Ganciclovir/valganciclovir dose monitoring in solid organ transplanted patients using bayesian prediction.

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BACKGROUND

Treatment of solid organ transplant (SOT) patients with ganciclovir (GCV) or valganciclovir (VGCV) following the manufacturer's dosing recommendations may result in either over or underexposure to the drug. However, Bayesian prediction based on a population pharmacokinetics (PPK) model has been suggested to more accurately optimize GCV/VGCV dosing thus, achieving more steadily desirable area under the curve (AUC) therapeutic target values (between 40-50 ugh/mL).

AIMS:

Main aim: Percentage of patients achieving target AUC values between 40 and 50 µg·h/mL .

Secondary aim: Time needed to achieve target AUC values, correlation of drug exposure with efficacy and adverse events.

METHODS

Single-center prospective randomized superiority trial in SOT patients treated with GCV/VGC, for prophylaxis or treatment of CMV disease. Patients were randomized in two groups: group A was dosed as manufacturer's strategy. Group B: first doses were calculated based on the PPK model and the following doses were adjusted depending on drug levels and based on Bayesian prediction. Exclusion criteria was a creatinine clearance (CLCR) <10mL/min.

Steady state GCV levels were determined (0.5-1.5, 4-5 and 6-8 h after drug intake) after the first dose, when there was a modification in dose regimen or change in CLCR >10 mL/min, according to the protocol approved by the local Ethics Committee.

Drug exposure achieved was evaluated in both groups.

RESULTS

Baseline characteristics:

There were no clinical or statistically relevant differences in baseline characteristics between groups.

	Group A (N = 27)	Group B (N =26)	p-value
Type of treatment (N)			
Prophylaxis	14	13	NS[1]
Infection	13	13	
Sex N (%)			
Female/male	9 (33.3) / 18 (66.7)	13 (50) / 13 (50)	NS[1]
Age (year)			
Mean ± SD	52.6 ± 19.6	55.1 ± 14.7	NS[2]
Transplanted organ N (%)			NS[1]
Kidney	23	25	
Liver	2	0	
Heart	2	1	
Donor/Recipient CMV IgG serostatus at time of transplantation N (%) **			NS[1]
	10 (37.0)	4 (16)	
D+/R-	15 (55.6)	16 (64)*	
D+/R+	2 (7.4)	4 (16)*	
D-/R+	0	1 (3.8)	
D-/R-			
Induction immunosupression N (%)			NS[1]
ATG	9 (33.3)	10 (38.5)	
Basiliximab	17 (63)	16 (61.5)	
None	1 (3.7)	0	
Rejection episode N (%)			NS[1]
Yes/No	3 (12) / 22 (88)	2 (8.7) / 21 (91.3)	

Table 1. Main baseline characteristics of the study group. [1]chi-square. [2] t-test.

	Group A (N = 12)	Group B (N =11)	p-value
Previous anti CMV strategy N (%)			
Prophylactic	5 (58.3)	1 (9.1)	NS[1]
Preemptive	7 (41.7)	10 (90.9)	
Median baseline viral load (copies/mL) (N)	5513	4100	NS[2]
Patients with previous prophylactic treatment	64459	4809	NS[2]
Patients under preemptive treatment	3542	3379	NS[2]

Table 2. Baseline viral data characteristics - Per-protocol treated patients for CMV infection (viremia/disease). [1]chi-square. [2] t-test.

Evaluation of systemic exposure

-Median systemic exposure over time for each patient: 88.4% (23/26) of patients in Group B achieved the target AUC values as compared to only 18.5% (5/27) of patients in Group A thus, fulfilling the 40% superiority margin in target AUC values established as a primary end-point (p<0.001, 95% CI for the difference: 54-86%). Mean AUC values by CRCL cutoff interval are shown in Figure 1.

-Considering all AUC determinations: the Bayesian prediction approach resulted in a higher proportion of AUC values falling within the therapeutic range (Group A: 18.7% vs. Group B: 65.9%, p<0.001, 95% CI for the difference: 36-59%) and fulfilling the 40% superiority margin.

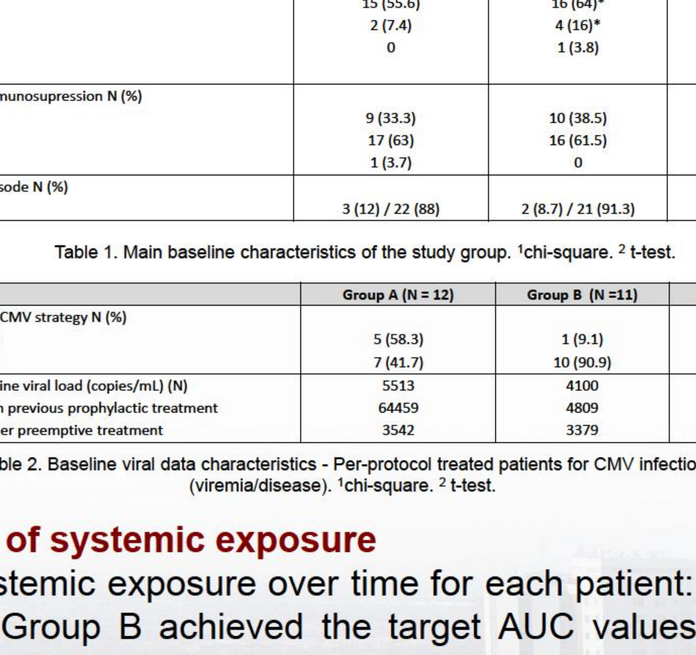

Figure 1. Average estimated systemic exposure of GCV following administration of iv GCV or oral VGC by CRCL cut-off values.

Time to achieve target AUC

The required time to reach target AUC values was significantly longer in Group A as compared to Group B (55.9 8.2 vs 15.8 2.3 days respectively, p<0.001). (Figure 2)

Analysis of efficacy

Viral eradication:

A numerically shorter time to viral clearance was observed in Group B as compared to Group A (12.5 vs. 17.6 days, p=0.125, respectively) (Figure 3). The incidence of CMV relapse (Group A: 66.67% (8/12); Group B: 9.01% (1/11)) and late CMV disease(Group A: 36.7% (4/11; Group B: 7.7% (1/13)) were both higher in Group A than in Group B.

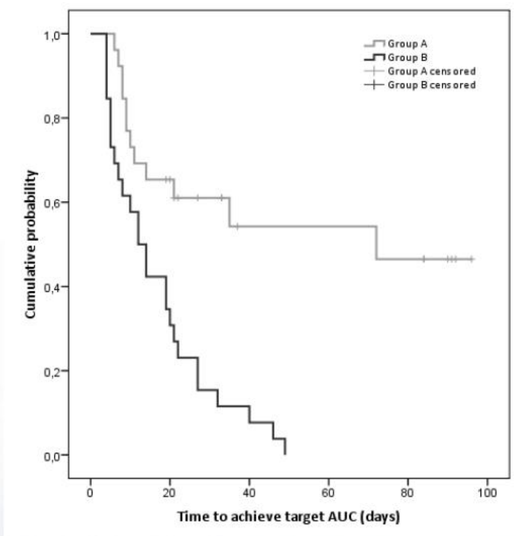

Figure 2. Rate of first achievement of AUC target according to randomization group over the follow up period (Kaplan–Meier analysis using log rank statistics) for all patients included

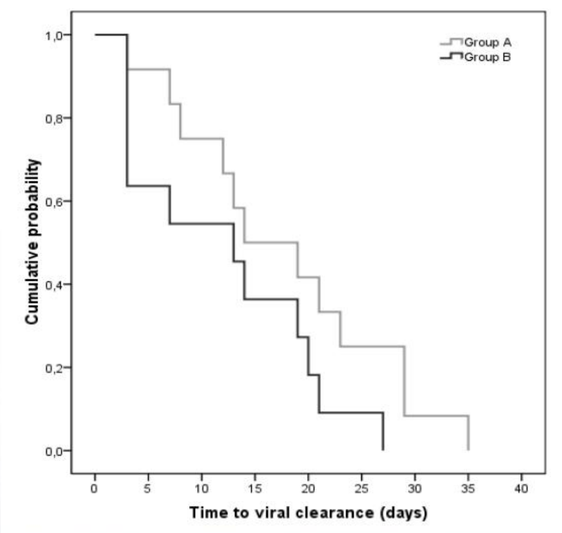

Figure3. Kaplan-Meier curves showing cumulative probability of viral clearance in patients treated with either oral VGCV or iv GCV

Late CMV disease and relapse (6 months follow-up):

The number of patients with CMV recurrence was higher in Group A than in Group B (66.67% (8/12) vs. 9.01% (1/11), respectively).

There were no incident cases of CMV viremia during the prophylactic period. The incidence of late-onset infection during the 3 months following discontinuation of prophylaxis was lower in Group B than in Group A (7.7% (1/13) vs. 36.7% (4/11), respectively).

Correlation of systemic exposure with adverse events:

Differences in toxicity were not observed among both groups.

Dose of GCV and VGCV analysis:

Patients in Group B received higher doses of either iv GCV (480 vs 325 mg/day) or oral VGCV (900 vs 600 mg/day) than patients in Group A. The median daily dose of oral VGCV for patients under prophylaxis was lower in Group B (450 mg/day) than in Group A (900 mg/day).

CONCLUSIONS

GCV/VCGV dose adjustment based on a population pharmacokinetics Bayesian prediction model optimizes GCV/VGCV exposure and shortens the time to achieve a therapeutic AUC target in SOT patients. Therapeutic Drug Monitoring of GCV with only 2 or 3 time points allow dose optimization to achieve a target plasma exposure that could improve the outcome in SOT patients.

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