Population Pharmacokinetic and Pharmacodynamic Analysis of Valganciclovir for Optimizing Preemptive Therapy of Cytomegalovirus Infections in Kidney Transplant Recipients

Population pharmacokinetic and pharmacodynamic analysis of valganciclovir for optimizing preemptive therapy of cytomegalovirus infections in kidney transplant recipients

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Abstract

This study aimed to develop a population pharmacokinetic/pharmacodynamic (PK/PD) model of valganciclovir for preemptive therapy of cytomegalovirus (CMV) infection in kidney transplant patients. A population PK/PD model was developed with Monolix. Ganciclovir concentrations and CMV viral loads were obtained retrospectively from kidney transplant patients receiving routine clinical care. Ten-thousands Monte Carlo simulations were performed with the licensed dosages adjusted for renal function to assess the probability of attaining a viral load target ≤290 and ≤137 IU/mL. Fifty-seven patients provided 343 ganciclovir concentrations and 328 CMV viral loads for PK/PD modelling. A one-compartment pharmacokinetic model coupled with an indirect viral turnover growth model with stimulation of viral degradation pharmacodynamic model was devised. Simulations showed that 1- and 2-$\log_{10}$ reduction of CMV viral load mostly occurred between a median of 5-6 and 12-16 days, respectively. The licensed dosages achieved a probability of reaching the viral load target ≥90% at days 35-49 and 42-56 for the thresholds of ≤290 and ≤137 IU/mL, respectively. Simulations indicate that in patients with estimated glomerular filtration rate of 10-24 mL/min/1.73m^2, a dose increase to 450 mg every 36h may reduce time to optimal viral load target to days 42 and 49 from a previous time of 49 and 56 days for the thresholds of ≤290 and ≤137 IU/mL, respectively. Currently licensed dosages of valganciclovir for preemptive therapy of CMV infection may achieve a viral load reduction within the first two weeks, but treatment should continue for ≥35 days to ensure viral load suppression.

Introduction

Kidney transplant (KT) recipients are at high risk of cytomegalovirus (CMV) infection and disease. CMV is a double-stranded DNA virus that is part of the *Herpesviridae* family causing both direct and indirect effects in KT recipients (1). Direct effects predominantly include end-organ CMV disease such as pneumonia, retinitis, colitis, and nephritis (1). Indirect effects can include graft rejection, propagation of atherosclerosis and vascular disease, and reduced renal function (2-4). Therefore, CMV viremia and disease prevention is of critical importance in mitigating the negative sequelae following KT.

The risk of CMV disease, viremia and associated sequelae may be reduced with antivirals such as valganciclovir (5-7). Valganciclovir is an oral prodrug of ganciclovir with an improved bioavailability over the parent drug (~65%), which is rapidly converted to ganciclovir after reaching the bloodstream (8). Ganciclovir is renally eliminated, necessitating dose adjustments in renal failure, which is a critical consideration given the high potential for renal function fluctuations in KT patients. Therapeutic drug monitoring (TDM) of ganciclovir is used in some centres and could represent a valuable tool to minimize the likelihood of subtherapeutic drug dosing in KT patients, which may increase the risk of CMV viremia (9-11).

A problem in the implementation of TDM is the sparse data describing associations between ganciclovir exposure with efficacy and toxicity. In one study, a ganciclovir 24h-area under the concentration-time curve (AUC_{24h}) >50 mg·h/L was associated with CMV viremia suppression, but the findings were not confirmed in two smaller studies (12, 13). Other recent studies did not find any appreciable difference in viremia suppression when an AUC_{24h} >50 mg·h/L target was achieved using a low (450 mg daily) or a high (900 mg daily) dose of valganciclovir (13-15). A recent clinical pharmacokinetic/pharmacodynamic (PK/PD) study demonstrated a slow decline of the viral load among patients receiving either valganciclovir orally or ganciclovir intravenously for preemptive therapy, taking approximately 12.5 days to achieve a 1-$\log_{10}$ DNA copies/mL viral load decrease (16). Finally, in another study, ganciclovir trough concentrations (C_{trough}) >2.6 mg/L were associated

with adverse events such as myelosuppression; however a paucity of data exists adequately describing the toxicodynamics of valganciclovir (10). Overall, these findings suggest that optimal dosing and therapeutic targets of valganciclovir in patients receiving preemptive therapy remain unclear.

The aim of this study was to perform a population PK/PD analysis to describe the CMV viral load in relation to ganciclovir exposure over time in a cohort of KT patients receiving preemptive therapy for CMV infection and to simulate the attainment of CMV viremia suppression thresholds associated with the licensed doses.

Results

Demographics and clinical data

Fifty-seven patients were included in this PK/PD analysis (Figure 1). The median (min-max range) age, weight and estimated glomerular filtration rate (eGFR) of included patients were 55 (30 - 75) years, 73 (43 - 103) kg and 36.9 (4.5 - 76.2) mL/min/1.73 m^2, respectively (Table 1). At the start of valganciclovir treatment, 36.8% (21/57) patients had eGFR <30 mL/min/1.73m^2, while 15.8% (9/57) patients had eGFR ≥60 mL/min/1.73m^2. The median (min-max range) duration of valganciclovir treatment was 49 days (14 - 138 days). The median (min-max range) number of valganciclovir concentration and CMV viral load assessments per patient were 5 (1 - 13) and 5 (2 - 12), respectively. The median (min-max range) C_{trough} was 1.06 (0.18 - 10.75) mg/L. The median CMV viral load at baseline was 4.09 log_{10} IU/mL, with a wide inter-individual variability (CV% of 247.33%). One patient had CMV re-activation after 54 days following an undetectable viral load. Another patient had persistent viremia after 18 days of treatment.

Population PK/PD modelling

A total of 343 ganciclovir plasma concentrations were included in the pharmacokinetic model. A one-compartment model with first-order absorption and elimination was used as the base model and eGFR was included as a covariate on clearance (CL) in the final population pharmacokinetic model. The final covariate model showed a coefficient of determination of the observed versus population-predicted concentration of R^2 = 0.53 and of the observed versus individual-predicted concentration of R^2 = 0.82 (Figure 2, panel A and B, respectively). The population ganciclovir PK posterior parameters mean (SD) values were 10.88 (3.32) L/h for CL, 28.40 (40.52) L for volume of distribution (Vd), 0.39 (0.84) h^{-1} for rate constant of valganciclovir absorption (ka) and 0.74 (0.15) for oral bioavailability.

Bayesian individual posterior median estimates of the pharmacokinetic parameters were used as covariates in the pharmacodynamic model. The fit of the linked PK/PD model to the data was

acceptable, with an $R^2 = 0.67$ for the observed versus population-predicted values (Figure 2, panel C) and an $R^2 = 0.98$ after the post-hoc Bayesian step (Figure 2, panel D). The visual predictive check plot of the pharmacodynamic model demonstrated acceptable predictive performance of the dataset viral load values given that the 10^{th}, 50^{th} and 90^{th} percentiles of the observed data were inside the simulated prediction intervals (Figure 3). The parameter estimates of the pharmacodynamic model are summarized in Table 2. All pharmacodynamic parameters were estimated with good precision. A relatively high residual squared error (RSE)% was observed for the EC_{50}, but the absolute value was consistent with ganciclovir plasma concentrations observed in patients.

Monte Carlo simulation

The $\log_{10}$ CMV viral load-versus-time trend of the 10000 Monte Carlo simulated subjects (Table 3; Figure S1) showed that all but one of the four valganciclovir dosages adjusted for renal function followed a similar decline over time. All dosing regimens achieved 1-$\log_{10}$ decline within 5-6 days of treatment; however, patients with severe renal dysfunction needed three more days compared to patients in all the other classes of renal function (16 vs. 12-13 days) to achieve a viral load reduction of 2-$\log_{10}$. Consequently, we simulated an alternative dosage in patients with severe renal dysfunction, namely 450 mg administered every 36 h. Simulations showed that this higher dosage did not shorten time to 2-$\log_{10}$ decrease in patients with severe renal dysfunction but reduced the time to achieve the optimal viral load target of CMV viral load ≤290 and/or ≤137 IU/mL (Table 4).

Currently licensed dosing regimens reduced the viral load to <290 IU/mL by 35, 42 and 49 days in patients with normal-mild, moderate and severe renal function, respectively. Likewise, regarding the more restrictive threshold of ≤137 IU/mL, 42 to 49 days were required for patients with normal renal function and in those with mild-to-moderate renal dysfunction respectively to achieve the target viral threshold. Conversely, patients with severe renal dysfunction required 56 days of treatment. Of note, intensifying the dosage in patients with severe renal dysfunction from 450 mg

administered every 48 h to 450 mg every 36 h reduced the time to achieve optimal viral load target to those comparable to the other licensed doses (namely, 35 days for time to ≤290 IU/mL and 49 days for time to ≤137 IU/mL).

Discussion

In this study, we developed a pharmacodynamic model of valganciclovir for preemptive therapy of CMV infection in KT patients. Our joint PK/PD population model was based on real-world clinical data that describe changes in CMV viral loads over time. Overall, we found that standard doses of valganciclovir produced a rapid decline of viral load within the first 1-2 weeks, but a longer duration of therapy up to 42-49 days may be required for CMV suppression.

A separate population PK/PD model studied the effect of valganciclovir in reducing CMV viral load in a mixed population of 17 hematopoietic stem-cell and solid organ transplant patients who received either intravenous ganciclovir or oral valganciclovir as prophylaxis, pre-emptive treatment or therapy for established infection caused by CMV and/or HHV-6 (16). The differences in study design and patient population impede a direct comparison of results. However, the EC_{50} value in the previously described study was 200-fold higher than in ours [13.86 mg/L or 54 µM vs. 0.12 mg/L (0.47 µM)], with our estimation in line with previously reported *in vitro* data (range 0.04-37.2 µM) (17). Additionally, the time to achieve a 1-log_{10} decline in the CMV viral load in that study was more than double compared to our model (12.5 vs. 5-6 days).

Monte Carlo simulations showed that the profile of the viral decline over time was quite similar with the approved dosages among different classes of renal function. Most patients achieved a 2-log_{10} decline within 16 days. After that time, the further decrease of viral load was slow. Of interest, the initial reduction in the viral load was not influenced by the viral load at baseline (R0). In contrast, the achievement of the target thresholds depends on patient initial viral load, suggesting that higher initial viral loads may require more time for clearance. Moreover, the dosing regimen licensed for the lowest level of renal function, namely 450 mg every 48 h, was associated with the longest time to reach optimal target attainment. In this regard, a dose increase to 450 mg every 36 h in patients with eGFR 10-24 mL/min/1.73 m^2 may be considered. However, the target PTAs are always achieved after day 35.

From a clinical perspective, these findings support a pre-emptive treatment duration of 14 days, as currently recommended by international guidelines (18, 19). An extension of treatment of other 3-6 weeks may be considered in patients who have yet to achieve sustained viral load suppression with the current licensed dosages adjusted for renal function. Additionally, clinicians should also consider the possibility of acquired resistance to ganciclovir, due to the UL97 or UL54 genetic mutations in patients who fail to clear the CMV viraemia (20).

The PK/PD of antivirals is not well-defined, even at a pre-clinical level (21). In fact, for antivirals there is no standard pharmacodynamic parameter such as the minimum inhibitory concentration (MIC) for testing antiviral susceptibility as is available for bacterial infections. Thus, the ganciclovir AUC_{24h} has been used as a surrogate metric of efficacy. The exposure-response relationship of ganciclovir has been mainly based on results from two prospective clinical trials in solid organ transplant recipients that associated systemic exposure with the risk of developing CMV viremia. Wilthshire et al. in 372 solid organ transplant (SOT) recipients found that an AUC_{24h} of 50 mg·h/L predicted an average incidence of viremia of 1.3%, whereas an AUC_{24h} <25 mg·h/L was associated with eight-fold risk increase (22). Padulles at al. observed that an AUC_{24h} of 40-50 mg·h/L in 55 SOT patients was associated with shorter time to CMV clearance, less CMV viremia breakthrough and less CMV disease recurrence (23).

We are aware that this study has some limitations. First, its retrospective nature and the number of pharmacokinetic and pharmacodynamic observations that was limited for some patients. This may have generated individual posterior parameters that were more affected by the population values than by the individualized estimates. Second, we did not have the possibility to collect clinical outcome data to verify delayed-onset CMV disease after completion of preemptive treatment. We recognize toxicity warrants further investigation especially when considering dosages that are higher than currently recommended. On the other hand, our model had the advantage of accounting for CMV load values below the limit of quantification of the assay method. This approach is innovative as it enabled to overcome the LOQ of the analytical method, thus allowing us to obtain complete CMV

profiles over time for all patients. Third, even if our population was homogenous in terms of type of transplant and immunosuppressive regimen, we recognize the effect of baseline CMV viral loads, as this may affect the required duration of therapy to achieve viral clearance (24). Finally, we recognize that newer analytic methods for TDM of ganciclovir which are more specific and sensitive than ours are available (25).

In conclusion, we developed a PK/PD model of valganciclovir for pre-emptive therapy of CMV in KT patients. We observed that approved dosages produce a rapid decline of viral load over the first two weeks. Further viral load reductions occur at a slower rate and more than 35 days of drug administration may be required to achieve viral load suppression. A prospective study is warranted to confirm the reliability of our findings.

Materials and Methods

Setting

This was a retrospective single-centre study conducted among adult *de novo* KT recipients who received valganciclovir for preemptive therapy against CMV infection at the Santa Maria della Misericordia University Hospital of Udine, Italy. The study was approved by the Ethics Committee of the Friuli-Venezia Giulia Region. Due to the retrospective nature of this investigation, informed written consent was waived.

Study Population

Pre-emptive therapy with valganciclovir was started in those patients with high risk D+/R- and/or R+ status and with a detectable CMV DNA viral load (>2.46 $\log_{10}$ IU/mL equal to >500 copies/mL, 1 UI/mL = 1.72 copies/mL) identified during routine weekly monitoring. Patients requiring renal replacement therapy and those with a previous kidney rejection were excluded. All the patients received an immunosuppressive regimen that included tacrolimus (C_{trough} targeted at 5-8 ng/mL), mycophenolate and prednisone. Valganciclovir therapy was started at the dosages recommended by the Summary of Product Characteristics according to the different classes of renal function [900 mg every 12h in patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2, 450 mg every 12h for eGFR 40-59 mL/min/1.73m^2, 450 mg every 24h for eGFR 25-39 mL/min/1.73m^2 and 450 mg every 48h for eGFR 10-24 mL/min/1.73m^2].

Local protocols recommended that ganciclovir plasma concentrations were measured at trough with a target range of 0.31-1.63 mg/L, according to (26). Our approach to dose adjustments of valganciclovir was to increase the dose if plasma trough concentration were <0.3 mg/L and to reduce the dose when >2 mg/L. Blood samples were collected after 72 h from starting therapy, immediately prior to dose administration and, whenever feasible, 2h after administration for assessing

the maximum plasma concentration (C_{peak}). All patients were administered the drug at empty stomach. Ganciclovir concentrations and CMV DNA were assessed every one or two weeks up to end of treatment. Therapy was discontinued when CMV DNA viral load was undetectable after two consecutive weekly assessments.

The following demographic and clinical data were retrieved from each patient's medical record: age, gender, weight, height, donor/recipient serological status, serum creatinine, ganciclovir concentration and CMV viral load. Differently from what is reported in the Summary of Product Characteristics of valganciclovir in which dose adjustments are based on creatinine clearance estimated by means of the Cockcroft-Gault formula, in this study eGFR by means of the CKD-EPI formula (27) was used. This because at our Institution eGFR based on CKD-EPI has been adopted for reporting glomerular filtration rate, as it showed higher accuracy than creatinine clearance based on Cockcroft-Gault formula (28).

Sample Measurement

Ganciclovir concentrations were analyzed with a validated high-performance liquid-chromatography methods with ultraviolet detection, as previously described (29). Precision and accuracy were assessed by replicate analysis of quality control samples against calibration standards. Intra- and inter-assay coefficients of variation were always <10%. The lower limit of detection was 0.2 mg/L.

CMV viral load was measured in plasma by collecting 5 mL of venous blood samples treated with EDTA. Nucleic acids were extracted using the VERSANT® kPCR Molecular System SP (Siemens Healthcare). Detection and quantification of CMV specific DNA was performed with the RealStar® CMV PCR Kit 1.0 (Altona Diagnostics GmbH, Hamburg, Germany) on the real-time PCR VERSANT® kPCR Molecular System AD (Siemens Healthcare). The lower limit of quantification (LOQ) was 290 UI/mL (500 copies/mL).

Population pharmacokinetic/pharmacodynamic analysis

In order to overcome model instability and avoid biases when fitting simultaneously the pharmacokinetic and pharmacodynamic data in a joint PK/PD model, a sequential model was used, as already performed (16). Firstly, a pharmacokinetic model was built and fitted to the data. This PK model was based on the previously developed population pharmacokinetic model of Tangden et al. (30). The median Bayesian posterior estimates of the pharmacokinetic parameters were obtained for each patient. Secondly, a pharmacodynamic model was developed and fitted to the individual CMV viral load profiles over time. For this purpose, the pharmacokinetic posterior estimates were supplied as covariates and the CMV viral loads were expressed in IU/mL and converted to $\log_{10}$ scale. Patients undergoing renal replacement therapy were excluded.

Population pharmacokinetic modeling was conducted with the non-parametric adaptive grid (NPAG) approach implemented within Pmetrics (version 1.5.2) (31) for R (version 3.6.1). Since most ganciclovir concentrations were C_{trough}, modelling was based according to the one-compartment model developed by Tangden et al. (30) which included mainly C_{trough} values and eGFR as covariate of ganciclovir total clearance. Moreover, a non-parametric approach was preferred to a parametric one, as it allows more flexibilities in parameter estimates considering that it holds the ability to accommodate parameter probability distribution of any shape (32). The Bayesian pharmacokinetic posterior estimates obtained from each patient were extracted from Pmetrics and implemented as covariates in the pharmacodynamic model.

Pharmacodynamic modelling was performed using Monolix software (version 2021R1, Lixofit, Antony, France). The structural pharmacodynamic model was an indirect viral turnover model with stimulation of the viral degradation as follows:

$$\frac{dR}{dt} = kin - kout \times \left(1 + \frac{Emax \times Cp}{EC50 + Cp}\right) \times R$$

where R represents the response (i.e., CMV viral load in plasma); $\frac{dR}{dt}$, represents the changing rate of viral load in plasma relative to time, *Cp,* is the ganciclovir plasma total concentration; *kin* and *kout*, represent the increasing and declining growth and elimination rates of CMV viral load in plasma respectively; $EC_{50,}$ the ganciclovir concentration causing half-maximal rate of killing, and *Emax*, the maximum rate of CMV viral load decline. The initial CMV viral load at time 0 (R0) was equivalent to the *kin/kout* ratio (R0=$kin/kout$).

In addition, the Monolix software offered the chance of handling censored values, namely values of CMV viral load below the LOQ. The SAEM algorithm of Monolix may simulate below-limit of quantification (BLQ) values by taking into account the prediction at the time of the BLQ and its respective residual error distribution. If the sampled residual error is within the censored interval, then the simulated BLQ value is obtained, otherwise it is rejected and the iteration repeated. Simulated BLQs are then used for fitting and producing the observed versus predicted plots. In this way, censored values were incorporated into the model analysis.

Evaluation of the PK/PD model was based on the following goodness-of-fit plots: observation versus individual and population predictions, residual-based plots (individual weighted residuals and population-weighted residuals), and the visual predicted check (VPC) plot. The VPC plot depicts the time course of the 10^{th}, 50^{th}, and 90^{th} percentiles of ganciclovir concentrations or CMV viral loads and the corresponding 90% prediction intervals calculated from 500 Monte Carlo samples. One thousand nonparametric bootstrap iterations with resampling of each population parameter were simulated with the Rsmlx package of R (R speaks Monolix) and median (IQR) values of each parameter were reported. A comparison of the performances of the joint and the sequential PK/PD models is reported as supplemental material (Table S1 and Figure S2). The observed vs. predicted concentration plot of both the pharmacokinetics and pharmacodynamics were replotted in R.

Monte Carlo simulation and probability of viral load target attainment

Monte Carlo simulations were performed by means of Simulx 2020R1. The developed PK/PD was used to generate 10000 CMV viral load vs. time profiles for each of the four valganciclovir dosing regimens approved for pre-emptive therapy in relation to the different classes of renal function (900 mg every 12h for eGFR 60-130 mL/min/1.73m^2, 450 mg every 12h for eGFR 40-59 mL/min/1.73m^2, 450 mg every 24h for eGFR 25-39 mL/min/1.73m^2 and 450 mg every 48h for eGFR 10-24 mL/min/1.73m^2). Simulations were conducted in Simulx using the PK/PD population parameters with their respective inter-individual variability (omega values) and by re-parameterizing the population clearance with eGFR according to a power function as previously described (30).

The decline of CMV viral load over time was calculated for each simulated profile and expressed as 1- and 2-$\log_{10}$ decline from the initial value.

The probability of viral load target attainment using thresholds of ≤290 and ≤137 IU/mL with the four different recommended dosing regimens were calculated. The threshold of 290 IU/mL corresponded to the LOQ of our CMV-DNA monitoring assay. The threshold of 137 IU/mL was selected based on the findings of Razonable et al. (24) who showed that this value was associated with CMV suppression level predictive of clinical disease resolution among the 267 solid organ transplant patients included in the VICTOR clinical trial (33). Optimal target attainment was defined as ≥90%.

If one or more of the licensed doses appreciably differed from the others, alternate dosing regimens were simulated to achieve a similar viral suppression.

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Authorship

PGC, FP, JR, TT and AJH conceptualized the study, conducted the analysis and drafted the manuscript. PGC and PDS acquired and interpreted clinical data. CT, JR and FP supervised the project and reviewed the entire contents of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Table 1. Demographics and clinical characteristics

Patient demographics	
Total number of patients	57
Age (years)	55 (49 - 63)
Gender (male/female)	43/14
Body weight (kg)	73.0 (68.5 - 82.0)
Height (m)	1.70 (1.68 - 1.78)
eGFR (mL/min/1.73m^2)	36.9 (28.1 - 52.9)
Ganciclovir treatment	
Median dose (mg)	491.45 (425.77 - 652.50)
Length of treatment (days)	49.0 (29.0 - 63.0)
No. of TDM assessment per patient	5.0 (4.0 - 8.0)
Pharmacokinetics	
Ganciclovir trough concentration (mg/L)	1.06 (0.65 - 1.75)
Pharmacodynamics	
Baseline CMV load (log_{10} IU/mL)	4.09 (3.66 - 4.68)
Time to undetectable viral load (days)	16.0 (7.75 - 23.25)

Data are presented as median (IQR) for continuous variables, and as number (%) for dichotomous variables.

eGFR, estimated glomerular filtration rate

Table 2. Summary of the population pharmacodynamic model

Parameter	Value (%RSE)	Median (25th to 75th percentiles) of the bootstrap
Fixed Effects		
R_0 (IU/mL)	4.13 (2.63)	4.13 (4.05 - 4.21)
k_{out} (h^{-1})	0.00045 (24.3)	0.00042 (0.00033 - 0.00051)
E_{max}	6.16 (21.2)	7.14 (5.28 - 7.80)
EC_{50} (mg/L)	0.12 (70.3)	0.01428 (0.0073 - 0.162)
Standard deviation of the Random Effects		
ω R_0	0.16 (14.2)	0.15 (0.141 - 0.161)
ω K_{out}	0.60 (24.5)	0.51 (0.444 - 0.588)
ω E_{max}	0.40 (40.8)	0.42 (0.261 - 0.468)
ω EC_{50}	0.74 (43.3)	1.33 (0.861 - 1.611)
Residual variability		
b (proportional)	0.12 (10.9)	0.12 (0.108 - 0.126)

Table 3. Simulated median (25^{th}-75^{th} percentiles) time to 1- and 2-$\log_{10}$ CMV viral load decline with the recommended dosages of valganciclovir for preemptive therapy adjusted for renal function

eGFR (mL/min/1.73m^2)	Recommended dosage	Days to 1-log decline	Days to 2-log decline
60-130	900 mg q12h	6.0 (3.0-10.0)	13.0 (7.0-23.0)
40-59	450 mg q12h	5.0 (3.0-9.0)	12.0 (7.0-21.0)
25-39	450 mg q24h	6.0 (4.0-10.0)	13.0 (8.0-24.0)
10-24	450 mg q48h	6.0 (4.0-11.0)	16.0 (11.0-33.0)
	450 mg q36h*	6.0 (4.0-10.0)	16.0 (9.0-25.0)

* dose suggested (not licensed) for patients with eGFR of 10-24 mL/min/1.73 m^2

Table 4. Probability of target attainment (PTA) of CMV viral load ≤290 IU/mL and ≤137 IU/mL over time with the recommended valganciclovir dosages for preemptive therapy adjusted for renal function

CMV viral load threshold (IU/mL)	eGFR (mL/min/1.73m^2)	Recommended dosage	PTA at days:							
			7	14	21	28	35	42	49	56
≤290	60-130	900 mg q12h	37.7	67.4	80.1	86.7	90.3	92.5	93.9	94.8
	40-59	450 mg q12h	40.3	70.6	83.3	89.5	92.7	94.8	95.9	96.6
	25-39	450 mg q24h	36.7	66.3	79.2	85.9	89.5	92.1	93.7	94.7
	10-24	450 mg q48h	35.1	63.3	76.9	83.3	87.5	89.7	91.7	92.9
		450 mg q36h*	38.1	68.4	80.5	86.9	90.5	92.7	94.3	95.2
≤137	60-130	900 mg q12h	26.8	56.6	71.9	80.8	85.5	88.7	90.6	92.3
	40-59	450 mg q12h	28.1	59.6	75.4	83.9	88.4	91.6	93.3	94.9
	25-39	450 mg q24h	25.2	55.2	71.0	79.9	84.9	87.9	90.2	91.8
	10-24	450 mg q48h	23.9	52.0	68.7	77.1	82.4	85.3	87.9	89.1
		450 mg q36h*	26.6	57.3	72.7	81.2	85.9	88.7	91.1	92.7

* dose suggested (not licensed) for patients with eGFR of 10-24 mL/min/1.73 m^2

Figure Legend

Figure 1

Flow chart of patient inclusion and exclusion criteria

Figure 2

Diagnostic plot for the population pharmacokinetic (top panels) and pharmacodynamic (bottom panels) models. Shown are observed versus population-predicted concentrations (top-left) and individual-predicted concentrations (top-right) in plasma, and observed versus population-predicted CMV viral loads (bottom-left) and individual-predicted CMV viral loads (bottom-right) in plasma. Blue dots are the observed CMV viral loads, orange dots are the simulated CMV viral load below the limit of quantification. Solid lines refer to linear regression between observed and predicted values. Dashed lines are the identity lines between observed and predicted values

Figure 3

Prediction-corrected visual predictive check for the population pharmacodynamic model. Blue lines represent the median, 10^{th} and 90^{th} percentiles of the observed values; shaded areas are the prediction intervals for the median (red central area) and 10^{th} and 90^{th} percentiles (light blue lower and upper areas)