

POPULATION PHARMACOKINETICS OF VALGANCICLOVIR IN SOLID ORGAN TRANSPLANT RECIPIENTS INFECTED BY CYTOMEGALOVIRUS

Armendariz Y², Caldes A², Colom H¹, Gilvernet S², Péraire C¹, Domenech J¹, Grinyó JM², Wilkins JJ³, Karlsson MO³.

¹Dept. of Pharmacokinetics. Faculty of Pharmacy, University of Barcelona. Spain. ²Nefrology Service, Hospital Universitari de Bellvitge, Barcelona. Spain. ³Dept. of Pharmaceutical Biosciences. Faculty of Pharmacy, Uppsala University. Sweden.

Introduction and Objectives

Cytomegalovirus (CMV) is a leading cause of disease in immunocompromised subjects, such as solid organ transplant recipients. Valganciclovir (VGC), a L-valyl ester prodrug of ganciclovir, was developed to offer an alternative to long-term IV and low oral bioavailability of ganciclovir (GCV). The aim of this study was to establish the population pharmacokinetics of GCV after oral VGC as treatment of CMV infection in heart, liver and kidney transplant recipients, and explore the influence of patient covariates on drug disposition.

Methods

Sixteen patients (10 renal, 2 hepatic and 4 cardiac transplant) from the Hospital Universitari de Bellvitge were recruited for this study. Demographic and biochemical data were recorded. Patients received 5 mg/kg/12 h of GCV for five days as a 1-hour intravenous infusion, followed by oral VGC doses (900 mg/12 h), given for 15 days. In both cases doses were adjusted by creatinine clearance (CRCL). Blood samples were collected over 12 h post-dose, at steady-state. A population pharmacokinetic (PK) analysis was performed using NONMEM V. An internal validation was performed to confirm the model by simulating new data sets of GCV plasma profiles and determining the 95% confidence interval (CI) of the simulated concentrations.

Table 1. Population pharmacokinetic parameters of Ganciclovir in solid organ transplant recipients infected by cytomegalovirus

Parameter	Units	Estimate
CL	$L \cdot h^{-1}$	0.15(6.5)*CRCL
V ₁	L	34.3(15.4)*(WT/65)
CL _{D1}	$L \cdot h^{-1}$	9.1(22.1)
V ₂	L	29.9(29.5)*(WT/65)
K _A	h^{-1}	0.96(23.0)
F ₁	-	0.88(8.4)
LT	h	0.39(6.1)
IIV _{CL}	%	24.7(24.8)
IIV _{V1}	%	52.4(22.8)
IIV _{KA}	%	74.0(21.5)
IIV _{F1}	%	17.4(21.5)
Correlation (CL, V ₁)	-	0.74(66.0)
RE(proportional)	%	16.2(30.1)
RE (additive)	g/mL	0.44(31.5)
IIV _{RE}	%	35.4(65.1)

WT: body weight; 65:mean population body weight value; CRCL:creatinine clearance
Parameters are listed as the model estimate with the coefficient of variation (%) in parenthesis.
Estimates of the inter-individual variability in PK parameters (IIV), inter-individual variability in residual error (IIV_{RE}) and residual error (proportional component) are also reported as CV%.

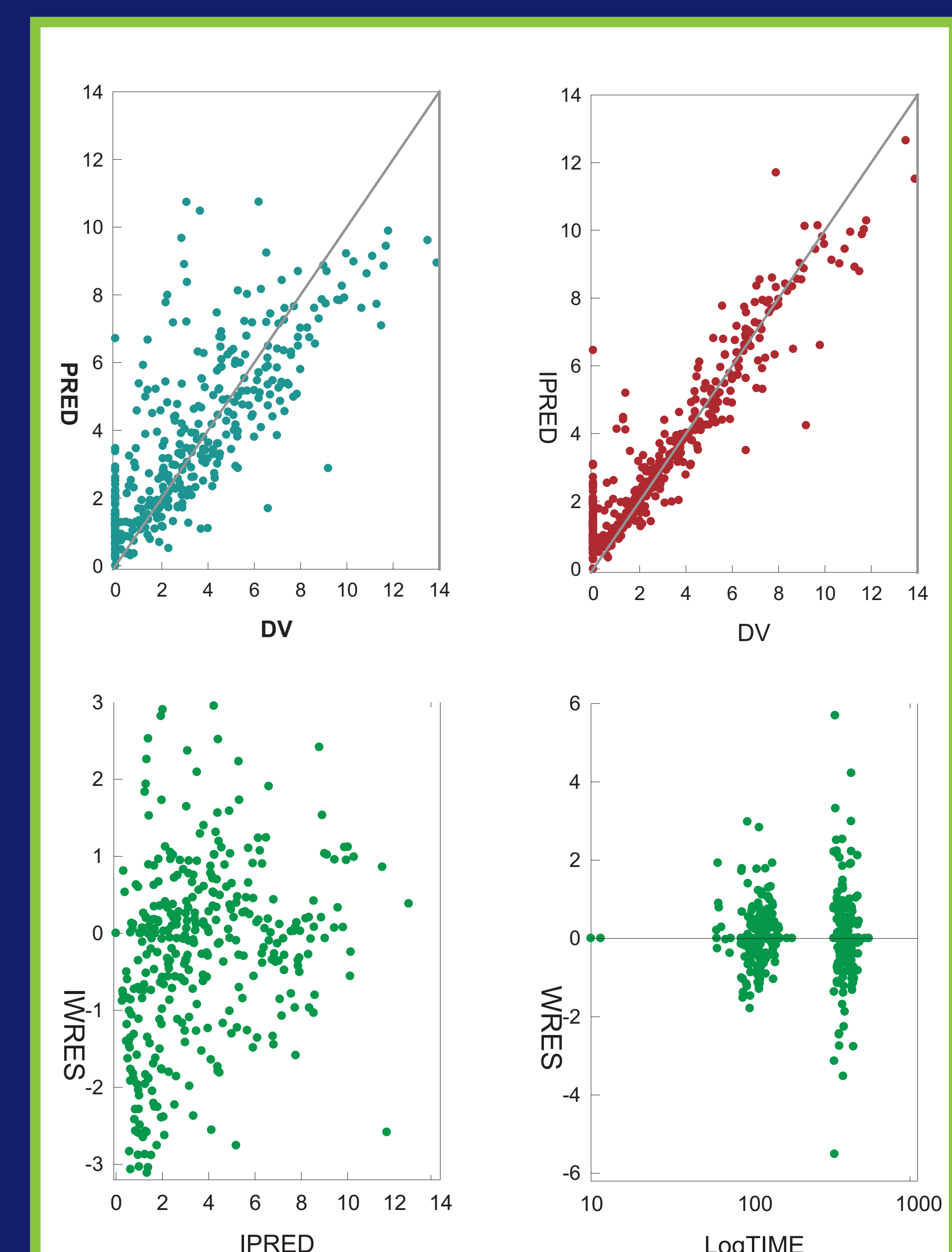
Conclusions

A population PK model for GCV, after GCV IV and VGC PO, has been developed. It incorporates measure of renal function and body weight to predict total drug clearance and distribution volumes, respectively. Validation of this model with external patients should be performed in order to assess the suitability of further GCV therapeutic drug monitoring.

Results

As previously reported (1), the PK of GCV was best described by a two compartment open model with elimination from the central compartment. Interindividual variability (IIV), modeled as log-normally distributed, was included in total plasma clearance (24.7%), central distribution volume (52.4%), absorption rate (74.0%) and bioavailability (17.4%). The bioavailability was constrained to be between 0 and 1 by logit-transformation. Residual variability consisted of combined error (additive: 0.44 g/mL; proportional: 16.2%) and IIV was included (35.4%). A correlation between CL and V₁ was found. The FOCE estimation method was used with interaction. Accommodating interindividual variability in the residual error model resulted in an improvement in individual fits. A covariate model based on CRCL in clearance and body weight in distribution volumes was the most appropriate model to describe part of the interindividual variability. A model for time-varying CRCL(2) was applied. The final estimates of PK parameters (CL, total plasma clearance; V₁ and V₂, volumes of distribution of the central, and peripheral compartments, respectively; CLD₁, intercompartmental clearance; F, bioavailability; K_A, absorption rate constant; LT, absorption lag time) are shown in Table 1. Results from the validation confirmed that observations dropped into the 95%CI, the 2.30% and 1.97% of them being below or above the 95% prediction interval, respectively.

Figure 1. Goodness of fit plots



References

1. Czock D. et al. Pharmacokinetics of valganciclovir and ganciclovir in renal impairment. *Clin Pharmacol Ther* 2002;72:142-150.
2. Wählby U. Thomson AH, Milligan PA, Karlsson MO. Models for time-varying covariates in population pharmacokinetic-pharmacodynamic analysis. *Br J Clin*