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ORIGINAL RESEARCH ARTICLE

Valganciclovir Pharmacokinetics in Patients Receiving Oral Prophylaxis Following Kidney Transplantation and Model-Based Predictions of Optimal Dosing Regimens

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Abstract

Background and Objectives Valganciclovir is used as oral prophylaxis for cytomegalovirus (CMV) infection in kidney transplant recipients. However, limited pharmacokinetic data exist to guide dosing in this patient group. This study aimed to describe the population pharmacokinetics of valganciclovir in a large sample of kidney transplant recipients and predict optimal dosing based on Monte Carlo simulations.

Methods Therapeutic drug monitoring (TDM) data from adult kidney transplant recipients who received valganciclovir prophylaxis during a 10-year study period were collected retrospectively. A non-parametric pharmacokinetic analysis and Monte Carlo simulations to determine the probabilities of reaching an area under the drug concentration–time curve (AUC) target of 40–50 mg·h/L with various dosing regimens at different levels of renal function were conducted using the Pmetrics™ package for R.

Results This study included 792 ganciclovir concentration measurements derived from 97 patients. A one-compartment oral absorption model best described the data. The final covariate model was as follows: CL(ganciclovir) = TVCL × $(CL_{CR}/51)^{0.75}$, where CL is the clearance, TVCL is the typical value of ganciclovir clearance, creatinine clearance (CL_{CR}) according to the Cockcroft-Gaultt equation and 51 is the mean CL_{CR} determined in the study. In the simulations, the probability of reaching the targeted AUC was insufficient when using the recommended dosing regimens for prophylaxis, especially in patients with impaired renal function at $CL_{CR} < 50$ mL/min.

Conclusions Higher doses of valganciclovir corrected to renal function are suggested for use as oral prophylaxis for CMV infection in kidney transplant recipients. Further study is required to establish TDM targets to ensure adequate drug concentrations while avoiding potentially toxic drug exposures.

Key Points

Valganciclovir is routinely used as oral prophylaxis for cytomegalovirus infection in kidney transplant recipients but limited pharmacokinetic data exist.

Based on the results of this study higher doses of valganciclovir corrected to renal function are suggested for this patient group.

Further study is needed to establish therapeutic drug monitoring targets to ensure adequate drug concentrations while avoiding potentially toxic drug exposures.

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1 Introduction

Ganciclovir is routinely used in kidney transplant recipients as oral prophylaxis for cytomegalovirus (CMV) infections during the first 100 days after transplantation. These patients are at high risk of not only developing clinical CMV infections but also other opportunistic infections as well as acute/chronic graft injury or rejection resulting from significant immunosuppression [1]. The incidence of CMV infection is higher in cases of a donor-positive and recipient-negative (D+/R−) serological status, in which the risk is estimated to be 60–80% unless adequate antiviral prophylaxis is prescribed [2].

Ganciclovir is available for intravenous and oral administration. For oral administration, ganciclovir is administered as a prodrug, valganciclovir, which enhances bioavailability and increases the likelihood of achieving therapeutic concentrations. Valganciclovir has a ten-fold higher mean bioavailability than ganciclovir (60.9 vs. 5.6%) [3]. The prodrug is rapidly hydrolysed to the active drug by esterases in the intestines and liver and ganciclovir is subsequently almost exclusively eliminated by renal excretion. The terminal half-life has been reported to be 4 h in CMV- and HIV-positive patients and healthy volunteers and longer (6.5 h) in solid-organ transplant recipients, probably because of concurrent treatment with nephrotoxic immunosuppressive drugs [4]. Dose reduction is required in patients with impaired renal function to avoid adverse effects such as bone marrow suppression (neutropenia, leukopenia, anaemia) and diarrhoea.

In a pivotal study, valganciclovir 900 mg once daily was shown to yield superior viral suppression compared with oral ganciclovir 1000 mg every 8 h in high-risk (D+/R–) solid-organ transplant recipients [5]. The area under the drug concentration–time curve (AUC) of ganciclovir was 1.7-fold higher in patients receiving valganciclovir and was hypothesised to be the reason for better outcomes in that group [6]. In this study, viral suppression was correlated to an AUC of 40–50 mg·h/L or higher. Therefore, an AUC target of 45 or 50 mg·h/L has been used in later population pharmacokinetic studies. In contrast, only a weak association was shown between AUC and leukopenia or neutropenia in this study. Other studies have demonstrated an association between AUC from time zero to 24 h (AUC_{24}) values > 50 mg·h/L and higher incidence of anaemia [15]. Still, there are no established pharmacokinetic targets for toxicity.

Several pharmacokinetic models have been developed for different patient populations, including solid-organ transplant recipients [7, 8]. However, some variability has been shown for the drug distribution and clearance and limited data exist to guide optimised dosing and dose adjustments in kidney transplant recipients. This study aimed to describe the population pharmacokinetics of valganciclovir in a large sample of kidney transplant recipients and to use Monte Carlo simulations to predict optimised dosing regimens for patients with various degrees of renal impairment.

2 Methods

2.1 Setting and Patients

This was a retrospective study using therapeutic drug monitoring (TDM) data from adult kidney transplant recipients who received oral valganciclovir as prophylaxis for CMV infection and were admitted to the Division of Nephrology of the Santa Maria della Misericordia University Hospital of Udine, Italy, between September 2007 and August 2016. None of the patients received renal replacement therapy. The study was approved by the Regional Ethics Committee and conducted in accordance with the Declaration of Helsinki and national and institutional standards. Informed written consent was waived due to the retrospective observational nature of the study.

2.2 Study Protocol, Treatment and Therapeutic Drug Monitoring

Prophylaxis was started within 10 days post-transplantation and was normally discontinued after 100 days. Valganciclovir was prescribed at dosage regimens ranging from 900 mg every 12 h to 450 mg every 48 h. The initial dosing regimens were based on estimated renal function according to the Standard Product Classification (Table 1). Longer inter-dose intervals were sometimes used during the maintenance phase if required to reach the target drug concentrations (as described below). Blood samples to determine creatinine and ganciclovir concentrations were taken from participants at least once weekly upon initiation of prophylaxis in order to individualise the valganciclovir dosage based on estimated renal function, which is often variable over time after transplantation, and measured drug concentrations. According to institutional guidelines, valganciclovir doses for prophylaxis were individualised to attain a plasma AUC_{24} of 40–50 mg·h/L [6] and trough concentration (C_{trough}) values of ≥ 0.3 mg/L [9]. As maximum concentrations (C_{max}) were only occasionally determined in the study patients and the exact sampling time in relation to administration had not been documented, the developed pharmacokinetic model was based on C_{trough} values only.

Table 1 Recommended dosing of valganciclovir for cytomegalovirus prophylaxis after solid organ transplantation and treatment of cytomegalovirus infection according to the Summary of Product Characteristics (SPC)

CL_{CR} (mL/min)	Prophylaxis	Treatment
≥ 60	900 mg (2 tablets) q24 h	900 mg (2 tablets) q12 h
40–59	450 mg (1 tablet) q24 h	450 mg (1 tablet) q12 h
25–39	450 mg (1 tablet) q48 h	450 mg (1 tablet) q24 h
10–24	450 mg (1 tablet) twice a week	450 mg (1 tablet) q48 h
< 10	Not recommended	Not recommended

CL_{CR} creatinine clearance, *qxh* every *x* h

2.3 Sample Handling, Storage and Analysis

Ganciclovir concentrations were analysed by means of a validated high-performance liquid chromatography (HPLC) method with UV detection, as previously described [10]. Precision and accuracy were assessed by performing replicated analysis of quality control samples against calibration standards. Intra- and inter-assay coefficients of variation were less than 10%. The lower limit of detection was 0.2 mg/L.

2.4 Population Pharmacokinetic Modelling

One- and two-compartment linear models with zero-order administration and first-order elimination from the central compartment were created and fitted to the observed concentrations using the non-parametric adaptive grid (NPAG) approach embedded within the Pmetrics™ package for R (Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA, USA; available at http://www.lapk.org) [11, 12]. Lambda was chosen for the error model. Individual pharmacokinetic parameters (total clearance [CL], volume of distribution [V_d] of the central compartment, first-order rate constant of elimination from the central to the peripheral compartment [k_{cp}] and vice versa [k_{pc}]) were computed using a maximum a posteriori (MAP) probability Bayesian technique. Initially, a base model without covariates that was parametrised only for ganciclovir CL and V_d was developed. Potential relationships between the population estimates for CL and V_d from each patient with a number of plausible clinical characteristics for inclusion as covariates, including the serum creatinine concentration, estimated creatinine clearance (CL_{CR}) according to the Cockcroft–Gault [13] and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations [14], body weight and sex, were examined using a forward inclusion process. Linear correlation and allometric scaling with a fixed exponent of 0.75 were tested. Covariates that significantly reduced the log likelihood ($P < 0.05$) and improved the goodness-of-fits plots were included in the model. A final multivariable model which included all the significant covariates was then constructed and refitted to the data.

2.5 Model Diagnostics

The goodness of fit of each model was evaluated by visual inspection of the population and individual observed versus predicted concentration plots. The coefficient of determination of the linear regression of the observed–predicted values and the log likelihood values from each run were also used to assess the goodness of fit. Further, mean prediction error (bias) and mean bias-adjusted squared prediction error (R^2, imprecision) for the population and individual predictions were evaluated. The accuracy of the final covariate model was assessed using a visual predictive check (VPC) after bootstrap resampling ($n = 1000$) and normalised prediction distribution errors [15].

2.6 Dosing simulations and Probability of Target Attainment

Monte Caro simulations ($n = 1000$) were performed using Pmetrics™ software to determine the probability of reaching an AUC_{24} of 30, 40, 50 or 60 mg·h/L with seven dosing regimens of valganciclovir (900 mg every 12 h, 900 mg + 450 mg every 24 h, 450 mg every 12 h, 900 mg every 24 h, 450 mg every 24 h, 450 mg every 48 h and 450 mg every 72 h) at different levels of renal function (15, 30, 50, 70, 90 and 110 mL/min). Dosing regimens that were associated with a 75–80% probability of achieving an $AUC_{24} > 40$ mg·h/L were considered permissible. An AUC of 50 mg·h/L was used as a tentative toxicity threshold according to the work by Padullés et al. [16], who observed that among 53 solid-organ transplant patients the incidence of anaemia was higher in patients with ganciclovir $AUC_{24} > 50$ mg·h/L than in other subjects (51.9 vs. 26.6%).

3 Results

3.1 Demographics and Clinical Data

Ninety-seven patients, 70 (72%) male, with a median age of 55 years (range 27–75 years) were included in the study. The mean serum creatinine concentration was 173 μmol/L

Table 2 Patient characteristics, serum creatinine concentrations and estimated clearance

Variable	Median	Mean (SD)	Range
Age (years)	55	53 (12)	27–75
Weight (kg)	73	74 (13)	45–114
Height (cm)	172	172 (8)	151–190
S-creatinine (μmol/L)[a]	158	173 (60)	87–384
CL_{CR} (mL/min)	46	48 (19)	17–118

CL_{CR} creatinine clearance estimated using the Cockcroft-Gault formula, *SD* standard deviation

[a]At initiation of therapy

(range 87–384 μmol/L) and the mean estimated CL_{CR} was 48 mL/min (range 17–118 mL/min) at initiation of therapy (Table 2). In total, 792 ganciclovir concentrations measurements were included. The median number of samples per patient was seven (range 1–25).

3.2 Pharmacokinetic Model

A one-compartment oral absorption model including a lag-time parameter for absorption best described the data. Only estimated CL_{CR} resulted in a significant reduction in the log likelihood (956 vs. 1048; $P = 0.018$) and was supported as a covariate in the final model. The final covariate model was as follows: $CL(ganciclovir) = TVCL \times (CL_{CR}/51)^{0.75}$, where TVCL is the typical value of ganciclovir clearance and 51 is the mean estimated CL_{CR} (in mL/min) determined in the study. The population parameter estimates are shown in Table 3. The diagnostic plots confirmed the appropriateness of the model (Fig. 1 and Fig. S1 in the Electronic Supplementary Material).

3.3 Dosing Simulations

Monte Carlo simulations of the probabilities of target attainment with varying renal function and dosing regimens are depicted in Fig. 2. The probability of target attainment when using the recommended dosing regimens for prophylaxis was approximately 75% for patients with estimated renal clearances of 70–90 mL/min and 64% of patients with CL_{CR} of 110 mL/min. For patients with an estimated CL_{CR} of 50 mL/min the AUC target was achieved in 50% of the patients and the lowest rates of target attainment (<25%) were predicted for patients with CL_{CR} values of 15 or 30 mL/min. The probability of AUC_{24} values exceeding the threshold of 50 mg·h/L, indicative of potential overexposure, is reported in Table 4.

Table 3 Parameter estimates for ganciclovir (administered as oral valganciclovir) from the final population pharmacokinetic model

Parameter	Mean (SD)	Coefficient of variation (%)	Median
CL (L/h)	9.03 (3.7)	40.80	8.63
V_d (L)	27.30 (15.9)	58.41	22.80
k_a (h^{-1})	0.395 (0.64)	161.50	0.077
F	0.71 (0.12)	17.03	0.655
Tlag (h)	0.46 (0.46)	100.19	0.266

CL population clearance of ganciclovir, *F* fraction of valganciclovir absorbed (bioavailability), k_a rate constant for the valganciclovir absorption from the intestinal tract, *SD* standard deviation, *Tlag* delay after an absorbed dose before observed in the blood, V_d apparent volume of distribution

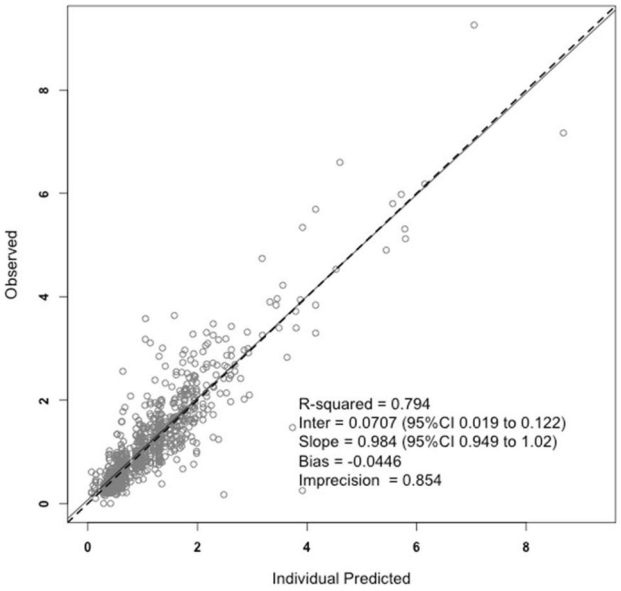

Fig. 1 Diagnostic plot of the observed versus individual predicted ganciclovir concentrations

4 Discussion

To our knowledge, this is the largest study describing the population pharmacokinetics of oral valganciclovir, measured as ganciclovir, in kidney transplant recipients. Estimated CL_{CR} was the main determinant of drug clearance in our study, which is expected due to the renal elimination of the drug. The pharmacokinetics of ganciclovir has previously been described with two-compartment models with an apparent V_d in the central compartment of 31.9 L [7] in one study and 0.391 × body weight in another study [8], which would correspond to 28.5 L in our study (mean weight 73 kg). Mean drug clearance has been reported to be 8.22 L/h [4], 7.49 × (CL_{CR}/57) L/h [7] or lower [8] in solid-organ transplant recipients and 14.06 L/h in healthy volunteers and HIV patients [3]. Our one-compartment model with an estimated mean V_d of 27.3 L and CL_{CR} of 9.03 L/min differs to some extent from other studies, which

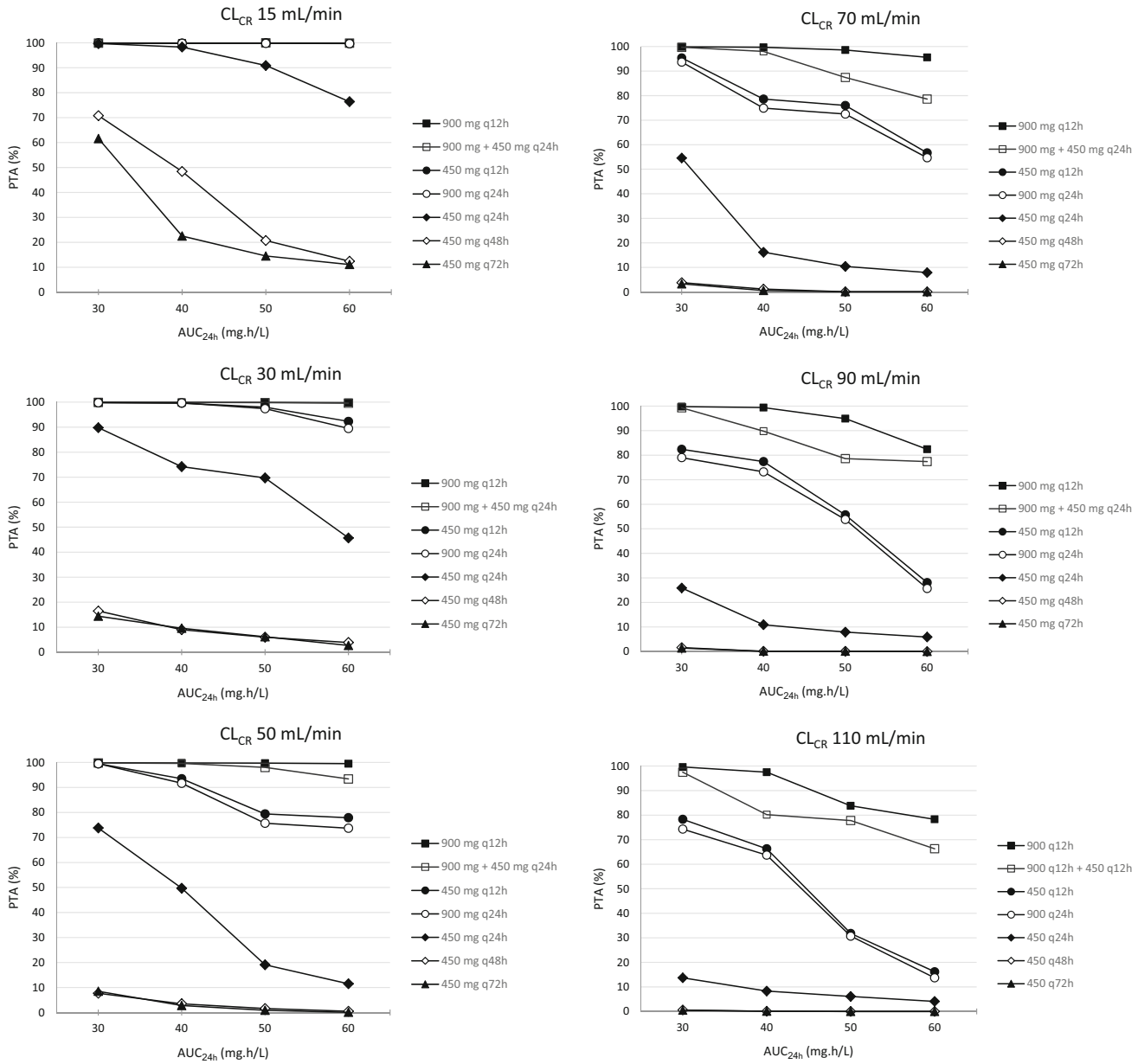

Fig. 2 Probabilities of target attainment (PTA) for area under the drug concentration–time curve from time zero to 24 h (AUC_{24}) of 30, 40, 50 or 60 mg·h/L with various dosage regimens at (CL_{CR}) means estimates according to Cockcroft-Gault ranging from 15 to 110 mL/min. *qx h* every *x* h

may in part be due to variations in patient populations. Caldés et al. [7] used data obtained from 20 solid-organ transplant recipients, of which ten were kidney transplants, treated with intravenous ganciclovir and oral valganciclovir for a total duration of 15 days [7]. In the study of Yuen et al. [8], data were derived from 53 CMV-infected patients treated with intravenous ganciclovir, only five of whom were kidney transplant recipients. The finding that a one-compartment model best described the data, in contrast with previous studies, is likely related to the fact that our model was based only on C_{trough} values.

Body weight was found a significant covariate in some previous studies [4, 8] but not all [7]. It is expected that we did not observe an effect of weight because the model was built only on C_{trough} values at assumed pharmacokinetic steady state, where CL_{CR} rather than weight would likely have influenced the observed concentration most. Sex was not supported as a separate covariate in the final model, although it is a component of the Cockcroft-Gault equation. This finding is in contrast with the study of Caldés et al. [7]. However, as pointed out by the authors, the correlations found in that study are uncertain due to the small

Table 4 Probabilities of reaching the therapeutic target of AUC_{24} 40 mg·h/L and tentative toxicity threshold of AUC_{24} 50 mg·h/L at various levels of renal function using recommended dosage for prophylaxis and treatment, respectively, according to the Summary of Product Characteristics (SPC)

CL_{CR} (mL/min)	Variable	Prophylaxis	Treatment
110	Recommended dose	900 mg q24 h	900 mg q12 h
	Probability of $AUC_{24} \geq 40$ (%)	64	98
	Probability of $AUC_{24} \geq 50$ (%)	31	84
90	Recommended dose	900 mg q24 h	900 mg q12 h
	Probability of $AUC_{24} \geq 40$ (%)	73	99
	Probability of $AUC_{24} \geq 50$ (%)	54	95
70	Recommended dose	900 mg q24 h	900 mg q12 h
	Probability of $AUC_{24} \geq 40$ (%)	75	100
	Probability of $AUC_{24} \geq 50$ (%)	73	99
50	Recommended dose	450 mg q24 h	450 mg q12 h
	Probability of $AUC_{24} \geq 40$ (%)	50	94
	Probability of $AUC_{24} \geq 50$ (%)	19	79
30	Recommended dose	450 mg q48 h	450 mg q24 h
	Probability of $AUC_{24} \geq 40$ (%)	9	74
	Probability of $AUC_{24} \geq 50$ (%)	6	70
15	Recommended dose	450 mg twice a week[a]	450 mg q48 h
	Probability of $AUC_{24} \geq 40$ (%)	23	48
	Probability of $AUC_{24} \geq 50$ (%)	15	21

AUC_{24} area under the drug concentration–time curve from time zero to 24 h, *CL_{CR}* means estimates according to Cockcroft-Gault, *qxh* every *x* h

[a]450 mg q72 h was used in the simulations

sample size and may have been subject to confounding as the female subgroup consisted of a high proportion of kidney transplant recipients. Estimates of bioavailability, lag time and the absorption constant were within the range of those reported in other studies [3, 4, 7]. Still, these values should be interpreted with caution considering the poor precision of estimates (Table 3) and the lack of sampling during the absorption and distribution phases, which is a main limitation of our study.

Few pharmacokinetic/pharmacodynamic investigations have been conducted to correlate ganciclovir exposure values with data on clinical outcomes, both for prophylaxis and treatment of CMV disease. In the case of prophylaxis, a randomised prospective study including 372 patients receiving ganciclovir or valganciclovir for prophylaxis of CMV diseases demonstrated viraemia suppression when the ganciclovir AUC_{24} target was between 40 and 50 mg·h/L. In this study, an AUC_{24} of 50 mg·h/L was associated with an average incidence of breakthrough viraemia of 1.3% at day 100, whereas AUC values lower than 25 mg·h/L were correlated with up to eight-fold higher viral replication rates [6]. However, according to our Monte Carlo simulations, the attainment of this target range with the recommended doses for prophylaxis was largely unsatisfactory, especially when CL_{CR} was <50 mL/min. This observation is consistent with the findings of two previous population pharmacokinetic studies. Padullés et al. [16] showed that the proportion of patients reaching AUC_{24} values of 40–50 mg·h/L when prescribed the recommended dosing regimen adjusted for renal function for prophylaxis was very low (21.3%) [16]. Similarly, in a mixed paediatric and adult solid-organ transplant patient population who received valganciclovir administered irrespective of renal function but according to time post-transplantation, Vezina et al. [17] showed that while 900 mg every 24 h gave an adequate therapeutic exposure (median AUC from time zero to infinity [AUC_{∞}] of 57.4 mg·h/L), the 450 mg every 24 h regimen did not attain the desired range (median AUC_{∞} of 34.3 mg·h/L) [17].

Consistent with this, to attain a probability of target attainment of approximately 75–80%, a refinement of the dosing strategy of valganciclovir toward the use of higher doses might be pursued. The following dosing regimens according to renal function variability might be suggested: 900 mg + 450 mg every 24 h at $CL_{CR} > 90$ mL/min, 450 mg every 12 h or 900 mg every 24 h at CL_{CR} 31–90 mL/min and 450 mg every 24 h at CL_{CR} 15–30 mL/min. In many cases, this will result in an $AUC_{24} > 50$ mg·h/L, which was associated with a high incidence of anaemia in the work by Padullés et al. [16]. However, only a weak correlation between exposure and adverse effects was found by others [5], and more research is required to validate the AUC target for toxicity. Monitoring for signs of toxic effects remains important in these patients and TDM

should ideally be used to individualise dosing as the window between therapeutic and toxic concentrations seems to be narrow.

5 Conclusion

Our results suggest that the currently recommended dosing regimens for prophylaxis are insufficient to reach the target of AUC of 40–50 mg·h/L, which is correlated with suppression of CMV viraemia in solid transplant recipients. Further study is warranted to evaluate the effect of optimised dosing on the prevention of CMV infection and the clinical validity of our findings. Furthermore, research to describe exposure targets for toxicity is required. Due to the variability between studies and patients, identification of suitable sampling points and concentration ranges would be valuable to enable improved TDM and optimised individualised dosing in this patient group.

Compliance with Ethical Standards

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Conflict of interest Thomas Tängdén, Pier Giorgio Cojutti and Federico Pea declare no conflicts of interest. Jason A. Roberts has received investigator-initiated grants from, or has consulted for, bioMérieux, Astellas, MSD and Cardeas Pharma.

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