ± 4.56, and 14.80 ± 5.47h × μg/mL for groups 1–4, respectively. One subject in group 1, a 7-year-old liver transplant patient, had an unusually high $AUC_{0-\tau}$ (28.11h × μg/mL) relative to other children receiving the 250-mg dose and, in fact, had the highest AUC estimated for all children in the study. Exclusion of this patient's estimate resulted in an $AUC_{0-\infty}$ for group 1 of 9.86 ± 1.51 h × μg/mL.

The plasma $T_{1/2}$ was similar among cohorts, with mean values of 2.06–2.48 h. These half-life estimates indicate that attainment of steady state was assured by the time of pharmacokinetic sampling on day 3 of dosing. Apparent oral clearance and volume of distribution appear lower for group 1 relative to the other cohorts, possibly reflecting the higher bioavailability for the lower 250-mg dose. Normalization of apparent clearance and volume of distribution to either body weight or BSA resulted in estimates generally showing somewhat smaller variability (coefficient of variation) compared with the nonnormalized parameters. With the exception of the 1 patient with high $AUC_{0-\infty}$, acyclovir pharmacokinetics in the liver transplant patients (all 3 in group 1) were similar to those observed for the other subjects who received the 250-mg twice a day regimen.

Table 3 shows the statistical evaluations of dose proportionality and of the effect of age and/or body size on acyclovir pharmacokinetics. For the dose proportionality assessment (group 1 vs. group 2), dose-normalized comparisons of acyclovir pharmacokinetic parameters indicated that C_{max} and $AUC_{0-\infty}$ from the 250-mg dose were greater than would be expected for dose-independent kinetics. The LS_{mean} ratio (90% CI) for C_{max} was 1.64 (1.08–2.51), P = .057 and for $AUC_{0-\infty}$ 1.51 (1.04–2.19), P = .073. The high ratios probably reflect a decrease in acyclovir bioavailability with the higher valacyclovir dose. There were no differences detected in values for C_{min} or $T_{1/2}$ between these cohorts.

In assessment of the effects of age and/or size on pharmacokinetics (group 2 vs. group 3), no differences were found in C_{max}, C_{min}, or $AUC_{0-\infty}$. $T_{1/2}$ appeared somewhat shorter in the younger/smaller children (LS_{mean} ratio, 0.79 [90% CI, 0.67–0.94], P = .03). Acyclovir pharmacokinetics was very similar between groups 3 and 4, with the anticipated exception of lower trough concentrations from valacyclovir administration twice a day as compared with 3 times a day (LS_{mean} ratio, 0.28 [90% CI, 0.14–0.57], P = .006).

Safety. In all, 67 adverse events were reported for 18 of the 28 subjects enrolled. The most common were pain (27 reports in 13 patients; e.g., headache, abdominal, or gastrointestinal pain), fever (9 observations in 7 patients), and vomiting and diarrhea (4 patients each). One child reported dizziness. Adverse events were generally considered mild or moderate in intensity and consistent with disease and treatment expectations for the children in the study. Most children with adverse events (11/18) had acute lymphoblastic leukemia and 10 of the 13 with this diagnosis received chemotherapy during study participation. No child discontinued therapy because of an adverse event.

Only 1 adverse event, a mild increase in haptoglobin in a patient with acute lymphoblastic leukemia observed 5 days after administration of the last of 5 500-mg valacyclovir doses, was thought possibly to be related to valacyclovir; the event was not considered serious. One acute lymphoblastic leukemia patient died of septic shock after participating in the study for 6 days. The only other serious adverse event was a case of gastrointestinal viral infection with mild and intermittent viral diarrhea beginning 2 days after the onset of dosing in a 5-year-old boy in group 2 with histiocytosis-X. The event was considered unrelated to study drug and resolved within 2 days without dosage adjustment. There were no other serious adverse event reports. One case of severe mucositis in a 5-year old with lymphoblastic leukemia that started 5 days after the end of valacyclovir administration was treated and resolved

Table 3. Summary of statistical analysis (ANOVA) of acyclovir pharmacokinetic parameters after valacyclovir administration to children.

Parameter, group comparison (test vs. reference)	Geometric LS_{mean}		Test reference ratio (90% CI for ratio)	ANOVA *P* value
	Test	Reference		
$AUC_{0-\infty}$ (h × μg/mL)				
Group 1 vs. group 2	22.28[a]	14.76	1.51 (1.04–2.19)	.073
Group 2 vs. group 3	14.76	12.59	1.17 (0.77–1.78)	.52
Group 3 vs. group 4	12.59	13.88	0.91 (0.61–1.35)	.68
C_{max} (μg/mL)				
Group 1 vs. group 2	7.79[a]	4.74	1.64 (1.08–2.51)	.057
Group 2 vs. group 3	4.74	4.76	0.99 (0.62–1.59)	.98
Group 3 vs. group 4	4.76	4.87	0.98 (0.62–1.53)	.93
C_{min} (μg/mL)				
Group 1 vs. group 2	0.14[a]	0.12	1.17 (0.60–2.28)	.69
Group 2 vs. group 3	0.12	0.10	1.19 (0.57–2.50)	.68
Group 3 vs. group 4	0.10	0.36	0.28 (0.14–0.57)	.006
$T_{1/2}$ (h)				
Group 1 vs. group 2	2.08	1.98	1.05 (0.90–1.23)	.59
Group 2 vs. group 3	1.98	2.50	0.79 (0.67–0.94)	.030
Group 3 vs. group 4	2.50	2.31	1.08 (0.92–1.28)	.42

NOTE. $AUC_{0-\infty}$, area under concentration-time curve; C_{max}, peak concentration; C_{min}, trough concentration; CI, confidence interval; $T_{1/2}$, elimination half-life.

[a] $AUC_{0-\infty}$, C_{max}, and C_{min} for 250-mg dose (group 1) were normalized to 500 mg for dose proportionality comparison.

with intravenous acyclovir. All other adverse events were mild or moderate in intensity.

Serum creatinine measurements on study day 4 and at follow-up showed no changes relative to prestudy screen. Median serum creatinine values from all subjects at baseline, day 4, and at follow-up were 49, 50, and 49 μM (or 0.6 mg/dL at each assessment), respectively. As for this overall result, there were no apparent changes in serum creatinine within dose groups. Similarly, there were no other apparent changes in hematology or clinical chemistry that were considered clinically significant or related to valacyclovir administration. Monitoring for development of TMA-like events revealed no signs or symptoms suggestive of this diagnosis.

Discussion

In this pilot study, we obtained preliminary pharmacokinetic, safety, and tolerability information for valacyclovir after multiple dose oral administration to immunocompromised children aged 5–12 years. The 250- and 500-mg valacyclovir regimens appeared to be well tolerated, and adverse events were consistent with disease-related expectations and concomitant medications received by the immunocompromised children. Serum creatinine levels remained unchanged relative to baseline in the study as a whole and in individual dose groups. No signs or symptoms that could relate to TMA were observed.

At the 500-mg twice a day valacyclovir dosage, no apparent differences in acyclovir pharmacokinetics were observed between cohorts of different age or body size (group 2 vs. group 3, table 3). However, such differences may not have been detectable in this pilot investigation due to the small number of subjects per cohort and enrollment of subjects ⩾5 years old.

Differences in dose-normalized acyclovir pharmacokinetic parameters from patients of comparable age and size who received 250 compared with 500 mg of valacyclovir doses (group 1 vs. group 2, table 3) suggest a decrease in acyclovir bioavailability with increasing dose. In a previous study, the average acyclovir systemic clearance from intravenous acyclovir administration to immunocompromised children aged 2–12 years was 360 ± 120 mL/min/1.73m^2 [12]. In the current study, the average CL/F estimate (normalized to comparable units) from all subjects was 753 ± 270 mL/min/1.73m^2, suggesting that acyclovir bioavailability averaged about 48% overall. However, the mean (±SD) CL/F estimate was 603 ± 159 mL/min/1.73m^2 for the children who received 250 mg of valacyclovir and 827 ± 286 mL/min/1.73m^2 for those receiving 500 mg of valacyclovir. Compared with the acyclovir clearance from intravenous dosing, these CL/F values indicate that acyclovir bioavailability was about 60% from the 250-mg dose (mean, 11.6 mg/kg of valacyclovir; range 9.4–13.3) and about 44% from the 500-mg dose (mean, 19.0 mg/kg of valacyclovir; range, 13.2–27.0). These estimates are consistent with observations of dose-dependent acyclovir bioavailability and similar in range to estimates of 42%–64% from valacyclovir administration to adults [14, 15]. In addition, the overall estimate of 48% is similar to the absolute bioavailability estimate of 45% in studies [18] of immunocompromised children given intravenous acyclovir and oral valacyclovir.

As with previous findings in adults [14, 15], valacyclovir was rapidly absorbed and converted to acyclovir in children. In comparison with adults with normal renal function who received doses of 250 and 500 mg of valacyclovir [15], mean (±SD) acyclovir peak concentrations were higher in the children (250 mg, 2.20 ± 0.39 vs. 4.11 ± 1.41 μg/mL; 500 mg, 3.37 ± 0.97 vs. 5.19 ± 1.96 μg/mL for groups 2–4 combined). Similarly, acyclovir AUC values after valacyclovir dosing in children were greater than for adults (250 mg, 5.68 ± 0.82 vs. 9.86 ± 1.51 h × μg/mL; 500 mg, 11.13 ± 1.75 vs. 14.49 ± 4.69 h × μg/mL for groups 2–4 combined). Given the apparent similarity in bioavailability, the higher acyclovir exposures seen in children at these fixed dose levels of valacyclovir probably reflect the higher doses in children relative to body size. On a body weight basis, the 250- and 500-mg doses administered to the children in this study ranged from 9.4 to 27.0 mg/kg. In contrast, comparable doses in adult men of normal weight (70–75 kg) would correspond to valacyclovir doses of 750–2000 mg.

Figure 1 shows C_{max} and AUC values based on body weight for children and adults. Children and adults experience similar decreases in acyclovir bioavailability with increasing valacyclovir dose. The renal excretion of acyclovir suggests that the lower C_{max} and AUC values for children at a given milligram per kilogram (mg/kg) dose reflect the higher renal clearance in chil-

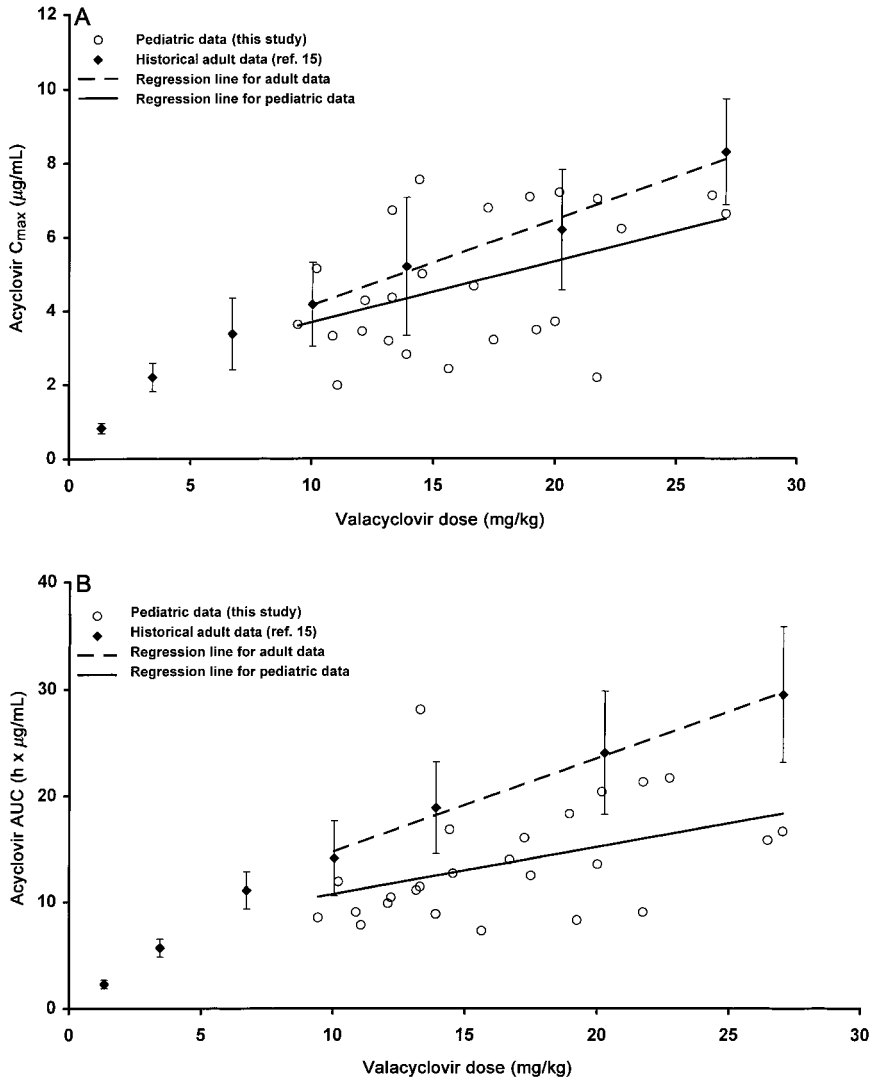

Figure 1. Valacyclovir administration to immunocompromised children. *A,* Acyclovir peak concentration (C_{max}). *B,* Acyclovir area under concentration time curve ($AUC_{0-\infty}$) over a steady-state dosing interval. Linear regression results for children given valacyclovir doses based on mg/kg body weight. For comparison (mg/kg basis), historical results (mean ± SD) from healthy adults given fixed doses of 100, 250, 500, 750, 1000, 1500, and 2000 mg of valacyclovir are displayed (data from [15]).

dren compared with adults. Given comparable bioavailability, comparison of the regression lines for AUC in figure 1*B* suggests that acyclovir renal clearance was about 1.5 times greater for children 5–12 years old in this trial than for adults. This is consistent with normal age-related changes in renal function [23].

In this study we observed slightly reduced variability in parameter estimates for clearance and volume of distribution when these were normalized to either body weight or BSA (table 2). Although the variabilities were similar whether normalized by weight or BSA, dosing on the basis of body weight is simple and convenient.

Intravenous acyclovir regimens of 10 or 20 mg/kg every 8 h or of 250 or 500 mg/m^2 every 8 h are used for the treatment or prophylaxis of herpesvirus infections in adults and children. Assuming an acyclovir systemic clearance of 360 ± 120 mL/min/1.73m^2 in children after intravenous acyclovir [12], intravenous administration of 250 mg/m^2 of acyclovir every 8 h should provide a mean (±SD) daily AUC (AUC_{0-24}) of 60 ± 20h × μg/mL in children with normal renal function. Figure 2 displays the range of daily acyclovir AUC values resulting from this intravenous regimen along with estimates for individual subjects from 3 times a day oral valacyclovir administration data generated in the current study.

Modest extension of the regression line suggests that a daily acyclovir AUC value comparable to that from 250 mg/m^2 in-

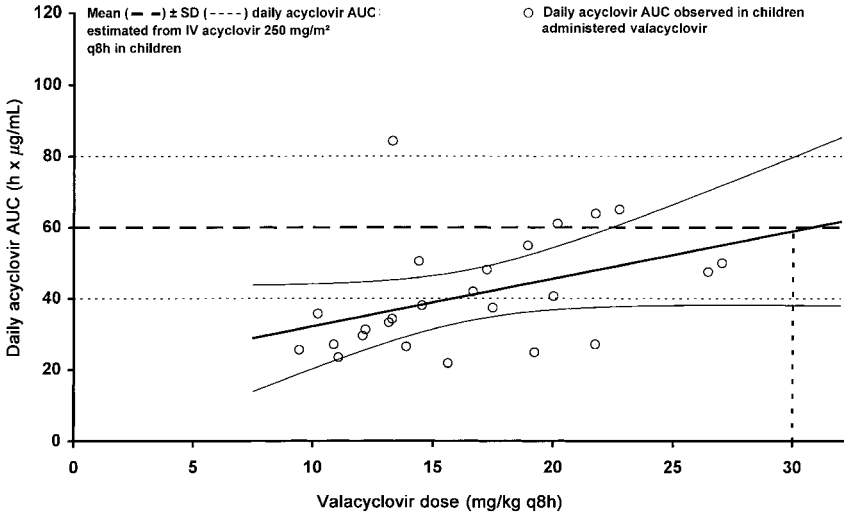

Figure 2. Mean daily acyclovir AUC from oral valacyclovir administration (mg/kg) every 8 h (○) compared with mean ± SD estimate from intravenous acyclovir 250 mg/m^2 every 8 h in immunocompromised children. Best-fit line (solid line) and its 95% confidence interval (dashed line) from regression of daily AUC on mg/kg dose are displayed. Intravenous acyclovir AUC was estimated by assuming an acyclovir systemic clearance of 360 ± 120 mL/min/1.73m^2 [12].

travenous acyclovir 3 times a day would be obtained with a valacyclovir regimen of about 30 mg/kg 3 times a day. Allowing for variability in the data generated in our study, the 95% CI for the regression line indicates that a regimen of 22–25 mg/kg 3 times a day may be sufficient to provide comparable average systemic exposures. Peak acyclovir concentrations from intravenous dosing in pediatric patients average 10.3 ± 4.0 and 20.7 ± 5.0 μg/mL from 250 and 500 mg/m^2 dosing every 8 h, respectively [12]. By comparison, the projected acyclovir C_{max} from 30 mg/kg of valacyclovir is about 7–8 μg/mL (figure 1*A*). This reduced peak concentration should provide an added margin of safety relative to intravenous acyclovir.

Acyclovir suspension or tablets (≤800 mg/dose) administered 4 or 5 times a day is commonly used to treat or prevent HSV or VZV infections in immunocompromised children. These result in typical acyclovir peak plasma concentrations of about 1.5–2 μg/mL [12, 16, 24]. Assuming a 20% oral acyclovir bioavailability, 20 mg/kg of oral acyclovir 5 times a day should provide a daily AUC of about 40h × μg/mL in children with normal renal function. With its higher bioavailability, a comparable daily AUC would be expected from about 20 mg/kg of valacyclovir 3 times a day. The expected acyclovir C_{max} from this valacyclovir regimen (~5–6 μg/mL) would be greater than from oral acyclovir and similar to that for adults receiving 1000 mg of valacyclovir 3 times a day for the treatment of herpes zoster (figure 1*A*).

Potential valacyclovir dosage regimens for use in immunocompromised children with normal renal function are proposed in table 4. These regimens account for the fact that acyclovir constitutes about 69% of valacyclovir labeled strength. No valacyclovir dosage regimen can be derived from available data to correspond to high-dose intravenous acyclovir (500 mg/m^2 or 20 mg/kg every 8 h). The regimens include body weights outside of the range evaluated in the current study but are included for completeness based on available tablet strengths and mg/kg dose considerations. Of importance, as with acyclovir, added caution is needed and doses must be reduced for patients with renal impairment.

As an alternative to the valacyclovir dosing considerations with fixed tablet strengths, physicians may wish to consider use of the extemporaneous suspension preparation described by Fish et al. [25]. Pharmacokinetic results from comparison of

Table 4. Valacyclovir dosage regimens corresponding to intravenous and oral acyclovir regimens for consideration in children with normal renal function.

Proposed valacyclovir weight-based regimen by body weight range[a]	Valacyclovir dosage regimen (mg 3×/day)	Current standard acyclovir regimen
30 mg/kg, 3×/day		250 mg/m^2 or 10 mg/kg 3 times/day iv
4–12 kg	250[b]	
13–21 kg	500	
22–29 kg	750	
≥30 kg	1000	
20 mg/kg, 3×/day		20 mg/kg 4 or 5 times/day orally
6–19 kg	250[b]	
20–31 kg	500	
≥32 kg	750	

NOTE. Dosage reduction is required for children with renal impairment. Only low-dose intravenous (iv) acyclovir regimens are included due to limitations in data from the current study.

[a] Children with body weights of <18.5 or >38 kg were not within weight range of children 5–12 years old evaluated in this study.

[b] 250–mg valacyclovir tablets are not available in some countries.

this formulation with the marketed 500-mg tablet in 8 pediatric patients suggest similar, but slightly reduced, acyclovir bioavailability [20]. This approach would allow for refined mg/kg dosing and permit such dosage for young children who cannot swallow tablets. Crushed valacyclovir tablets in standard syrup BP usually are not palatable to children. Also, valacyclovir is unstable in aqueous solution or suspension. Thus, it may be necessary to administer valacyclovir via nasogastric tube in certain situations.

When considered clinically appropriate, oral valacyclovir could be substituted for intravenous acyclovir, avoiding the need for hospitalization. Oral valacyclovir may also be used in place of oral acyclovir, allowing less frequent administration and possibly providing improved efficacy because of higher drug levels and potentially increased compliance. The results from this study provide preliminary guidance for valacyclovir dosing to immunocompromised children and should facilitate the design of clinical trials to investigate the efficacy and safety of valacyclovir in pediatric populations.

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