17º CONGRESO BARCELONA

SCT BCN

22-24 marzo 2023

SOCIETAT CATALANA DE TRASPLANTAMENT

COMPARISON OF THREE RENAL FUNCTION FORMULAS FOR GANCICLOVIR/VALGANCICLOVIR DOSE INDIVIDUALIZATION USING A POPULATION APPROACH IN CMV TRANSPLANT PATIENTS

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Population PK analysis

To identify predictive factors (demographic, genetic, biochemical, Clinical…) of PK variability

CLCR as a predictor of GCV clearance (Cl)

Population Pharmacokinetics of Ganciclovir after Intravenous Ganciclovir and Oral Valganciclovir Administration in Solid Organ Transplant Patients Infected with Cytomegalovirus[▽]

A. Caldés,[1] H. Colom,[2*] Y. Armendariz,[1] M. J. Garrido,[3] I. F. Troconiz,[3] S. Gil-Vernet,[1] N. Lloberas,[1] L. Pou,[4] C. Peraire,[2] and J. M. Grinyó[1]

Antimicrobial Agents and Chemotherapy, Nov. 2009, p. 4816–4824

TVCL, TVV

Typical value

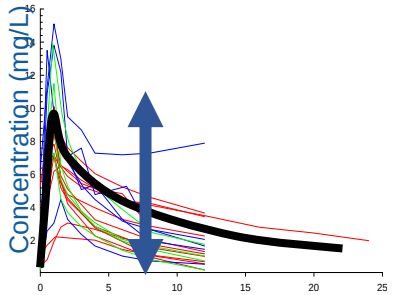

TABLE 1 Dosing adjustments based on CL_{CR} in the solid-organ transplant population of oral valganciclovir and i.v. ganciclovir

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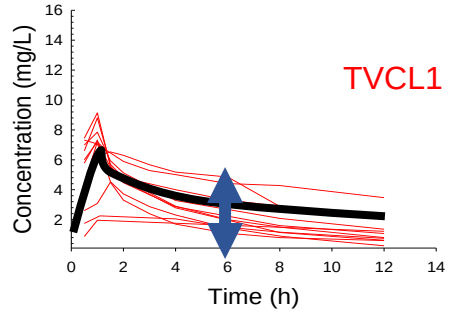
40–60	450 mg/12 h	450 mg/24 h	50–70	2.5 mg/kg/12 h
25–40	450 mg/24 h	450 mg/48 h	25–50	2.5 mg/kg/24 h
10–25	450 mg/48 h	450 mg twice per week	10–25	1.25 mg/kg/24 h

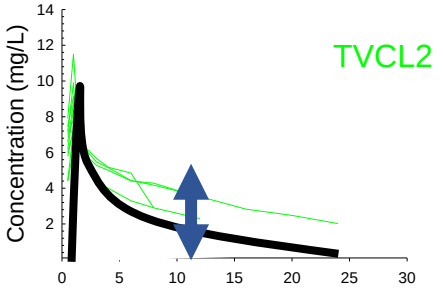
Subpopulations

CLCR=90 mL/min



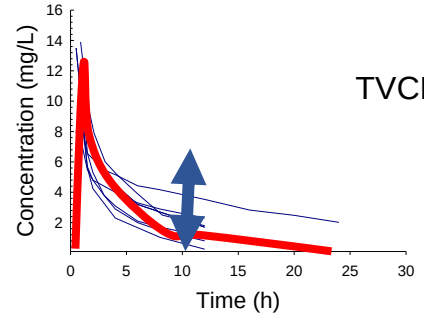
TVCL1

CLCR=60 mL/min



TVCL2

CLCR=30 mL/min



TVCL3

↑ Doses

↓ Doses

Ganciclovir, excreted in urine unchanged

Population Pharmacokinetics of Ganciclovir after Intravenous Ganciclovir and Oral Valganciclovir Administration in Solid Organ Transplant Patients Infected with Cytomegalovirus▽

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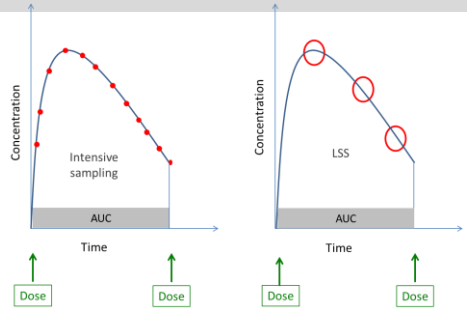
AUC muestreo intensivo→ LSS → Modelo PPK para diana AUC: 40-50 ug.h/ml



1. CLCR como predictor del aclaramiento de GCV (Cl) – 52.03%
2. No se encontró influencia del peso en los valores de Cl

Evaluación del régimen de dosificación convencional mediante simulaciones que determinaron el porcentaje de pacientes, que según la función renal (CLCLR), presentaban valores de AUC entre 40-50 µg·h/mL.

N=20 TX

16% pacientes →AUC: 40-50

>75% CLCR<30 ml/min →AUC >50

>75% CLCR>70 ml/min →AUC<40

Initial dosing according to manufacturer's instructions

CL_{CR} (ml/min)	IV		Oral	
	AUC (95% CI)	% of patients achieving target	AUC (95% CI)	% of patients achieving target
10	128.74 (67.88–247.90)	100.0	190.35 (71.31–393.63)	98.8
20	62.12 (34.85–123.22)	83.6	93.46 (30.94–196.96)	92.4
30	41.30 (22.67–79.41)	38.9	61.81 (19.87–134.64)	75.4
40	30.88 (17.03–60.83)	13.8	46.46 (14.27–99.48)	52.0
50	25.36 (13.49–47.05)	3.5	38.23 (12.63–78.10)	33.2
60	41.29 (22.13–81.13)	41.0	62.15 (20.39–133.25)	77.2
70	35.67 (18.19–71.31)	22.3	54.41 (16.90–117.60)	65.5
80	32.70 (17.22–61.83)	14.4	48.36 (15.19–105.25)	56.7
90	28.14 (15.47–53.09)	7.3	42.92 (13.50–89.43)	45.0
100	26.55 (13.81–51.58)	3.9	38.13 (9.43–79.44)	35.1

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Contribution of Population Pharmacokinetics to Dose Optimization of Ganciclovir-Valganciclovir in Solid-Organ Transplant Patients

A. Padullés,[a] H. Colom,[b] O. Bestard,[c] E. Melilli,[c] N. Sabé,[d] R. Rigo,[e] J. Niubó,[f] J. Torras,[c] L. Lladó,[g] N. Manito,[h] A. Caldés,[c] J. M. Cruzado,[c] J. M. Grinyó,[c] N. Lloberas[c]

OBJECTIVO PRINCIPAL : % pacientes en diana terapéutica

Grupo Profilaxis =N=27
Grupo Tratamiento = N=27

→ Grupo A =FT, Grupo B = PPK

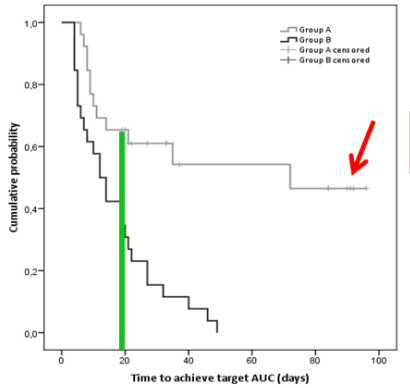
→ Grupo A =FT, Grupo B = PPK

Determinaciones de AUC

% measurements achieving the target AUC			
Group A	**Group B**	**Difference (95%CI)**	**p**
18.70	65.90	47.20 (36-59)	1.38×10^{-8}

Tiempo para alcanzar la diana terapéutica

GLOBAL



Grup A =FT
Grup B = PPK

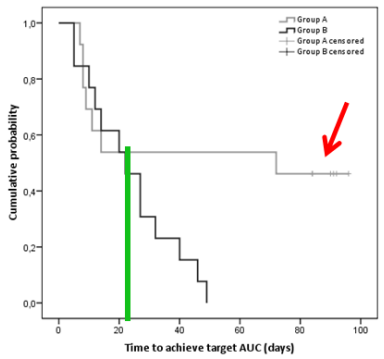
Group A: 56.7 days CI95% = [40.24-73.07]
Group B: 16.8 days CI95% = [11.67-21.87]
p=0.000083

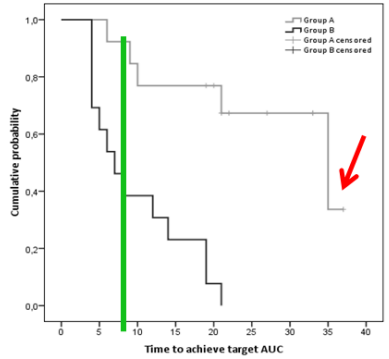
Group A: 54.23 days CI95% = [31.45-77.01]
Group B: 23.7 days CI95% = [15.72-31.81]

p=0,000029

Group A: 28.2 days CI95% = [21.62-34.73]
Group B: 9.8 days CI95% = [6.26-13.28]

PROFILAXIS





INFECCIÓN POR CMV

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

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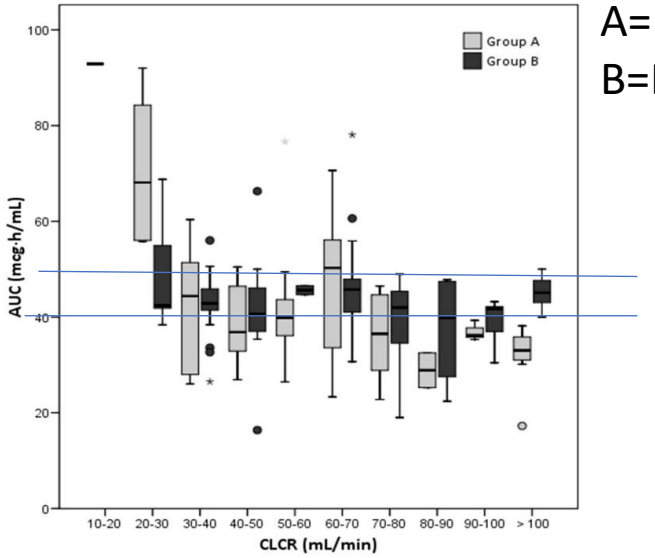
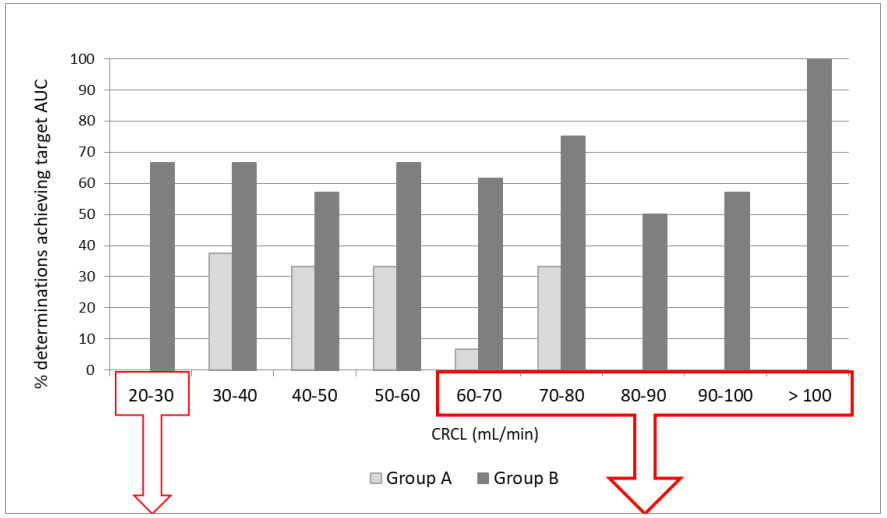
TABLE 5 Proportions of on-target AUC values by group, CL_{CR} cutoff value, and type of treatment

Classification variable for statistical analysis	% measurement achieving the target AUC (40–50 μg · h/ml)			
	Group A (= 73)	Group B (= 82)	% difference (95% CI)	*P* value
All patients included	19.2	65.9	47.0 (33–60)	<0.001
Patients with indicated CL_{CR} cutoff value				
<30 ml/min	0	71.4	71.4 (38–105)	0.008
30–40 ml/min	37.5	64.7	27.2 (−13–68)	0.467
40–50 ml/min	36.4	57.1	20.8 (−21–63)	0.582
50–60 ml/min	36.7	100	64.6 (35–92)	0.252
>60 ml/min	8.6	68.3	59.7 (43–77)	<0.001
Type of treatment				
Prophylaxis	21.3	62.9	41.6 (27–56)	<0.001
Treatment of CMV disease	15.4	71.4	56.0 (34–78)	<0.001

AUC target: 40-50 ug.h/ml



A=FT
B=PPK



66.7%

68.30%

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TABLE 2 Initial doses based on the PPK model in the solid organ transplant population of oral valganciclovir and iv ganciclovir

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CL_{CR} (ml/min)	Treatment dose	Prophylaxis dose	CL_{CR} (ml/min)	Treatment dose
100	1,000 mg/12 h	1,000 mg/24 h	100	10 mg/kg/12 h
95	950 mg/12 h	950 mg/24 h	95	9.5 mg/kg/12 h
90	900 mg/12 h	900 mg/24 h	90	9 mg/kg/12 h
85	850 mg/12 h	850 mg/24 h	85	8.5 mg/kg/12 h
80	800 mg/12 h	800 mg/24 h	80	8 mg/kg/12 h
75	750 mg/12 h	750 mg/24 h	75	7.5 mg/kg/12 h
70	700 mg/12 h	700 mg/24 h	70	7 mg/kg/12 h
65	650 mg/12 h	650 mg/24 h	65	6.5 mg/kg/12 h
60	600 mg/12 h	600 mg/24 h	60	6.0 mg/kg/12 h
55	550 mg/12 h	550 mg/24 h	55	5.5 mg/kg/12 h
50	500 mg/12 h	500 mg/24 h	50	5.0 mg/kg/12 h
45	450 mg/12 h[a]	450 mg/24 h[a]	45	4.5 mg/kg/12 h
40	400 mg/12 h	400 mg/24 h	40	4.0 mg/kg/12 h
35	350 mg/24 h	350 mg/48 h	35	3.5 mg/kg/12 h
30	300 mg/24 h	300 mg/48 h	30	3.0 mg/kg/12 h
25	250 mg/24 h	250 mg/48 h	25	2.5 mg/kg/24 h
20	200 mg/48 h	200 mg/72 h	20	2.0 mg/kg/24 h

AJUSTE GCV EN LA PRÁCTICA CLÍNICA

CASO 1. Paciente con tratamiento con GCV ev que no remite la carga viral

- Mala adherencia
- Infradosifación?
- Resistencia al GCV?

Peso: 48,2 Kg
Creatinina: 158 umol/L
FG=32, FG C-C=25,5
D: 150 mg/12h (3 mg/Kg/12h)

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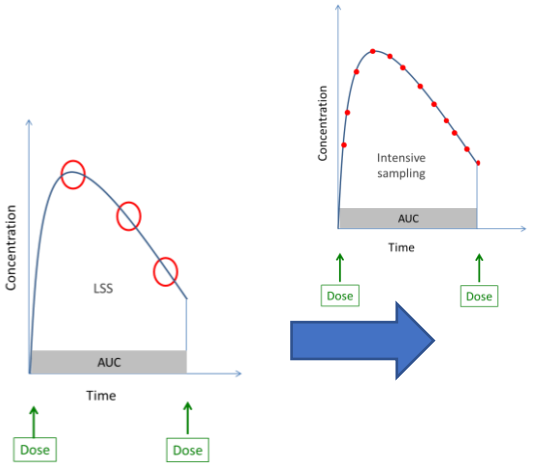
LSS:
0.5-1h: 3,346
5-6h: 2,08
8h: 1,577



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75	750 mg/12 h	750 mg/24 h	75	7.5 mg/kg/12 h
70	700 mg/12 h	700 mg/24 h	70	7 mg/kg/12 h
65	650 mg/12 h	650 mg/24 h	65	6.5 mg/kg/12 h
60	600 mg/12 h	600 mg/24 h	60	6.0 mg/kg/12 h
55	550 mg/12 h	550 mg/24 h	55	5.5 mg/kg/12 h
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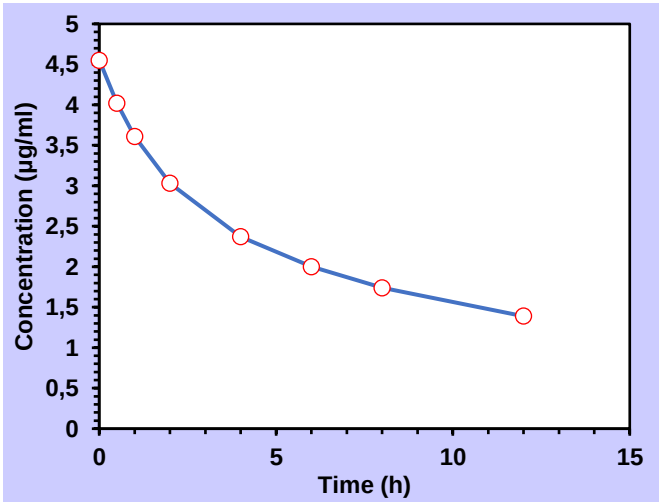
45	450 mg/12 h[a]	450 mg/24 h[a]	45	4.5 mg/kg/12 h
40	400 mg/12 h	400 mg/24 h	40	4.0 mg/kg/12 h
35	350 mg/24 h	350 mg/48 h	35	3.5 mg/kg/12 h
30	300 mg/24 h	300 mg/48 h	30	3.0 mg/kg/12 h
25	250 mg/24 h	250 mg/48 h	25	2.5 mg/kg/24 h
20	200 mg/48 h	200 mg/72 h	20	2.0 mg/kg/24 h

AUC: 27,14 (ug/mL).h



GCV-VGCV Target: 40-50 (ug/mL).h

Modelización PPK en función del CL actual:
Para AUC:45 →
D= 200mg/12h GCV (4 mg/Kg/12h)
D= 278 mg/24h → 300 mg/24h VGCV

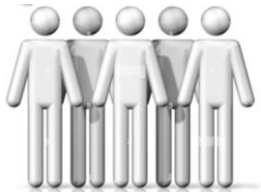
D=AUC.CL | D=AUC.CL/F

Ganciclovir/Valganciclovir dose optimization in CMV infected solid organ transplant patients using a population approach

AIMS

- To compare three different formulas for estimating renal function in SOT patients with CMV infection, using a population approach (CG, MDRD4, CKD-EPI)
- To evaluate the actual prophylaxis treatment and to propose new dosages if required

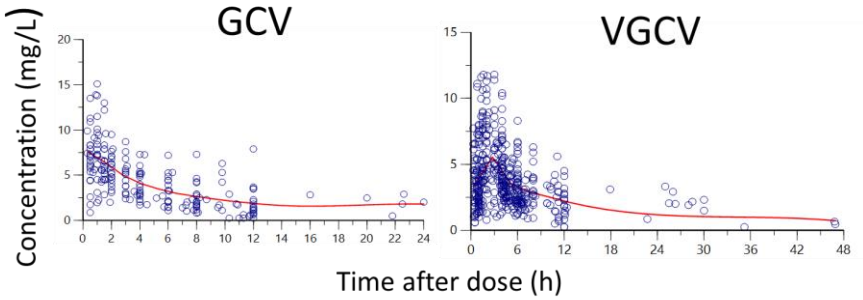
N=60 Tx



N=45 kidney transplant
N=10 Liver transplant
N=5 Heart transplant

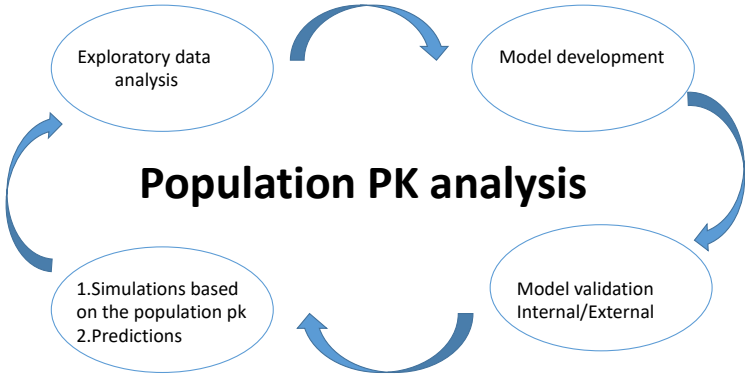
650 Cmin

Data exploration



Data: recording:

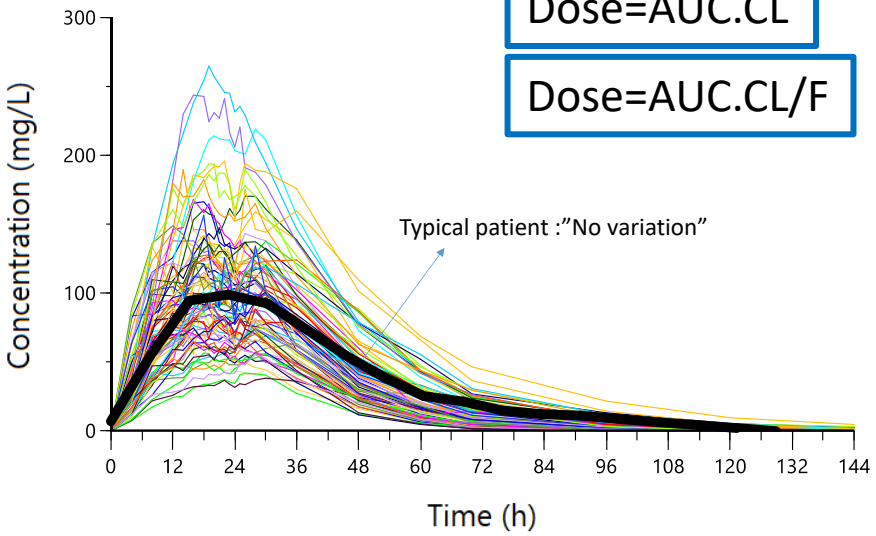
- Renal function: C-G, MDRD4, CKD-EDPI
- Anthropometric/body composition

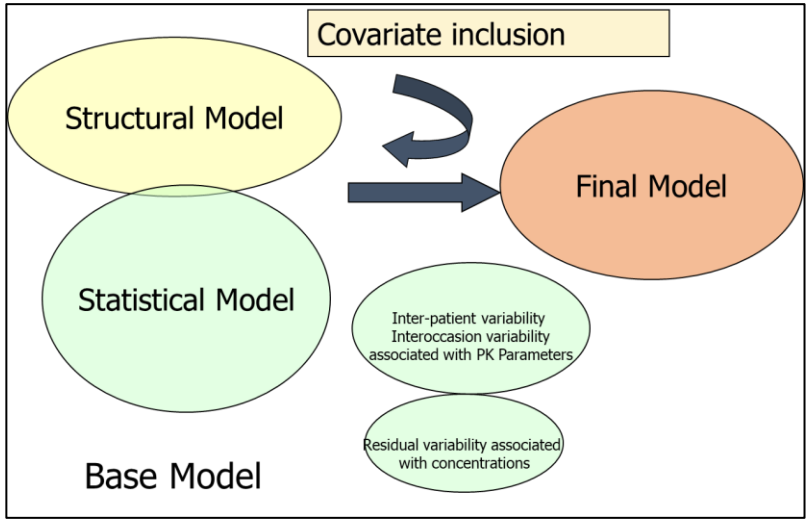


Model building, How?

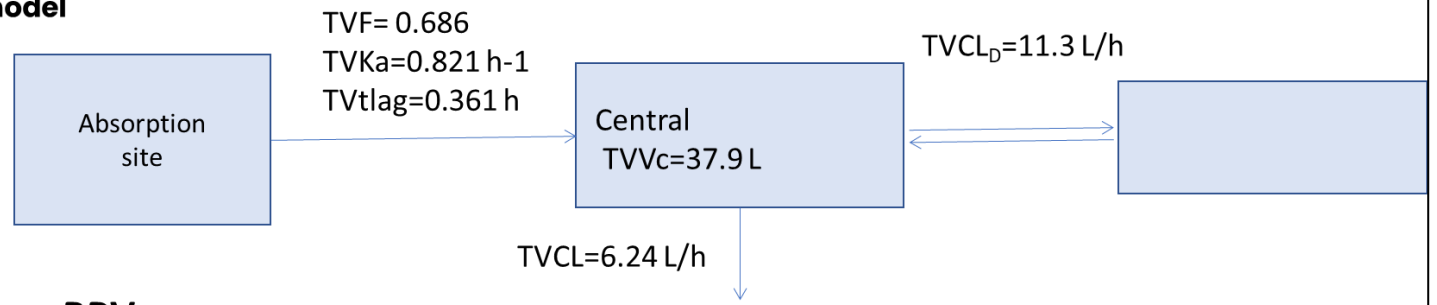
Dose=AUC.CL

Dose=AUC.CL/F





Base model



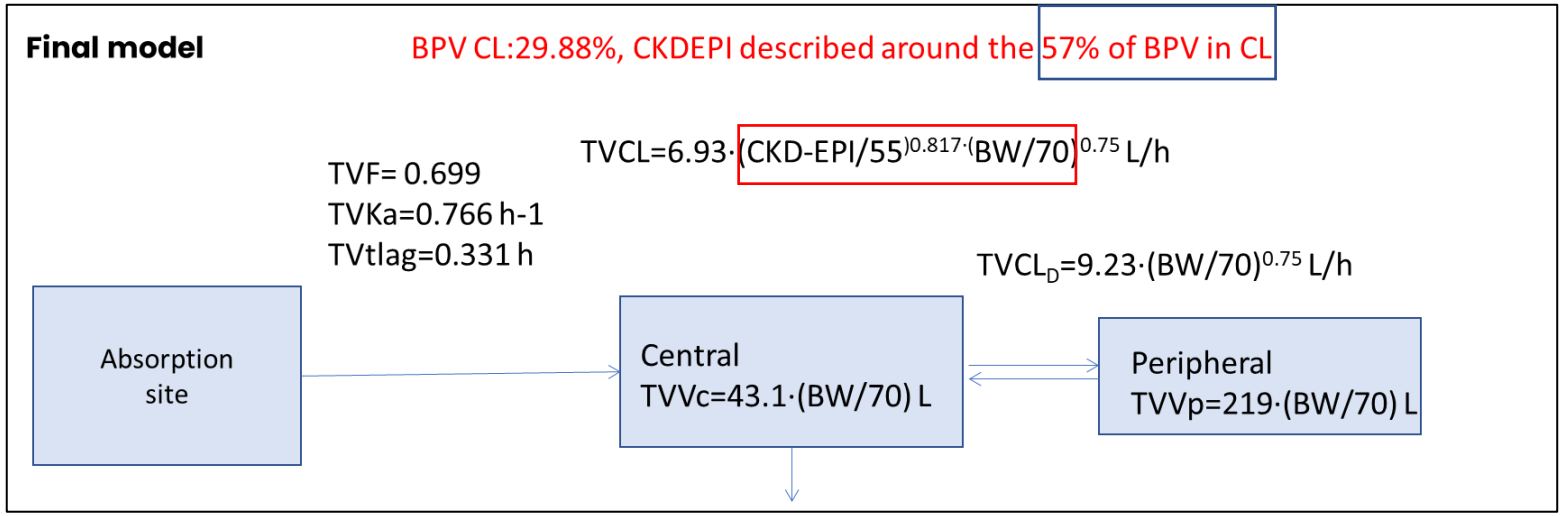
BPV:

CL 51.08%
Vc 43.36%
Vp 100%
Ka 52.9%
F 29.9%

Residual error: 26.5%

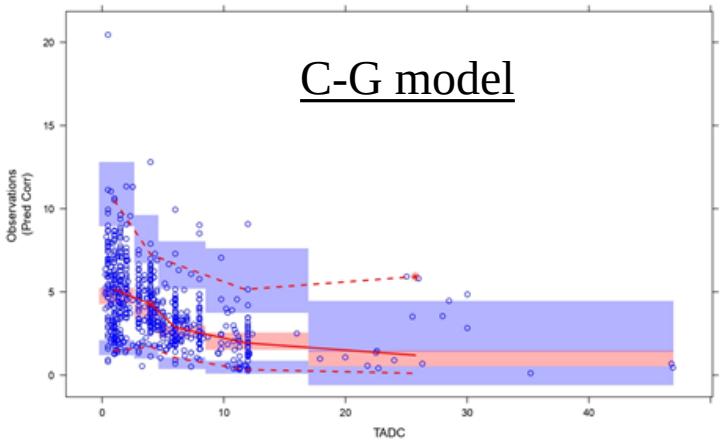
Final model

BPV CL:29.88%, CKDEPI described around the 57% of BPV in CL

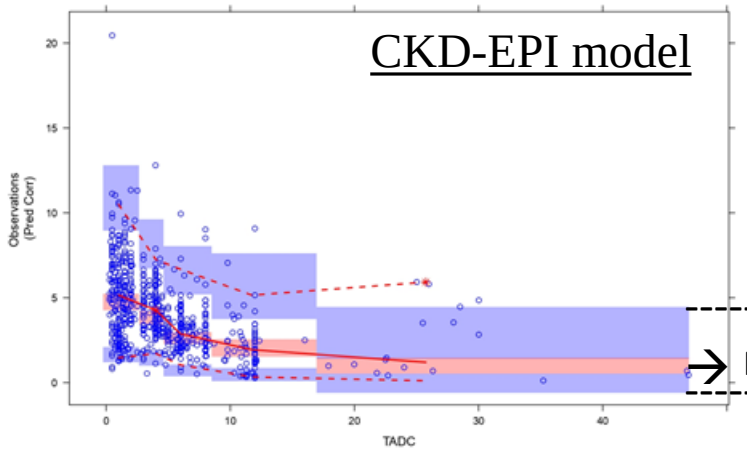


P5%, P50%, P95% Observed data are within the 90%CI of the P5%, P50%, P95% of the simulated data

C-G model

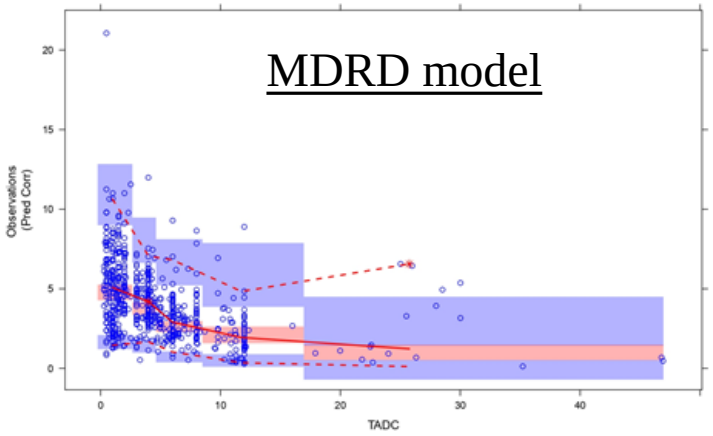


CKD-EPI model



CI 90%
CI 95%
Median simulations
CI 5%

MDRD model



$$MPE\% = (IPRED - OBS) \cdot 100$$

$$RMSPE\% = \sqrt{|IPRED - OBS|} \cdot 100$$

External evaluation

		Median	95%CI	
Bias	C_{peak}	-0.29	-6.28-4.89	Differences between Obs and Ipred maximum
	C_{trough}	-0.09	-1.82-2.08	Differences between Obs and Ipred minimum
Imprecision	C_{peak}	2.39	0.07-6.33	
	C_{trough}	0.29	0.03-2.10	

Prophylaxis doses

Model aplicability: Monte-Carlo simulations: Evaluation of actual prophylaxis doses

CLCR cut-off (mL/min)	Dose (mg)	Interval (h)
10-24	450	84
25-39	450	48
40-59	450	24
60-69	900	24

WGT

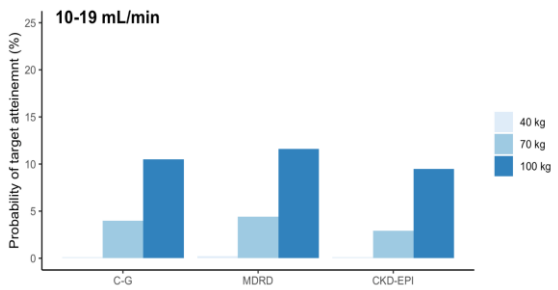
40 kg

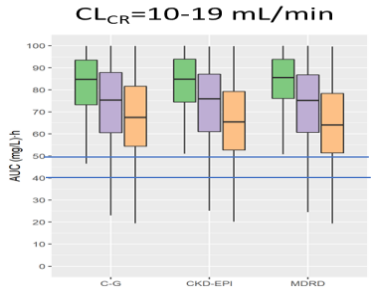
70 kg

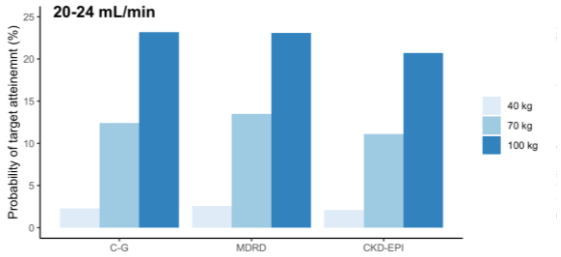
100 kg

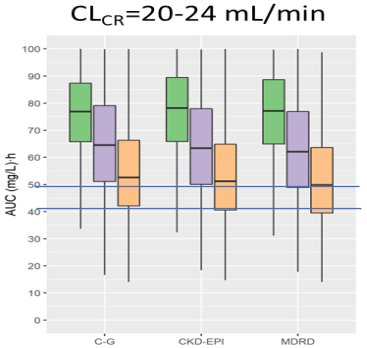
Percentages of target attainment based on AUC of 40-50 (mg/L)·h

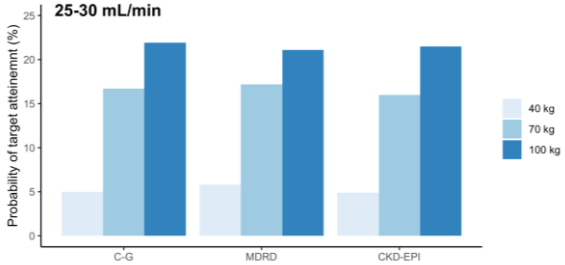
Simulated AUC values based on actual prophylaxis regimens

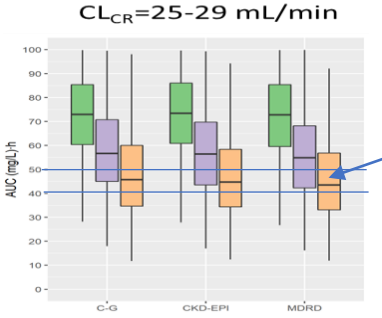












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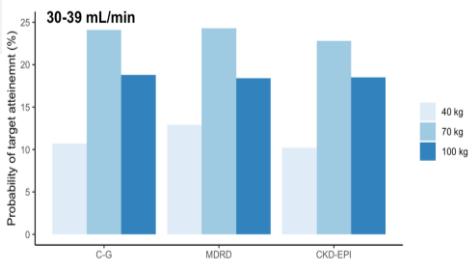

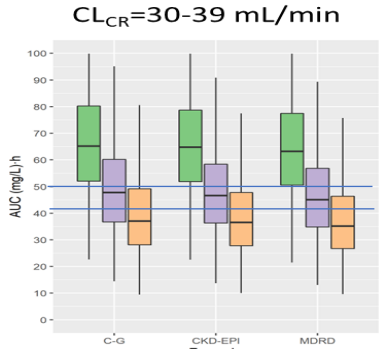

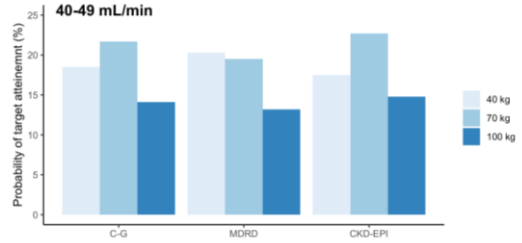

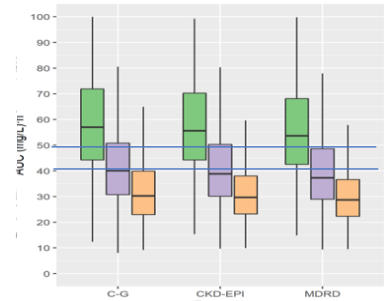

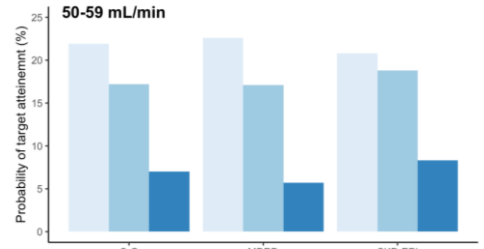

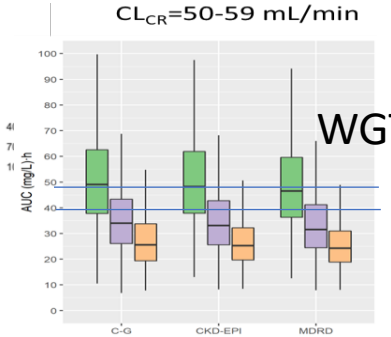

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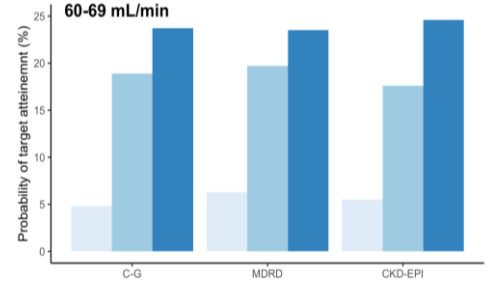
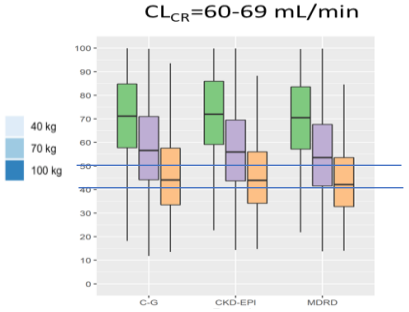
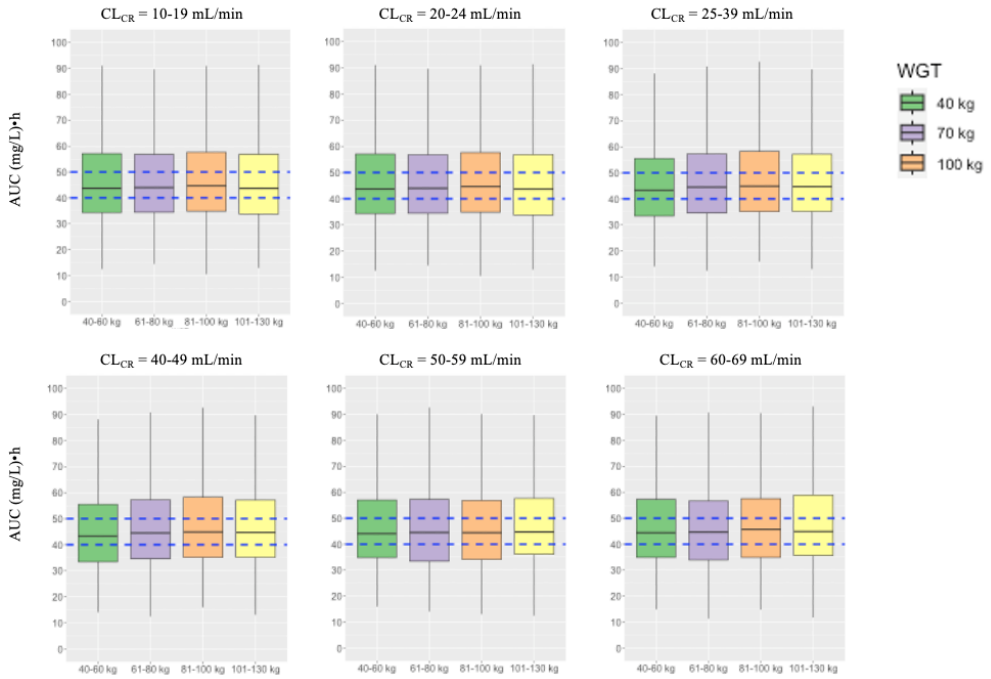




New initial dose recommendations



Simulations of increasing doses for CLCR cut-offs of 10-19, 20-24, 25-29, 30-39, 40-49, 50-59, 60-69 mL/min and body weights from 40 to 130 kg in steps of 20 kg.

Lower doses than those actually used, excepting for patients showing renal functions of :

25-39 mL/min and BW from 81 to 130 kg
50-59 mL/min and 101-130 kg
60-69 mL/min and 40-80 kg

Oral prophylaxis doses to achieve AUCs: 40-50ug*h/mL (CKD-EPI) considering renal function and BW

CLCR cut-off (mL/min)	Dose (mg)	Interval (h)
10-24	450	84
25-39	450	48
40-59	450	24
60-69	900	24

FT

Table 4. Percentages of patients achieving AUC_{target} around 40-50 ug*h/mL after manufacturers' recommended oral prophylaxis doses.

CRCL cutoff group (mL/min)	BW (kg)	NO BODY WEIGHT#			BW& (kg)	WITH BODY WEIGHT#*&		
		C-G	MDRD	CKD-EPI		C-G	MDRD	CKD-EPI
10 - 19	70	1.6%	4.2%	8.1%	40	0.1%	0.2%	0.1%
					70	2.9%	4.4%	4.0%
					100	9.5%	11.6%	10.5%
20-24	70	10.2%	9.9%	13%	40	2.1%	2.6%	2.3%
					70	11.1%	13.5%	12.4%
					100	20.7%	23.1%	23.2%
25-29	70	15.3%	13.2%	18.8%	40	4.9%	5.8%	5.0%
					70	16%	17.2%	16.7%
					100	21.5%	21.1%	21.9%
30-39	70	24.4%	18.8%	20.4%	40	10.2%	12.9%	10.7%
					70	22.8%	24.3%	24.1%
					100	18.5%	18.4%	18.8%
40 - 49	70	22.7%	20.5%	19.9%	40	17.5%	20.3%	18.5%
					70	22.7%	19.5%	21.7%
					100	14.8%	13.2%	14.1%
50 - 59	70	16.7%	15.9%	17.7%	40	20.8%	22.6%	21.9%
					70	18.8%	17.1%	17.2%
					100	8.3%	5.7%	7%
60 - 69	70	19.5%	15.3%	15.2%	40	5.5%	6.3%	4.8%
					70	17.6%	19.7%	18.9%
					100	24.6%	23.5%	23.7%

#No statistically significant differences (p=0.506) were found between mean values of %PTA estimated from the models including bodyweight with respect to those that not considered it.

*From models including bodyweight, no statistically significant differences were found between formulas (p=0.214), but statistical significant differences were found between bodyweights in all the cases (p<0.001), excepting in %PTA between 70 and 100 kg (p=0.312)

Oral valganciclovir

CL_{CR} (ml/min)	Prophylaxis dose
100	1,000 mg/24 h
95	950 mg/24 h
90	900 mg/24 h
85	850 mg/24 h
80	800 mg/24 h
75	750 mg/24 h
70	700 mg/24 h
65	650 mg/24 h
60	600 mg/24 h
55	550 mg/24 h
50	500 mg/24 h
45	450 mg/24 h[a]
40	400 mg/24 h
35	350 mg/48 h
30	300 mg/48 h
25	250 mg/48 h
20	200 mg/72 h

PPK

Renal function (mL/min)	Body weight (kg)	VGCV * (mg/kg)	VGCV * (mg)	Dosing interval
10 - 19	40 - 60	3.3	167	84 h
	61 - 80	3.1	215	
	81 - 100	2.9	259	
	101 - 130	2.7	311	
20 - 24	40 - 60	4.6	228	84 h
	61 - 80	4.2	293	
	81 - 100	3.9	354	
	101 - 130	3.7	426	
25 - 39	40 - 60	6.2	310	48 h
	61 - 80	5.7	398	
	81 - 100	5.3	481	
	101 - 130	5.0	578	
40 - 49	40 - 60	8.2	409	48 h
	61 - 80	7.5	526	
	81 - 100	7.1	636	
	101 - 130	6.6	764	
50 - 59	40 - 60	9.6	482	48 h
	61 - 80	8.9	620	
	81 - 100	8.3	749	
	101 - 130	7.8	900	
60 - 69	40 - 60	11.0	552	24 h
	61 - 80	10.2	711	
	81 - 100	9.5	858	
	101 - 130	9.0	1031	

*Doses calculated for the mean bodyweight of each interval, that is 50, 70, 90 and 115 kg

TAKE HOME MESSAGES

1. El aclaramiento de creatinina fue la variable que explicó el 52% de la variabilidad inter-individual en el modelo de PPK desarrollado
2. La inclusión del peso como variable ha permitido hacer una ajuste de dosis estimado más refinado.
3. El cálculo de dosis de VGCV utilizando la formula de C-G tal como se usa según la recomendación de la ficha técnica tiende a sobre-estimar la función renal.
4. Este modelo confirma que la fórmula CKD-EPI es la que major predice el aclaramiento de eliminación renal del GCV mediante estudios de PPK
5. CLCR bajos → AUCs más elevadas → Menos dosis
6. **CLCR bajos → Menor peso → AUCs altas y mayor riesgo a sobre-exposición** → Menos dosis
7. **CLCR altos → Mayor peso → AUCs bajas y mayor riesgo a infra-exposición** → Mayor dosis

El nuevo modelo basado en la estimación más precisa de la función renal con la fórmula CKD-EPI y el peso corporal, puede refinar las recomendaciones de dosis y contribuir a la individualización de la dosis de GCV y VGCV cuando sea necesario en la prevención o el tratamiento de la infección por CMV en pacientes con trasplante de órganos sólidos.

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