# Pediatric Dosage Calculation: Valganciclovir Pharmacokinetic Profiling in Pediatric Renal Transplant Recipients

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## Background

- Transplantation is a common practice for patients with end-stage renal disease.
- Infections are complications that are considered to be risk factors for morbidity and mortality in pediatric renal transplant patients.
- Despite 20 years of extensive clinical use of ganciclovir and valganciclovir as mainstay antiviral agents for cytomegalovirus (CMV) infections post-transplantation, debate remains about the most effective dosing methods in pediatric patients.

## Objectives

- This poster summarizes portions of this research completed to date.
- Objectives of this retrospective chart review study:
  - Investigate oral doses of valganciclovir administered to pediatric transplant patients.
  - Calculate pediatric valganciclovir dosages based on body weight.
  - Calculate pediatric valganciclovir dosages based on the manufacturer's dosing equation.
  - Relate valganciclovir doses to patient outcomes post-transplantation.
  - Calculate and model virtual valganciclovir pharmacokinetic behavior.

## Methods

Study Design & Data Collection

- The study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board (#6717).
- Open-label, single-center, retrospective chart review
- Study site: OHSU and Doernbecher Children's Hospital
  - Inclusion criteria: pediatric kidney transplant patients who required CMV prophylaxis with oral valganciclovir between 2006 to 2010. No exclusion criteria.
  - Sample size: Due to the exploratory nature of the study, statistical power considerations were not the basis for the sample size selected. All patients who entered the study were considered for the analysis.
- Data were collected via computerized medical and prescription records of pediatric kidney transplant patients using valganciclovir for CMV prophylaxis:
  - Demographic and dosing data: Age, height, weight, serum creatinine (SCr), start and end dates of valganciclovir therapy, and the prescribed valganciclovir doses.
  - Transplantation (Tx) data: Date of Tx, induction regimen, maintenance immunosuppression regimen, and presence or absence of transplant rejection and graft loss.
  - Outcomes data: CMV status pre- and post-Tx, BK viral status post-Tx, blood or plasma urea nitrogen, SCr, white blood cell count, hemoglobin, and platelet count.

## Procedures

- **Dosage Calculations:** Valganciclovir doses were calculated according to two different methods:

  1) Weight based dosing:
  Valganciclovir 18 mg/kg po once a day
  Reduce dose by 50% if creatinine clearance ($CL_{CR}$) < 50 mL/min/1.73m$^2$
  Reduce dose by 75% if $CL_{CR}$ < 25 mL/min/1.73m$^2$

  2) Manufacturer's recommended dosing equation:
  Pediatric Dose (mg) = 7 x Body Surface Area (BSA) x $CL_{CR}$, up to 900 mg po once a day
  Where $CL_{CR}$ was calculated using the Schwartz formula, and BSA was calculated using the Mostellar formula:

$$\text{Schwartz}\,CL_{CR}(\text{mL/min/1.73M}^2) = \frac{k \times \text{height(cm)}}{\text{Serum Creatinine(mg/dL)}}$$

$$\text{Mostellar BSA}(\text{m}^2) = \sqrt{\frac{\text{height(cm)} \times \text{weight(kg)}}{3600}}$$

- **Data Analysis:** Data were described as mean ± standard deviation (SD)

## Results

**Table 1. Patient Demographics and Renal Function**

| Subject Number | Age (years) | Weight (kg) | BSA[a] ($m^2$) | BUN[a] (mg/dL) | SCr[a] (mg/dL) | $CL_{CR}$[a] (mL/min/1.73m$^2$) |
|---|---|---|---|---|---|---|
| 1 | 6.36 | 20.0 | 0.81 | 21 | 0.23 | 282.89 |
| 2 | 14.98 | 46.6 | 1.44 | 24 | 1.23 | 91.34 |
| 3 | 6.49 | 22.7 | 0.85 | 13 | 0.40 | 156.20 |
| 4 | 19 | 64.0 | 1.63 | 58 | 13.01 | 7.00 |
| 5 | 7.52 | 20.9 | 0.81 | 5 | 0.40 | 153.59 |
| 6 | 2.48 | 12.7 | 0.55 | 8 | 0.28 | 167.16 |
| 7 | 8.70 | 18.3 | 0.79 | 12 | 0.39 | 172.05 |
| 8 | 18 | 87.9 | 2.10 | 87 | 5.19 | 28.70 |
| 9 | 15.09 | 66.5 | 1.79 | 19 | 1.25 | 97.16 |
| 10 | 17.35 | 46.9 | 1.37 | 18 | 0.62 | 109.50 |
| 11 | 10.20 | 33.4 | 1.12 | 23 | 0.70 | 105.68 |
| 12 | 13.04 | 75.3 | 1.78 | 18 | 0.94 | 112.52 |
| 13 | 18 | 65.4 | 1.75 | 18 | 1.80 | 61.56 |
| 14 | 5.15 | 17.6 | 0.71 | 9 | 0.40 | 143.55 |
| 15 | 15.08 | 43.8 | 1.36 | 16 | 0.90 | 117.83 |
| 16 | 17.75 | 56.0 | 1.54 | 15 | 0.80 | 101.03 |
| 17 | 16 | 37.7 | 1.22 | 34 | 3.30 | 29.91 |
| 18 | 5.68 | 18.1 | 0.76 | 26 | 2.10 | 27.80 |
| 19 | 16 | 47.8 | 1.41 | 6 | 0.60 | 136.77 |
| 20 | 16 | 49.8 | 1.47 | 13 | 1.40 | 61.29 |
| 21 | 15.30 | 67.8 | 1.72 | 11 | 0.60 | 143.92 |
| Mean ± SD. | 12.58 ± 5.18 | 43.8 ± 22.1 | 1.28 ± 0.44 | 22 ± 19 | 1.74 ± 2.84 | 109.88 ± 63.18 |

[a]BSA = Mostellar body surface area; BUN = blood/plasma urea nitrogen; SCr = serum creatinine; $CL_{CR}$ = creatinine clearance (Schwartz formula for age < 18 years; Cockcroft and Gault equation for age ≥ 18 years)

**Table 2. Initial Valganciclovir Dosing Regimen**

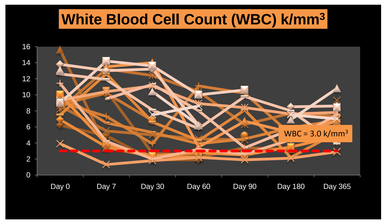
| Subject Number | Initial Valganciclovir Dosing Regimen | Actual Daily Dose (mg) | Manufacturer's Calculated Daily Dose (mg)[a] | FDA Revised Manufacturer's Calculated Daily Dose (mg)[a,b] | Weight Based Daily Dose (mg)[a] |
|---|---|---|---|---|---|
| 1 | 50 mg/mL oral suspension. 6 mL (300 mg) po QD | 300 | 1625 | 850 | 350 |
| 2 | 2 tabs (900 mg) po QD | 900 | 925 | 900 | 850 |
| 3 | 50 mg/mL oral solution. 8 mL (400 mg) po QD | 400 | 925 | 900 | 400 |
| 4 | 2 tabs (900 mg) po QD | 900 | 80 | 80 | 900 |
| 5 | 450 mg po QD | 450 | 875 | 850 | 375 |
| 6 | 60 mg/mL oral suspension. 2 mL (120 mg) po BID | 240 | 650 | 575 | 225 |
| 7 | 450 mg QOD | 225 | 950 | 825 | 325 |
| 8 | 450 mg po QD | 450 | 425 | 425 | 400 |
| 9 | 450 mg po QD | 450 | 1225 | 900 | 900 |
| 10 | 450 mg po QD | 450 | 1050 | 900 | 850 |
| 11 | 450 mg po QD | 450 | 825 | 825 | 600 |
| 12 | 450 mg po QD | 450 | 1400 | 900 | 900 |
| 13 | 450 mg po QD | 450 | 750 | 750 | 900 |
| 14 | 60 mg/mL oral suspension. 5 mL (300 mg) po QD | 300 | 725 | 725 | 335 |
| 15 | 450 mg po QD | 450 | 1125 | 900 | 775 |
| 16 | 450 mg po QD | 450 | 1090 | 900 | 1000 |
| 17 (CMV) | 450 mg po QD | 450 | 250 | 250 | 680 |
| 18 (CMV) | 60 mg/mL oral suspension. 2 mL (120 mg) po QD | 120 | 150 | 150 | 150 |
| 19 | 450 mg po QD | 450 | 1350 | 900 | 850 |
| 20 | 450 mg po QD | 450 | 650 | 650 | 900 |
| 21 | 450 mg po QD | 450 | 1725 | 900 | 1225 |

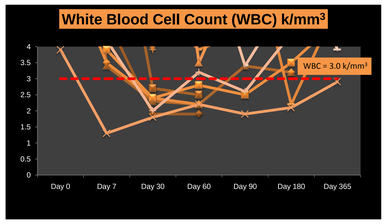
[a]Doses rounded to nearest 25 mg increment; [b]Maximum dose = 900 mg; upper limit $CL_{CR}$ = 150 mL/min/1.73m$^2$

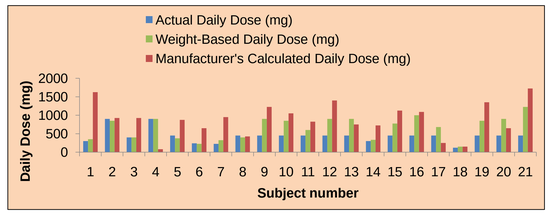
**Table 3. Patient Outcomes**

| Subject Number | Induction Regimen | Transplant Rejection, Graft Loss[a] | CMV[a] Status[b] | CMV [a] Disease | BK Viremia/ Viruria |
|---|---|---|---|---|---|
| 1 | Alemtuzumab | No | D -/R - | No | No |
| 2 | Alemtuzumab | No | D+/R - | No | No |
| 3 | Alemtuzumab | No | D+/R - | No | Day 90 |
| 4 | Alemtuzumab | No | D+/R+ | No | No |
| 5 | Daclizumab | No | D+/R - | No | No |
| 6 | Daclizumab | No | D+/R - | No | Day 365 |
| 7 | Alemtuzumab | No | D+/R+ | No | Day 60 |
| 8 | Alemtuzumab | No | D+/R - | No | Day 90 |
| 9 | Thymoglobulin | Yes, 6 months post –Tx. No graft loss. | D+/R+ | No | No |
| 10 | Alemtuzumab | No | D -/R - | No | No |
| 11 | Alemtuzumab | No | D+/R - | No | No |
| 12 | Daclizumab | No | D -/R - | No | No |
| 13 | Alemtuzumab | No | D+/R - | No | No |
| 14 | Daclizumab | No | D+/R+ | No | No |
| 15 | Alemtuzumab | No | D+/R - | No | No |
| 16 | Daclizumab | Yes, 11 & 12 months post-Tx. No graft loss. | D-/R+ | No | No |
| 17 | Daclizumab | Yes, 2, 6, 7, 8 months post-Tx. Graft loss 10 months post-Tx | D-/R- | CMV infection after 6 months on valganciclovir | No |
| 18 | Daclizumab | No | D+/R - | CMV viremia after 2 months on valganciclovir | No |
| 19 | Daclizumab | No | D+/R+ | No | No |
| 20 | Daclizumab | No | D-/R- | No | No |
| 21 | Daclizumab | Yes, 9 months post-Tx. No graft loss. | D+/R - | No | No |

[a]CMV = cytomegalovirus; [b]D = transplant donor ; R = transplant recipient ; - = negative; + = positive




## Conclusions

- Two patients (<10%) who received valganciclovir doses that were lower than weight-based or manufacturer's recommended dosing developed CMV viremia or infection.
- Eight patients (38%) developed leukopenia (WBC < 3.0 k/mm$^3$) during valganciclovir therapy, most likely due to chronic immunosuppressive therapy plus excessive valganciclovir dosing.
- No patients developed nephrotoxicity or thrombocytopenia during valganciclovir therapy (data not shown).
- Following the manufacturer's recommended valganciclovir dosing schedule can be associated with potential for overexposure, toxicity and greater drug costs compared to weight-based dosing.
- Ongoing studies include PK simulation to determine AUC arising from different dosing methods, comparison to target AUC of 40-50 mcg/mL, and evaluating the relationship to outcomes.