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Pharmacokinetics of oral valganciclovir solution and intravenous ganciclovir in pediatric renal and liver transplant recipients

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Abstract: In an open-label, prospective, pharmacokinetic assessment, we evaluated total drug exposure (area under the curve [AUC]) of intravenous (IV) ganciclovir (GCV) and oral (p.o.) valganciclovir when normalized for body surface area (BSA) in pediatric liver ($n = 20$) and renal ($n = 26$) transplant patients Reference doses for IV GCV (200 mg/m^2) and p.o. valganciclovir (520 mg/m^2) were based on adult doses, and adjusted for BSA initially, and BSA and renal function (estimated via creatinine clearance [CrCL]) thereafter. Renal transplant patients received GCV on days 1–2, valganciclovir 260 mg/m^2 on day 3, and valganciclovir 520 mg/m^2 on day 4. Liver transplant patients received twice daily GCV from enrollment to day 12, and then valganciclovir twice daily on days 13–14. GCV pharmacokinetics were described using a population pharmacokinetic approach. Type of solid organ transplant (kidney or liver) had no effect on GCV pharmacokinetics. Median GCV exposure following valganciclovir 520 mg/m^2 was similar to that with IV GCV, and to that reported in adults. Patients <5 years of age had AUC values approximately 50% of those compared with older age ranges; dosing based on both BSA and CrCL increased drug exposure in younger patients. A dosing algorithm based on BSA and CrCL should be tested in future studies.

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Cytomegalovirus (CMV) is a major cause of morbidity and mortality in children after solid organ transplantation (SOT) (1), because many of them are likely to be CMV seronegative at the time of transplantation. While the efficacy of ganciclovir (GCV) for the prevention and treatment of CMV in SOT recipients is well established in adults (2–4), its use in the management of CMV disease is limited by poor oral (p.o.) bioavailability (5), and thus the need for long-term intravenous (IV) administration.

Valganciclovir, the valine ester of GCV, overcomes the limitations of p.o. GCV and is a convenient alternative to IV administration. The 10-fold higher absolute bioavailability of p.o. valganciclovir compared with GCV (5, 6), means that, in adults, dosing with p.o. valganciclovir 900 mg once daily provides similar GCV exposure to IV GCV (5 mg/kg/day) (7). However, dosing with valganciclovir tablets may not be appropriate in some patients because of their inability to swallow solids for a variety of reasons. To this end, a p.o. valganciclovir solution has been developed to accommodate these patients that is bioequivalent to the tablet formulation and with a similar safety profile, thus allowing the 2 p.o. formulations to be interchangeable (8).

No universal rule exists for converting adult drug doses to doses for children (9). Adjusting according to body weight or body surface area (BSA) is not always successful (10, 11). Furthermore, a p.o. solution of valganciclovir would

also be useful for children unable to swallow tablets or capsules. To fill in this knowledge gap, we designed and conducted 2 independent studies of p.o. valganciclovir solution and IV GCV in *de novo* pediatric kidney or liver transplant recipients. We hypothesized that IV dosing of GCV and p.o. dosing of valganciclovir, normalized for BSA in pediatric liver and kidney transplant patients, would provide similar GCV area under the curve (AUC) values as those established for adults. Additionally, we hypothesized that BSA-normalized p.o. valganciclovir doses would provided comparable GCV AUC values to BSA-normalized IV GCV doses in this population.

Methods

Study design and patient population

Two open-label studies were conducted in 9 US centers (6 renal and 3 liver). Both studies were approved by the Institutional Review Boards at each institution and written informed consent was provided by patients' parents or guardians and assent by the children as appropriate.

Renal study

Children aged 3 months to 16 years considered at risk of developing CMV disease who had received their first kidney-only transplant were eligible for study entry. Patients were required to have absolute neutrophil count >1000 cells/μL; platelet count $>25{,}000$ cells/μL; hemoglobin >8.0 g/dL; and stable renal function with creatinine clearance (CrCL) >45 mL/min/1.73 m^2 (Schwartz et al. formula [12]). Exclusion criteria included allergic or other significant adverse reaction to acyclovir, GCV, or valacyclovir; severe, uncontrolled diarrhea or evidence of malabsorption; patients simultaneously participating in another trial, except as approved by the sponsor; female patients who were lactating and would not discontinue nursing before study entry; pregnancy; and liver function impairment of >5 times the upper limit of normal for aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

Liver study

The criteria for the liver trial were identical to those of the renal study, with the exception that children at risk of contracting Epstein–Barr virus (EBV) could also be included. Exclusion criteria were also identical, except for the exclusion of liver function impairment and the inclusion of evidence of graft rejection or antiviral prophylaxis with a treatment other than IV GCV between transplant and enrollment.

Calculation of dosage

According to BSA

Reference doses were based on adult dosages as follows. The standard 5 mg/kg IV GCV dose for a 70 kg adult with a BSA of 1.73 m^2 is 350 mg; this corresponds to a pediatric reference dose of 200 mg/m^2. The standard 900 mg dose of p.o. valganciclovir for an adult with BSA of 1.73 m^2 corresponds to a pediatric reference dose of 520 mg/m^2.

In both studies, IV GCV and p.o. valganciclovir dosages were calculated as follows:

$$\text{Full dose(mg)} = \text{Reference dose(mg/m}^2\text{)} \times \text{BSA of patient(m}^2\text{)},$$

where BSA was calculated using Mosteller's equation (13):

$$\text{BSA(m}^2\text{)} = \sqrt{[(\text{height(cm)} \times \text{weight(kg)})/3600]}.$$

In order to estimate the most appropriate dose of p.o. valganciclovir in children an additional dose level of p.o. valganciclovir (260 mg/m^2) corresponding to 50% of the reference p.o. valganciclovir dose was included in the renal study.

According to renal function

In both studies, the reference doses for both agents were adjusted for reduced renal function based on estimated CrCL, as outlined in Table 1. CrCL was estimated from serum creatinine using the Schwartz et al. formula (12):

$$\text{CrCL(mL/min/1.73 m}^2\text{)} = [k \times \text{height(cm)}]/[\text{serum creatinine(mg/dL)}],$$

where $k = 0.45$ for those aged <2 years, $k = 0.55$ for those aged ≥ 2 years to <13 years, and for those aged ≥ 13 years to ≤ 20 years, $k = 0.7$ for males and $k = 0.55$ for females.

Drug regimens and procedures

Renal study

Individual study drug dosing lasted for a total of 4 days. The shorter interval in the renal study compared with the 14 days in the liver study, resulted from the more rapid time to stability and discharge from the hospital for the renal transplant patients. Screening assessments were performed in the first week after transplantation after the stabilization of renal function, followed by 4 consecutive days of treatment with study drugs, a follow-up visit (day of last pharmacokinetic sample, 28–32 days post transplant), and a safety review visit (28 days after cessation of study drug $\pm$ 4 days). Serum creatinine used to estimate CrCL was measured on each day of treatment and at the follow-up visit. After stabilization of renal function following transplantation, subjects received treatment once daily between

Valganciclovir and ganciclovir dosing based on estimated creatinine clearance (CrCL)

Estimated CrCL (mL/min/1.73 m^2)	Proportion of full dose given (%)
$\geq$ 70	100
50–69	50
40–49	25
<40	Patient withdrawn from study

Reference doses were 200 mg/m^2 for intravenous ganciclovir and 260 or 520 mg/m^2 for oral valganciclovir solution.

Table 1

7 and 9 a.m. with a single dose of IV GCV on days 1 and 2 and a single dose of p.o. valganciclovir solution of 260 mg/m^2 on day 3 and 520 mg/m^2 on day 4. Blood samples for determination of GCV concentrations were collected on dosing-days 2, 3, and 4 as follows: pre-dose (up to 2 h before dosing), and 1 h (immediately before the end of the infusion), and between 2–3, 5–7, and 10–12 h post dose on day 2; pre-dose, and between 0.25–0.75, 1–3, 5–7, and 10–12 h post dose on day 3; and pre-dose, and between 0.25–0.75, 1–3, 5–7, 10–12, and 22–24 h post dose on day 4.

Liver study

Screening and enrollment were conducted between days 1 and 4 (day 0 was the day of the transplant); patients received study drugs from enrollment up to day 14 post transplant. The follow-up and safety reviews were on days 28–32 and 42 $\pm$ 4 post treatment, respectively. Serum creatinine used to estimate CrCL was measured on days 11–14. Study drugs were administered twice daily – between 7 and 9 a.m. for the first dose, and the second as close as possible to 12 h after the first dose. However, the AUC was calculated using only samples obtained during the 12-h period around the morning dose of drug. The 24-h AUC was calculated using non-linear mixed effect modeling (NONMEM) assuming once a day dosing.

Patients received treatment with IV GCV, initiated on enrollment (days 1–4 after transplantation) and continued to day 12 post transplant. On days 13 and 14 post transplant, patients received p.o. valganciclovir solution twice daily. Blood sampling was conducted on days 12 and 14 as follows: pre-dose (up to 2 h before dosing), and 1 h (immediately before the end of the infusion), and between 2–3, 5–7, and 10–12 h post dose on day 12; and pre-dose, and between 0.25–0.75, 1–3, 5–7, and 10–12 h post dose on day 14.

Drug administration

In both studies, IV GCV was given over 1 h as a constant rate infusion. GCV for IV infusion (Cytovene®, Roche, Nutley, New Jersey, USA) was provided as sterile, lyophilized powder in sealed vials containing 500 mg GCV for reconstitution in 10 mL of saline. Valganciclovir was provided as a strawberry-flavored 15 g powder blend containing 3 g valganciclovir; it was reconstituted with 50 mL water to give a final volume of 60 mL; the solution was sweetened with saccharine and was administered within 15 min of a meal. One batch of valganciclovir p.o. solution was used in each study.

Study assessments and procedures

Screening assessment in both studies included a limited physical examination, laboratory safety tests (hematology, serum chemistry), and a medical examination including assessment of concomitant illnesses, laboratory safety tests, assessment of puberty stage (Tanner stage [14]), pregnancy tests for females of child-bearing potential, measurement of serum creatinine, and estimated CrCL. In addition, the CMV serological status of the graft and recipient was determined in the renal study, and the CMV and EBV serological status of the graft and recipient was determined in the liver study.

Adverse events occurring since consent and medications to treat these adverse events were also recorded in both studies.

Drug assay

In each study, venous blood (1 mL) was collected into plastic ethylene diamine tetraacetic acid tubes and centrifuged (15 min at 1200 $\times g$) at 4°C within 30 min. Plasma samples were frozen immediately at $-$ 70°C pending analysis. The plasma concentration of GCV was determined by Analytico Medinet (Breda, the Netherlands) following deproteination, by adding trichloroacetic acid, using a validated specific liquid chromatography-tandem mass spectrometry method. GCV was provided by Hoffmann La-Roche (Basel, Switzerland). The dynamic range for the quantification of GCV was between 0.040 and 20 μg/mL, which was based on 8 different concentration levels (coefficient of correlation $\geq$ 0.99. The overall accuracy and inter-assay variability of the assay was 98.7–105% and 0.7–12.0%, respectively.

Because of the rapid conversion of valganciclovir to GCV, plasma valganciclovir concentrations are not detectable, and were therefore not measured in either study or included in the pharmacokinetic model.

Population pharmacokinetic modeling

Pharmacokinetic model

A 2-compartmental model for GCV was considered appropriate based on previous population pharmacokinetic analyses for GCV in adult SOT recipients (7). The model

parameters were clearance (CL), volume of distribution at steady state (V_{ss}), intercompartmental clearance (Q), peripheral volume of distribution (V_{periph}), first-order absorption (for valganciclovir), lag time, and bioavailability of GCV from valganciclovir (F1).

NONMEM software (Version V, Icon, Dublin, Ireland) and the first-order estimation method were used. NONMEM was developed at the University of California, San Francisco as software for fitting non-linear mixed effects (statistical regression-type) models. The methodology is particularly useful for population pharmacokinetic analyses and in situations such as in this trial, where there are few pharmacokinetic samples per subject. Inter-subject variability was assessed using an exponential function. A combined multiplicative and additive error model was used for the residual random effects.

Covariate selection was conducted on gender, age, height, puberty, body weight, BSA, type of SOT (kidney or liver), serum creatinine, AST, ALT, total bilirubin, and CrCL derived from the Cockroft–Gault formula (CrCLC) (15) and Schwartz et al. formula (CrCLS) (11). Stepwise generalized additive modeling in Xpose 3.102 was used initially to select the covariates to be tested within NONMEM. Then a comprehensive forward addition and backward procedure was followed to build the final covariate model. Model discrimination was based on a decrease in objective function values and visual inspection of goodness-of-fit plots.

Pharmacokinetic endpoints

The primary pharmacokinetic parameter in both studies was the extent of exposure (AUC) to GCV after administration of IV GCV and p.o. valganciclovir solution, determined as the area under the GCV concentration–time curve over 24 h (AUC_{0-24}) using population pharmacokinetic analysis. Population pharmacokinetic analysis was also used to determine secondary pharmacokinetic parameters, which included CL; F1; V_{ss}; V_{periph}; volume of central compartment (V_{cent}); absorption rate constant (K_a); maximum plasma concentration (C_{max}); and terminal elimination half-life ($t_{1/2}$). Individual parameters were calculated using individual *post hoc* estimates derived from population estimates and the individual data.

Statistics

No formal statistical tests or sample size calculations were performed. The planned target recruitment was 24 patients in the renal study and 20 patients in the liver study. These sample sizes were deemed adequate to derive the pharmacokinetic profile of GCV after administration of IV GCV and p.o. valganciclovir solution. Descriptive statistics were used to summarize the pharmacokinetic data.

Results

Renal study

Twenty-six patients were enrolled, aged ≤ 5 years ($n = 5$), 6–11 years ($n = 7$), and 12–16 years ($n = 14$) (Table 2). One patient withdrew prematurely after refusing treatment with valganciclovir p.o. solution, having received both doses of IV GCV. Data for this patient are included in all but the pharmacokinetic analyses. Two patients had their dose of study medication reduced because of poor renal function. The first patient (13 years old) received 25% of

Demographics and baseline characteristics of patient population

Variable	Renal study ($n = 26$)	Liver study ($n = 20$)
Male, *n* (%)	17 (65)	11 (55)
Race, *n* (%)		
Caucasian	13 (50)	18 (90)
Black	5 (19)	2 (10)
Oriental	–	–
Other	8 (31)	–
Median age (range) (years)	12 (1–16)	2 (0–16)
Median weight (range) (kg)	32.4 (10.6–81.6)	11.9 (5.7–56.9)
Median height (range) (cm)	137.0 (74.0–185.0)	82.5 (59–175)
Mean estimated CrCL (SD) (mL/min)	109.9 (43.6)	153.4 (75.3)
CMV status, *n* (%)[1]		
D + /R +	16 (62)	4 (20)
D + /R –	6 (23)	6 (30)
D – /R +	2 (8)	2 (10)
D – /R –	2 (8)	8 (40)
EBV status, *n* (%)[1,2]		
D + /R +		5 (25)
D + /R –		6 (30)
D – /R +		2 (10)
D – /R –		6 (30)
D_{ND}/R +		1 (5)

[1]Enrollment of patients who were donor seronegative/recipient seronegative for CMV and/or EBV was permitted because all pediatric patients were considered at risk, regardless of their serotype.
[2]EBV serological status not determined in study in renal transplant recipients.
CMV, cytomegalovirus; CrCL, creatinine clearance; D +, donor seropositive; D –, donor seronegative; EBV, Epstein–Barr virus; R +, recipient seropositive; R –, recipient seronegative; SD, standard deviation; ND, not determined.

Table 2

the BSA-adjusted dose of 200 mg/m^2 of IV GCV and 50% of the BSA-adjusted higher dose of p.o. valganciclovir solution (520 mg/m^2). The second patient (12 years old) received 50% of the BSA-adjusted dose of 200 mg/m^2 of IV GCV.

Liver study

In the liver study, 20 patients were enrolled: aged $\leq$ 5 years ($n = 15$), 6–11 years ($n = 2$), and 12–16 years ($n = 3$) (Table 2). One patient with renal function slightly outside of the 45 mL/min/1.73/m^2 inclusion criteria (CrCL = 41.7 mL/min/1.73 m^2) was inadvertently entered into the study; the subject's data were included in the analyses. Fifteen patients completed the study. Five of the 20 patients (all aged $<$5 years) were withdrawn.

Pharmacokinetic results

Final pharmacokinetic model (combined patient cohort)

Of the 46 patients enrolled, 43 were included in the pharmacokinetic model. One patient from the renal study was excluded from the pharmacokinetic model because plasma levels were not recorded. Two patients from the liver study were withdrawn before receiving study drug and were also excluded from the pharmacokinetic model. Three other liver transplant subjects did not complete the entire study but had sufficient data to include in the pharmacokinetic analysis. Of the 43 patients included in the model, data were included from a liver transplant recipient for whom GCV plasma concentrations only after administration of IV GCV were available because this patient was withdrawn before p.o. valganciclovir administration, and from another liver transplant recipient who received p.o. valganciclovir for only 1 day.

The final model for GCV plasma concentrations was a 2-compartmental model with first-order formation for p.o. valganciclovir, lag time, and relative bioavailability. Intersubject random variability was modeled for K_a, CL, V_{ss}, Q, and F1 as exponential errors. The residual error consisted of a multiplicative and an additive error arm. The multiplicative error was 29% and the additive error was 0.14 ng/mL, which is about 3-fold above the lower limit of quantification (0.04 ng/mL). The population pharmacokinetic parameters of the final model are presented in Table 3. The height of the patient and CrCLC were identified as statistically significant covariates for CL, V_{ss}, and V_{periph}. Neither age, gender, nor type of organ were significant covariates in this model. Inspection of the goodness-of-fit plots did not show any substantial bias thus indicating that the pharmacokinetic parameters were well estimated. There was no clinically relevant difference in covariate selection between using the Schwartz and Cockcroft Gault formulae for calculation of CrCL (Roche data on file).

Individual pharmacokinetic parameters

Summaries of the derived and individual estimated parameters from both studies are shown in Tables 4 and 5, respectively. AUC_{0-24} and C_{max} were calculated for the doses of 200 mg/m^2 for IV GCV and 520 mg/m^2 for p.o. valganciclovir solution. Two subjects had their doses decreased per the dosing algorithm (Table 1) and are included in this analysis. The first received 25% of the BSA-adjusted dose of 200 mg/m^2 IV GCV, resulting in an exposure to GCV of 22.96 mg · h/L, This subject also received 50% of the BSA-adjusted higher dose of p.o. valganciclovir syrup resulting in a GCV exposure of 58.35 mg · h/L. The second subject received 50% of the BSA-adjusted dose of 200 mg/m^2 of IV GCV, which resulted in a GCV exposure of 57.36 mg · h/L.

It was shown during modeling that pharmacokinetic values for the lower dose of 260 mg/m^2 of p.o. valganciclovir solution investigated in the renal study would be half of those shown in Table 4 for the 520 mg/m^2 dose due to linearity in the pharmacokinetics of valganciclovir.

Basic pharmacokinetic (PK) parameters of ganciclovir of the combined final population PK model

Description	PK parameter	Estimate	Standard error of estimate	Intersubject CV (%)
Absorption constant	K_a (h)	0.42	0.066	16
Bioavailability	F1	0.55	0.038	6.9
Lag time	T_{lag} (h)	0.22	0.0096	4.4
Clearance	CL (L/h)	5.4	0.29	5.4
Volume of distribution at steady state	V_{ss} (L)	20	1.2	6
Peripheral volume	V_{periph} (L)	15	1	6.7
Intercompartment clearance	Q (L/h)	8	1.5	19
Multiple error		0.29	0.034	12
Additive error (ng/mL)		0.14	0.046	33

Table 3

Derived pharmacokinetic parameters[1] of ganciclovir in pediatric renal or liver transplant recipients following treatment with oral valganciclovir and intravenous ganciclovir, by age group

	Intravenous ganciclovir (200 mg/m^2)			Oral valganciclovir (520 mg/m^2)		
Age group	0–5 years	6–11 years	12–16 years	0–5 years	6–11 years	12–16 years
Renal study	$n = 4$	$n = 7$	$n = 14$	$n = 4$	$n = 7$	$n = 14$
AUC_{0-24} (mg · h/L)	22.18 (17.13–27.1)	37.86 (15.78–43.59)	38.58 (21.01–89.29)	22.22 (16.15–24.52)	43.78 (14.45–55.07)	39.88 (20.95–70.64)
C_{max} (mg/mL)	10.19 (9.17–12.29)	9.03 (6.79–11.28)	9.40 (3.51–25.26)	5.10 (4.20–8.50)	6.01 (3.37–9.08)	5.40 (3.56–7.92)
Liver study	$n = 13$	$n = 2$	$n = 3$	$n = 13$	$n = 2$	$n = 3$
AUC_{0-24} (mg · h/L)	24.3 (14.1–38.9)	35.2 (27.1–43.2)	23.4 (19.2–25.8)	23.4 (11.8–40.6)	46.8 (35.2–58.4)	25.8 (25–30.9)
C_{max} (mg/L)	12.2 (9.17–15)	9.29 (4.73–13.9)	11.8 (11.6–12.4)	5.51 (2.72–7.18)	5.29 (3.79–6.79)	6.9 (5.59–7.04)

[1]Values are expressed as medians (range).
AUC_{0-24}, area under the concentration time curve from 0 to 24 h; C_{max}, maximum plasma concentration.

Table 4

Across both studies, exposure to GCV was noticeably low in very young patients (aged ≤ 5 years) for both IV GCV and the p.o. valganciclovir solution (Table 4). In addition, in all age groups, exposure to GCV following treatment with IV GCV was broadly similar to that following treatment with p.o. valganciclovir solution 520 mg/m^2. In both liver and kidney, C_{max} values for all ages were comparable, with means ranging 9.03–12.2 C_{max}. Values were notably lower for p.o. valganciclovir, but also comparable between age groups/transplant types with means of 5.10–6.9.

Individual estimated pharmacokinetic parameters[1] of ganciclovir in pediatric renal or liver transplant recipients by age group

	Age group (years)		
	0–5	6–11	12–16
Renal study	$n = 4$	$n = 7$	$n = 14$
CL (L/h)	4.71 (3.83–5.23)	4.92 (3.62–8.75)	7.40 (3.39–12.93)
F1	0.44 (0.40–0.59)	0.54 (0.46–0.80)	0.53 (0.42–0.77)
K_a (L/h)	0.80 (0.63–1.92)	0.67 (0.42–1.18)	0.72 (0.16–1.88)
V_{cent} (L)	7.20 (3.99–7.74)	15.03 (10.87–17.81)	22.07 (9.58–34.83)
V_{periph} (L)	5.71 (2.13–10.12)	9.94 (6.91–47.20)	18.84 (5.10–144.30)
V_{ss} (L)	13.19 (6.11–17.29)	24.99 (17.77–64.42)	40.81 (17.85–177.90)
Liver study	$n = 13$	$n = 2$	$n = 3$
CL (L/h)	4.05 (2.11–7.92)	2.86 (1.88–3.84)	15.1 (11.4–16.8)
F1	0.52 (0.39–0.83)	0.71 (0.7–0.72)	0.64 (0.57–0.72)
K_a (L/h)	0.45 (0.13–0.86)	0.35 (0.23–0.48)	0.42 (0.3–0.52)
V_{cent} (L)	1.66 (0.45–2.51)	5.74 (5–6.48)	12.8 (12.8–16.8)
V_{periph} (L)	5.65 (2.9–7.6)	14.6 (12–17.3)	30.7 (25.1–34.6)
V_{ss} (L)	7.62 (3.35–10.1)	20.4 (17–23.8)	43.5 (37.9–51.4)

[1]Values are expressed as medians (minimum–maximum).
CL, clearance; F1, bioavailability of ganciclovir from valganciclovir; K_a, absorption rate constant; V_{cent}, volume of central compartment; V_{periph}, volume of peripheral compartment; V_{ss}, steady-state volume of distribution.

Table 5

In the renal study, CL increased with age, as did drug exposure. Moreover, GCV exposure based on BSA alone in the renal study was generally lower in younger children, but was increased when corrected for both BSA and renal function (Fig. 1). The very low r value, when adjusting by both BSA and CrCl, indicates that AUC is no longer correlated with age, an important improvement in a dosing regimen. In contrast, in the liver study, there was no clear pattern in the age-related effect on clearance or exposure of GCV. This could be, in part, attributed to the skewed distribution of patients across the age groups in the liver study. In this study, the clearance of GCV was markedly lower in the 13 children aged ≤ 5 years than the 3 children aged 12–16 years; however, it was lower still in the 2 children aged 6–11 years (Table 5). The $t_{1/2}$ was shorter in younger children (median 1.65 h) than in those aged 6–11 and 12–16 years (6.80 and 4.35 h, respectively). Similarly, in the renal study, $t_{1/2}$ increased with increasing age; median values were 3.28 (range 1.97–6.31), 4.41 (range 3.06–12.77), and 5.62 (3.32–27.04) in the 0–5, 6–11, and 12–16 years age groups, respectively.

The estimated bioavailability of GCV from p.o. valganciclovir solution was only slightly lower in the younger children than the older children in both studies (Table 5); this suggests that there was essentially no dependence of F1 values on age.

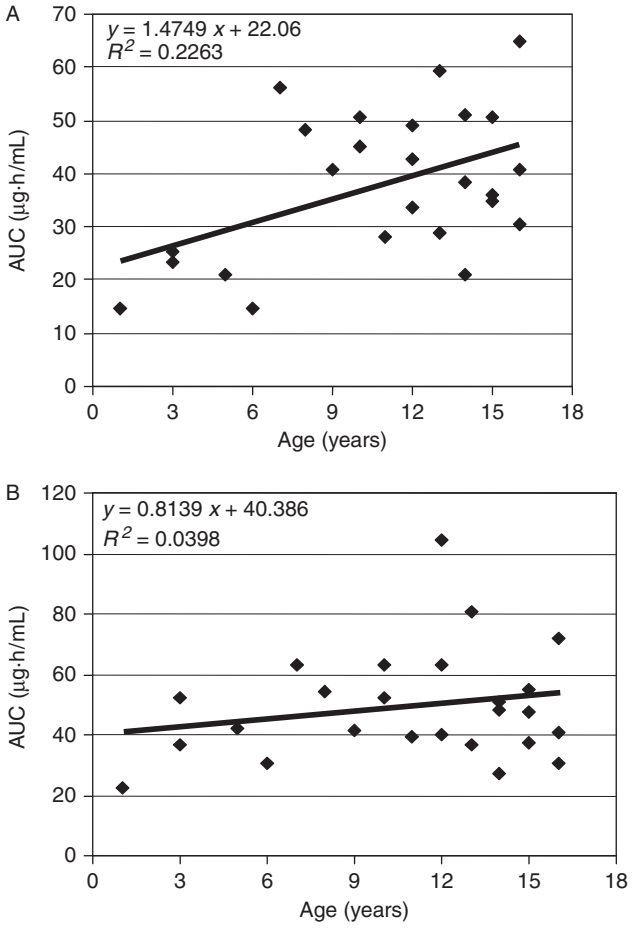

Fig. 1. Relationship between age and projected ganciclovir exposure from oral valganciclovir in patients receiving a renal transplant. Patients were dosed with study drug according to an algorithm based on (A) body surface area, and (B) body surface area and renal function.

Safety

In both studies, IV GCV and valganciclovir p.o. solution were generally well tolerated. The majority of treatment-emergent adverse events were of mild or moderate severity and were gastrointestinal in nature. There were no deaths in either study.

Renal study

Treatment-emergent adverse events were reported in 50% of patients in the IV GCV phase and in 32% of patients in the p.o. valganciclovir phase. Four patients experienced treatment-related adverse events; 3 while receiving p.o. valganciclovir solution (nausea $n = 1$, vomiting $n = 1$, and headache $n = 2$), and 1 while receiving IV GCV (thrombocytopenia). Four severe adverse events were reported, of which 1 occurred on treatment (sepsis; with valganciclovir solution). Four patients experienced 6 serious adverse events, of which 2 occurred on treatment with p.o. valganciclovir but were not considered treatment related.

Liver study

Treatment-emergent adverse events were reported in 90% of patients in the IV GCV phase of the study. There were only 2 adverse events in the p.o. valganciclovir treatment phase, which were not severe, serious, or treatment related. Three patients experienced a total of 6 adverse events that were remotely or possibly related to treatment with IV GCV (rash in 1 patient, anemia and renal impairment in 1 patient, and vomiting, diarrhea, and increased hepatic enzymes in 1 patient). Of 22 severe adverse events, 2 were life threatening (2 occurrences of post-procedural hemorrhage in 1 patient during IV GCV treatment and during the off-treatment phase of the study). Ten patients experienced 14 serious adverse events in the IV GCV phase, of which 2 were related to study treatment (vomiting and increased hepatic enzymes).

Discussion

The median exposure to GCV in older children receiving 520 mg/m^2 p.o. valganciclovir solution (39.88 mg · h/L in 12–16-year-olds in the renal study) was in agreement with

that observed in adult patients receiving 900 mg valganciclovir once daily (mean of approximately 46 mg · h/mL) (5, 7). In the renal study, the GCV exposure, based on BSA alone, was generally low in younger children; drug exposure was increased in this age group when corrected for both BSA and renal function (estimated via CrCL). The clear trend of decreasing exposure with younger age shown in the renal study was not observed in the liver study, presumably because there were limited number of patients in the 2 older liver transplant groups. The youngest children were underexposed to GCV by about 2-fold; this did not appear to be attributable to a lack of simultaneous adjustment for age in clearance because clearance of GCV was lower in the youngest age groups compared with the oldest age groups (median 4.7 L/h in 0–5-year-olds vs. 7.4 L/h in 12–16-year-olds in the renal study and 15.1 vs. 4.1 L/h in the liver study). These results suggest that a dosing algorithm based on BSA alone is inadequate to deliver similar GCV exposures across the age ranges investigated in these 2 pediatric studies.

Because the bioavailability of GCV from p.o. valganciclovir solution was essentially independent of age and the drug is eliminated almost exclusively unchanged in the urine, we propose that renal function (assessed via CrCLS) should be included as a standard criterion in addition to BSA in future dosing algorithms for p.o. valganciclovir in children. Estimated CrCL has been used previously as a predictor of systemic GCV clearance in a dosing algorithm in a population pharmacokinetic model in adult SOT recipients (7). An individualized dosing algorithm for p.o. valganciclovir solution or tablets (where dose = 7 × BSA × CrCL) has recently been shown in a pediatric population to provide GCV exposures similar to those obtained in adults, with age and type of SOT having limited impact on GCV pharmacokinetics. The dosing schedule used in this report was based on the data presented in this paper (16).

In our studies, the bioavailability and C_{max} of GCV from p.o. valganciclovir solution was similar to that previously obtained in adult SOT recipients (44–71% [both studies] vs. 61% (17) and 5–7 mg/L [renal study] vs. 5–6 mg/L (5), respectively). Previous data have shown that the pharmacokinetics of GCV are generally similar between neonates, children, and adults (18–21).

Given the short duration of these studies, and the extensive use of concomitant medications, it is difficult to assess causality or draw conclusions regarding the overall safety profile.

Significant fluid shifts and ascitic fluid losses can occur in the first 2 weeks after liver transplantation, and could have potentially influenced GCV clearance values in the liver study. However, in our model, the type of SOT was not found to be a significant covariate for clearance of the drug.

The dosage was adjusted for reduced renal function based on estimated CrCL calculated using the Schwartz et al. formula (CrCLS) (12). The Schwartz et al. formula may overestimate glomerular filtration rate (GFR) in the pediatric population, particularly at GFR levels <60 mL/min/1.73 m^2 (22). Nevertheless, CrCLS has good negative predictive value when CrCLS is >20 mL/min/1.73 m^2 (i.e., when CrCLS is >20 mL/min/1.73 m^2 there is a 95% chance that GFR measured by iothalamate clearance is >15 mL/min/1.73 m^2) (22). As a baseline CrCL of >45 mL/min/1.73 m^2 was required for enrollment, overestimation of GFR with the Schwartz formula may be less of a concern (provided renal function remained stable during the study period).

The systemic exposure to GCV in pediatric renal or liver transplant recipients was similar after administration of p.o. valganciclovir solution (520 mg/m^2) or IV GCV (200 mg/m^2). As a dosing algorithm based only on BSA resulted in under-exposure of younger children, an algorithm including individually estimated CrCL and BSA (dose = 7 × BSA × CrCL) is currently being investigated and should provide adequate GCV exposure in pediatric renal or liver transplant recipients for the prevention of CMV disease.

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