

The pharmacokinetics of valganciclovir prophylaxis in pediatric solid organ transplant patients at risk for Epstein–Barr virus disease

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Abstract: Antiviral prophylaxis with valganciclovir is used frequently in pediatric solid organ transplant patients to prevent Epstein–Barr virus (EBV)-induced infections and tissue-invasive disease including post-transplant lymphoproliferative disorder (PTLD). This approach is untested in clinical trials and valganciclovir dosing strategies in children are highly variable. Our objective was to characterize the pharmacokinetics of ganciclovir in the plasma of pediatric kidney and liver transplant patients taking valganciclovir for EBV prophylaxis. Virologic response was also evaluated. Ganciclovir was measured by liquid chromatography/ultraviolet detection. EBV DNA was quantified by TaqMan® polymerase chain reaction. NONMEM® VI was used for data analysis. Ganciclovir plasma profiles were consistent with a one-compartment model. Final model estimates of apparent oral clearance (L/h), apparent volume of distribution (L), and absorption rate constant were 7.33, 35.1, and 0.85, respectively. There was evidence of lower bioavailability in children younger than three years. All eight subjects achieved ganciclovir plasma concentrations above reported *in vitro* concentrations needed to inhibit EBV replication by 50%. However, four subjects had detectable EBV DNA with a median (range) of 18,300 (4,400 to 54,900) copies/mL of whole blood. These findings support the need for further studies of the clinical pharmacology and efficacy of valganciclovir for EBV prophylaxis.

Keywords: valganciclovir, ganciclovir, pharmacokinetics, Epstein–Barr virus, pediatrics, solid organ transplantation

Introduction

Antiviral prophylaxis with valganciclovir is used frequently in children after solid organ transplantation to prevent post-transplant lymphoproliferative disorder (PTLD), a tissue-invasive viral disease primarily induced by the Epstein–Barr virus (EBV).^{1–3} Approximately 2000 pediatric solid organ transplants are performed annually in the United States.⁴ The incidence of PTLD in pediatric solid organ transplant patients ranges from 1% to 20% with mortality rates greater than 50% in some cohorts.^{5–7} Those children at the greatest risk for PTLD are EBV-antibody seronegative at the time of transplantation and receive an organ from an EBV-antibody seropositive donor.^{8–10}

Valganciclovir, the oral prodrug of ganciclovir, with a 10-fold greater bioavailability, appears to reduce EBV viremia which can lead to the development of PTLD.^{11,12} Other data suggest that ganciclovir is protective against PTLD, particularly with prolonged use.¹⁰ Ganciclovir also has good *in vitro* activity against EBV. The ganciclovir concentration needed to inhibit viral replication by 50% (IC₅₀) has been reported to be as low as 0.05 µM, which is attainable at valganciclovir doses used clinically.¹³

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However, valganciclovir EBV prophylaxis has not been tested in randomized, placebo-controlled trials, and our knowledge about its efficacy is limited. In addition, the pharmacokinetics of this approach have not been established, and current pediatric valganciclovir dosing strategies are highly variable. The objective of this study was to characterize the pharmacokinetics of ganciclovir in pediatric kidney and liver transplant patients who were receiving valganciclovir for the prevention of EBV-associated PTLT.

Methods

Subjects

This study was conducted at the University of Minnesota and the General Clinical Research Center. The University of Minnesota Institutional Review Board approved the study. Written informed consent was obtained from parents or guardians prior to participation. For children aged 7 to 17 years, written informed assent was also obtained. Children younger than 18 years who were at least six weeks post-solid organ transplantation and receiving oral valganciclovir for anti-EBV prophylaxis were eligible for the study. Potential participants also had to have two stable serum creatinine measurements (defined as within ± 0.2 mg/dL of each other) obtained on two separate, consecutive occasions at least three days apart. Exclusion criteria were absolute neutrophil count less than 500 cells/mm³, platelet count less than 20,000 cells/mm³, and hemoglobin less than 6.5 g/dL.

Study design

This was a prospective, open-label pharmacokinetic study. Potential participants were initially identified by their primary providers at the University of Minnesota Transplant Center and referred to the research team for the study. The study consisted of a 12-hour study visit at the General Clinical Research Center and/or two study visits scheduled as part of routine transplant clinic appointments. Subjects could participate in one or both study visit categories, and their selection was documented in the consent and assent forms.

For the 12-hour study visit, subjects arrived at the General Clinical Research Center after an overnight fast, and had a saline lock placed in one arm to obtain serial venous blood samples for plasma ganciclovir concentrations. The date, time, and amount of the subject's last valganciclovir dose were recorded. Blood was drawn for a complete blood cell count with differential, electrolytes, serum creatinine, and a baseline ganciclovir plasma concentration. Subjects were given a standardized breakfast (641 Kcal; 5.1% protein, 12.7% carbohydrates, 3.4% fat) and immediately after completing

the meal took a dose of their own supply of valganciclovir with up to 237 mL of water. Additional blood samples were drawn at 1, 2, 4, 6, 8, and 12 hours post-dose.

For the two study visits that occurred as part of regularly scheduled transplant clinic appointments, subjects had blood drawn for ganciclovir plasma concentrations at the start and at the end of the appointments. The date, time, and amount of the last valganciclovir dose were recorded along with the sample draw time.

Throughout the study, subjects also had blood drawn at their regular transplant clinic appointments for routine quantitative EBV DNA (qEBV) analysis. The qEBV assays were performed at the University of Minnesota Medical Center's Clinical Virology Laboratory using a validated method.^{14,15} Quantitative EBV DNA data were reported as viral copies per mL of whole blood. The reliable limit of detection of the assay was 10 copies/reaction (coefficient of variation (CV%), 30%), which equates to 1000 copies/mL of whole blood. These clinical data were used to evaluate EBV replication among study participants.

Quantitation of ganciclovir in plasma

Plasma concentrations of ganciclovir were measured using a validated reversed phase high-performance liquid chromatography assay. Plasma (200 μ L) was subjected to protein precipitation with perchloric acid. The injection volume was 25 μ L of pH adjusted, protein free extract. The mobile phase consisted of 97.5% phosphate buffer (25 mM at pH 6) and 2.5% acetonitrile (vol/vol). The stationary phase was a 3 mm \times 150 mm YMC C4 reversed phase column (Waters Corporation, Milford, MA). The flow rate was 0.4 mL/min with detection at 266 nm. All analytic measurements were performed using an HP series 1100 LC system (Agilent Technologies, Palo Alto, CA). The assay internal standard was dideoxycytidine. Plasma standards ranged from 25 to 10,000 ng/mL. Accuracy and variability were determined using four quality controls (25, 75, 750, and 7,500 ng/mL) measured in triplicate on five separate days. A single factor analysis of variance was used for statistical analysis. Accuracy ranged from 97.4% to 106.6%. Within- and between-assay variability, expressed as CV%, ranged from 0.4% to 3.3% and 0.8% to 5.3%, respectively.

Pharmacokinetic analysis

Ganciclovir plasma concentration-time data from the 12-hour study visit and the two study visits that occurred during regularly scheduled transplant clinic appointments were combined and analyzed using a nonlinear mixed-effects modeling approach to determine ganciclovir pharmacokinetic

parameters. Doses for valganciclovir were recorded as milligrams of valganciclovir and not corrected for molecular weight differences between ganciclovir and valganciclovir. The model estimated parameters, apparent oral clearance (CL/F), and apparent volume of distribution (V/F) implicitly incorporate this difference into the bioavailability (F) term.

NONMEM® version VI, level 2.0 with PDxPOP version 3.0 (LLC, Globomax, Ellicott City, MD) and Compaq (Digital) Visual Fortran 6.0 Compiler (Houston, TX) were used for data analysis.¹⁶ Oral doses of valganciclovir were administered into an absorption depot compartment. Absorption of valganciclovir was modeled as a first-order process and conversion to ganciclovir in the central compartment was assumed to be instantaneous. A one-compartment model with first order elimination for ganciclovir disposition in plasma was specified with ADVAN2 and TRANS2. The model was parameterized in terms of CL/F, V/F, and absorption rate constant (K_a).

Between-subject variabilities on CL/F, V/F, and K_a were modeled using a proportional error model. This imposed a log normal distribution on the parameters with results expressed as a CV%. Residual unexplained variability was assumed to have a log normal distribution and was also expressed as a CV%. The estimation method implemented for all runs was the first-order conditional estimation with interaction method. Four significant figures were specified for the estimation procedure.

During the model development process, the importance of a patient-specific covariate on the pharmacokinetic parameters was determined using a generalized additive model analysis and the likelihood ratio test. The likelihood ratio test, which is approximately χ^2 distributed, is the primary statistic used to compare two nested models, and the objective function value is a measure of goodness of fit. When a covariate is added to the model, a statistically significant ($\alpha = 0.05$) improvement in the model is associated with an objective function value drop of 3.84 units. The covariates available for model building were age, weight, height, body surface area, creatinine clearance by the Schwartz method, transplant type (kidney or liver), and sex.^{17–19}

Metrics of ganciclovir exposure

Because a range of doses was administered to the subjects, the ganciclovir exposure metric of interest was the area under the concentration-time curve from time 0 to infinity (AUC_{inf}). This metric was derived from the empirical Bayes estimates

of an individual's clearance parameter and the valganciclovir dose that subject received.

Additional statistical analyses

As this was an exploratory analysis, no formal sample size calculations were performed to power a particular statistical test. All demographic, pharmacokinetic, and clinical data are summarized descriptively.

Results

Study population

Thirty-two patients were screened for the study. Eight patients receiving valganciclovir for EBV prophylaxis were enrolled in the study (Table 1) and included in the pharmacokinetic analysis. Of these eight subjects, two participated in both the intensive and sparse sampling study visit categories. The remaining six subjects participated in the sparse sampling study visit that took place during two of their regularly scheduled transplant clinic appointments. All eight subjects were taking a valganciclovir suspension that contained 90 mg/mL and was prepared by the University of Minnesota Medical Center's Fairview Specialty Pharmacy. The median (range) doses administered were 11.1 (10.1 to 12.1) mg/kg every 12 hours and 7.4 (5.3 to 11.3) mg/kg every 24 hours.

Ganciclovir pharmacokinetics

A total of 43 plasma samples were available for determination of ganciclovir concentrations and used in the pharmacokinetic analysis. The observed ganciclovir plasma concentration-time data are presented in Figure 1. An attempt was made to

Table 1 Baseline subject characteristics (N = 8)

Characteristic	Median value	Range
Age, years	2.1	1.3–6.2
Weight, kg	14.1	9.4–19.8
Height, cm	89.5	73–107
Body surface area, ¹ m ²	0.6	0.4–0.7
Creatinine clearance, ² mL/min/1.73 m ²	106	61.9–127
Sex, n (%)		
a. Male	6	75
b. Female	2	25
Organ transplant, n (%)		
a. Kidney	5	63
b. Liver	3	37

Notes: ¹Body surface area (m²) = the square root of [(weight (kg) × height (cm))/3600]; ²Schwartz method: $[k \times \text{height (cm)}] / [\text{serum creatinine (mg/dL)}]$ where $k = 0.45$ for patients aged <2 years, and $k = 0.55$ for boys aged 2 to <13 years and girls aged 2 to 16 years.^{17–19}

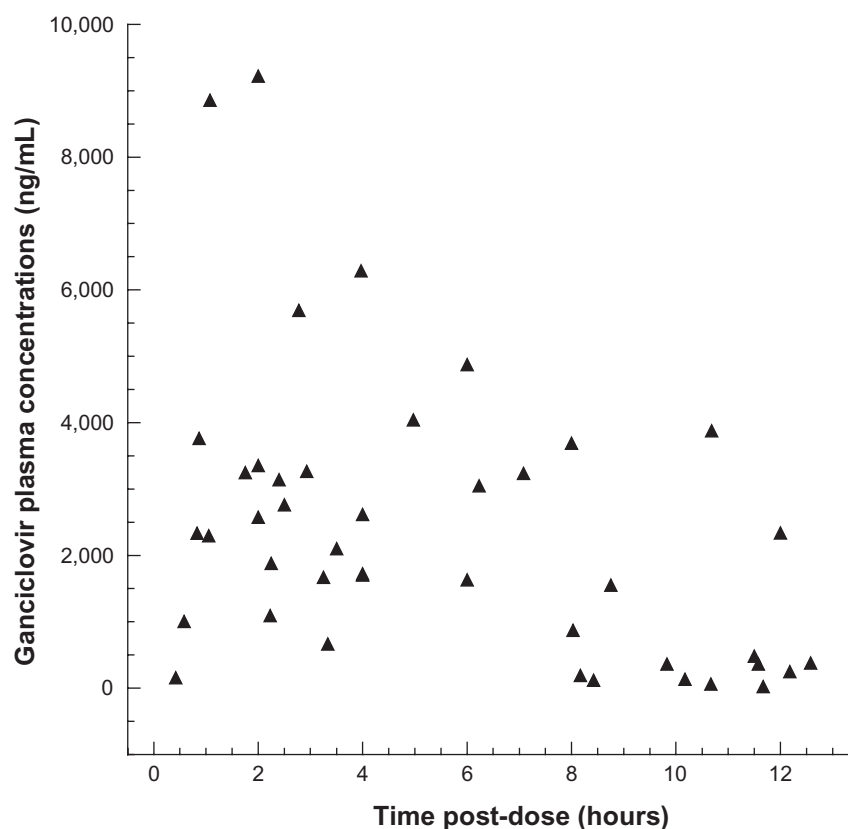


Figure 1 Concentration-time profile for ganciclovir in plasma following oral valganciclovir dosing.

fit these data to a two-compartment pharmacokinetic model in addition to a one-compartment model. The regression for the two-compartment model did not converge and the one-compartment model was chosen as the final pharmacokinetic model.

All parameter estimates and their relative standard errors for the final model are shown in Table 2. A plot of the observed versus the concentrations predicted under

the regression model is presented in Figure 2. Standard diagnostic plots suggested that the model was adequate to describe the data (data not shown). During model development an inverse relationship was observed for CL/F versus weight and CL/F versus age (Figures 3a and b). This is contrary to what was expected as CL (expressed in L/h) usually increases with an increase in body size (eg, weight, age, body surface area). However, in this case, the pharmacokinetic parameter is CL/F. We hypothesized that as age and weight increased, bioavailability could also be changing and confound the apparent relationship with CL. We explored an age effect on bioavailability to test this hypothesis and found evidence of decreasing bioavailability (F less than 65%) in subjects younger than three years compared with subjects older than three years but the signal was not sufficiently strong in this limited sample size to demonstrate statistical significance. Overall, none of the patient-specific covariates tested contributed statistically significant information about ganciclovir pharmacokinetic parameters. The median (range) *post hoc* estimated individual ganciclovir AUC_{inf} was 26.9 (16.5 to 51.5) ng · L/h for subjects with valganciclovir dosing every 12 hours and 13.5 (4.84 to 22.1) ng · L/h for dosing every 24 hours.

Table 2 Ganciclovir plasma pharmacokinetic parameters in 8 subjects following oral valganciclovir dosing

Parameter	Estimate	Relative SE
CL/F (L/h)	7.33	10.2%
V/F (L)	35.1	1.19%
Ka	0.85	20.8%
Variability in CL/F (CV%)	36.3%	25.5%
Variability in V/F (CV%)	41.4%	48.7%
Variability in Ka (CV%)	74.3%	237%
RUV (CV%)	33.5%	50.0%

Abbreviations: CL/F, apparent oral clearance; V/F, apparent volume of distribution; Ka, absorption rate constant; RUV, residual unexplained variability; CV, coefficient of variation for the between subject variability in the population; relative SE, measure of precision computed by dividing the standard error (SE) by the value of the estimate $\times 100$.

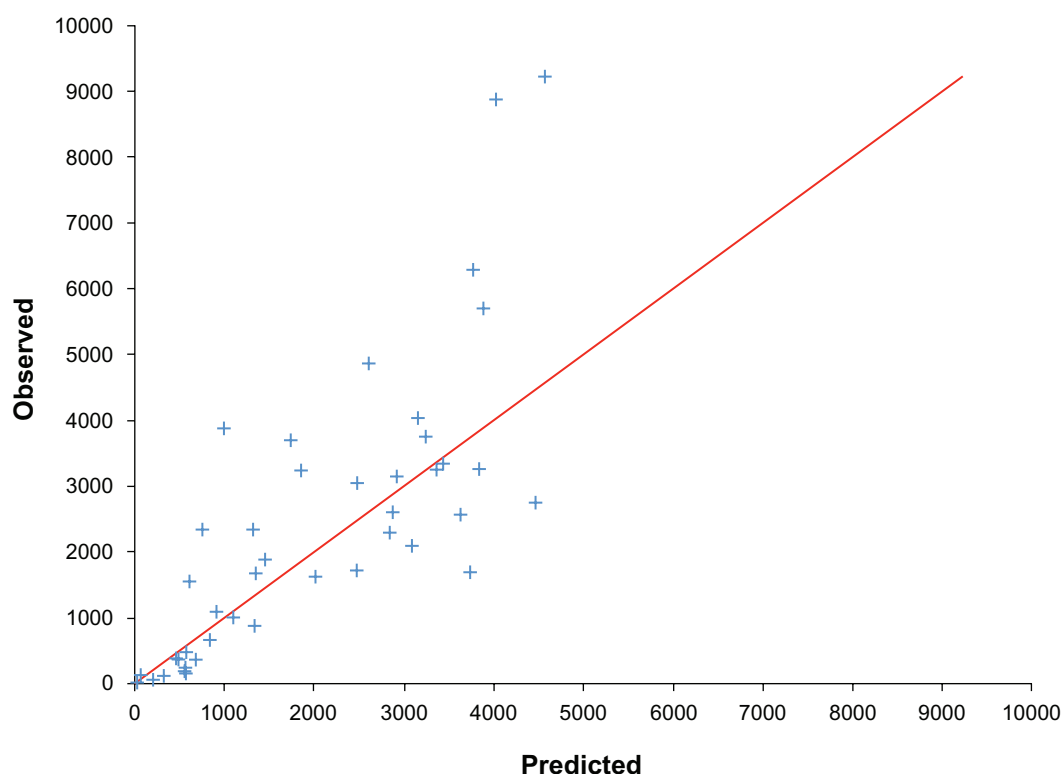


Figure 2 Observed versus model-predicted ganciclovir concentrations in plasma following oral valganciclovir dosing in eight subjects.
Note: The solid line is the line of identity.

Quantitative EBV DNA evaluations

Six out of eight subjects were EBV-antibody seronegative prior to transplantation. Five of these subjects seroconverted after receipt of their transplanted organ. During the study period, four out of eight subjects had undetectable qEBV measurements. In the remaining four subjects, the median (range) qEBV was 18,300 (4,400 to 54,900) copies/mL of whole blood. During the study, the median (range) duration of EBV viremia was 113.5 (36 to 238) days. In all eight subjects, measured ganciclovir plasma concentrations were well above the reported *in vitro* IC_{50} for EBV (as low as 0.05 μ M or 12.8 ng/mL).¹³ No subject in our cohort developed EBV-associated PTLD.

Discussion

Ours is the first report of the pharmacokinetics of ganciclovir following valganciclovir administration for the prevention of EBV-associated PTLD in pediatric kidney and liver transplant patients. Pharmacokinetics and drug exposure data are emerging for valganciclovir when it is used for the treatment of congenital cytomegalovirus (CMV) infection in neonates and for the prevention of CMV disease in children receiving solid organ transplantations.^{12,20–25} Our median (range) ganciclovir AUC_{inf} of 26.9 (16.5 to 51.5) ng · L/h

and 13.5 (4.84 to 22.1) ng · L/h for every 12-hour and every 24-hour dosing period, respectively, compare reasonably well to mean \pm standard deviation (SD) daily AUC values of 51.8 ± 11.9 μ g · h/mL, 61.7 ± 29.5 μ g · h/mL, and 58.0 ± 21.8 μ g · h/mL reported for pediatric kidney, liver, and heart transplant patients, respectively, who were receiving valganciclovir CMV prophylaxis. The study by Vaudry and colleagues²⁵ did not report parameter estimates for CL/F, V/F, and K_a . In addition, the investigators assessed ganciclovir pharmacokinetics after using a novel valganciclovir dosing algorithm that incorporated creatinine clearance by the Schwartz method and body surface area. Our transplant center uses weight-based valganciclovir dosing adjusted for changes in renal function. Different dosing strategies between institutions could explain the lower AUC estimates observed in some of our subjects who were receiving valganciclovir every 24 hours.

We also observed an inverse relationship between CL/F and age and CL/F and weight during covariate model development. Furthermore, we found evidence of a lower F in children younger than three years compared with children older than three years although this was not statistically significant. We attributed our findings to physiologic changes in bio-availability that occur during human growth and development.

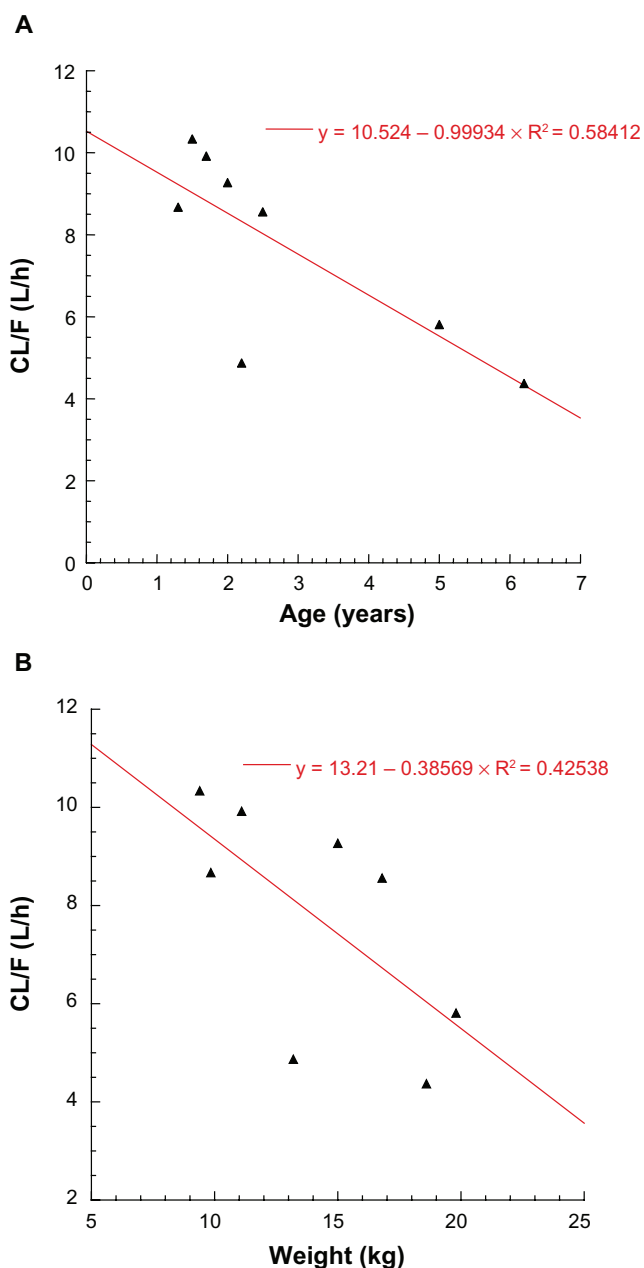


Figure 3 Ganciclovir apparent oral clearance (CL/F) versus **A**) age and **B**) weight.

The oligopeptide transporter PEPT1 facilitates the absorption of valganciclovir from the small intestine.²⁶ Even though little is known about the ontogeny of PEPT1 in humans, its expression has been shown to change markedly during early development in animal models.²⁷ Larger pharmacokinetic studies are needed to thoroughly explore inter-subject variability in F and the potential impact of bioavailability differences on valganciclovir dosing in children.

All eight subjects in our study achieved ganciclovir concentrations well above the reported *in vitro* IC₅₀ value for EBV but caution must be exercised when comparing

in vitro concentrations to those measured *in vivo* because of known differences in protein binding. However, only half of the subjects had undetectable qEBV measurements while receiving valganciclovir prophylaxis. This may have been due to multiple factors including inconsistent medication adherence, the presence of a resistant strain of EBV, or the circulation of latent, nonreplicating EBV DNA, which is not susceptible to antiviral therapy.

Conclusions

In conclusion, ganciclovir pharmacokinetics in pediatric kidney and liver transplant patients receiving valganciclovir for the prevention of EBV-associated PTLTD were well described by a one-compartment model. Bioavailability varied across subjects and based on moderately strong negative correlations between CL/F and age and CL/F and weight, F appears to be lower in children younger than three years. Virologic response to valganciclovir EBV prophylaxis was also variable. These data suggest that a larger clinical study of this preventative approach in pediatric solid organ transplant patients is warranted.

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References

1. Hanto DW, Frizzera G, Gajl-Peczalska J, et al. The Epstein-Barr virus (EBV) in the pathogenesis of posttransplant lymphoma. *Transplant Proc.* 1981;13:756–760.
2. Hanto DW, Sakamoto K, Purtilo DT, Simmons R, Najarian JS. The Epstein-Barr virus in the pathogenesis of posttransplant lymphoproliferative disorders. Clinical, pathologic, and virologic correlation. *Surgery.* 1981;90:204–213.
3. Hanto DW, Gajl-Peczalska KJ, Frizzera G, et al. Epstein-Barr virus (EBV) induced polyclonal and monoclonal B-cell lymphoproliferative diseases occurring after renal transplantation. Clinical, pathologic, and virologic findings and implications for therapy. *Ann Surg.* 1983;198:356–369.
4. The United States Department of Health and Human Services Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. 2007. *Annual Report: Pediatric Transplantation in the United States, 1997–2006*. Available from: http://www.ustransplant.org/annual_reports/current/chapter_iii_AR_cd.htm?cp=4. Accessed on September 21, 2009.

5. Newell KA, Alonso EM, Whittington PF, et al. Posttransplant lymphoproliferative disease in pediatric liver transplantation. Interplay between primary Epstein-Barr virus infection and immunosuppression. *Transplantation*. 1996;62:370–375.
6. Boyle GJ, Michaels MG, Webber SA, et al. Posttransplantation lymphoproliferative disorders in pediatric thoracic organ recipients. *J Pediatr*. 1997;131:309–313.
7. Mendoza F, Kunitaka H, Laks H, Odim J. Post-transplant lymphoproliferative disorder following pediatric heart transplantation. *Pediatr Transplant*. 2006;10:60–66.
8. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis*. 1995;20:1346–1353.
9. Ellis D, Jaffe R, Green M, et al. Epstein-Barr virus-related disorders in children undergoing renal transplantation with tacrolimus-based immunosuppression. *Transplantation*. 1999;68:997–1003.
10. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. *Am J Transplant*. 2005;5:2894–2900.
11. Razonable RR, Brown RA, Humar A, Covington E, Alecock E, Paya CV. Herpesvirus infections in solid organ transplant patients at high risk of primary cytomegalovirus disease. *J Infect Dis*. 2005;192:1331–1339.
12. Venturi C, Bueno J, Gavalda T, et al. Impact of valganciclovir on Epstein-Barr virus polymerase chain reaction in pediatric liver transplantation: preliminary report. *Transplant Proc*. 2009;41:1038–1040.
13. Lin JC, Smith MC, Pagano JS. Prolonged inhibitory effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine against replication of Epstein-Barr virus. *J Virol*. 1984;50:50–55.
14. Balfour HH Jr, Holman CJ, Hokanson KM, et al. A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis. *J Infect Dis*. 2005;192:1505–1512.
15. Hayden RT, Hokanson KM, Pounds SB, et al. Multicenter comparison of different real-time PCR assays for quantitative detection of Epstein-Barr virus. *J Clin Microbiol*. 2008;46:157–163.
16. Beal SL, Sheiner LB. *NONMEM User Guide*. San Francisco, CA: NONMEM Project Group; 1992.
17. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics*. 1976;58:259–263.
18. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. *J Pediatr*. 1984;104:849–854.
19. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr*. 1985;106:522–526.
20. Galli L, Novelli A, Chiappini E, et al. Valganciclovir for congenital CMV infection: a pilot study on plasma concentration in newborns and infants. *Pediatr Infect Dis J*. 2007;26:451–453.
21. Acosta EP, Brundage RC, King JR, et al; for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. *Clin Pharmacol Ther*. 2007;81:867–872.
22. Muller A, Eis-Hubinger AM, Brandhorst G, Heep A, Bartmann P, Franz AR. Oral valganciclovir for symptomatic congenital cytomegalovirus infection in an extremely low birth weight infant. *J Perinatol*. 2008;28:74–76.
23. Kimberlin DW, Acosta EP, Sanchez PJ, et al; for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis*. 2008;197:836–845.
24. Vethamuthu J, Feber J, Chretien A, Lampe D, Filler G. Unexpectedly high inter- and inpatient variability of ganciclovir levels in children. *Pediatr Transplant*. 2007;11:301–305.
25. Vaudry W, Ettenger R, Jara P, et al; on behalf of the Valcyte WV16726 study group. Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. *Am J Transplant*. 2009;9:636–643.
26. Sugawara M, Huang W, Fei YJ, Leibach FH, Ganapathy V, Ganapathy ME. Transport of valganciclovir, a ganciclovir prodrug, via peptide transporters PEPT1 and PEPT2. *J Pharm Sci*. 2000;89:781–789.
27. Shen H, Smith DE, Brosius III FC. Developmental expression of PEPT1 and PEPT2 in rat small intestine, colon, and kidney. *Pediatr Res*. 2001;49:789–795.

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