Incidence, risk factors, and consequences of neutropenia in cytomegalovirus (CMV)-seronegative kidney transplant recipients of seropositive donors (D+/R-), treated with prophylactic valganciclovir

N. Lorcy[1], E. Oger[2], E. Polard[2], J. Rivalan[1], P. Tattevin[3], C. Vigneau[1], P. Le Pogamp[1]

1 : Nephrology – Rennes University Hospital – France / 2 : Pharmacology – Rennes University Hospital – France / 3 : Infectiology – Rennes University Hospital – France

Background

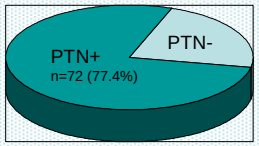
Post-transplant neutropenia (PTN) is a major complication of valganciclovir (V-GCV) use in CMV D+/R- kidney transplant recipients, most frequently in association with the chronic use of mycophenolic acid (MPA). In our monocentric cohort of kidney transplant recipients, we found that **76.3% of CMV D+/R- patients presented a PTN** vs. 39.7% in other patients. Limited data are currently available regarding incidence, risk factors and consequences of PTN. More information on this potentially fatal event may better inform controversies on the optimal prophylactic strategy for CMV disease in this population.

Methods

Retrospective, observational, study performed in the Rennes University Hospital, France. During the study period (2003-2011), prophylactic V-GCV was routinely initiated in CMV D+/R- patients during the week following kidney transplant. CMV D+/R- kidney transplant recipients were identified through our computerized database. Data were extracted from medical charts and from the laboratory databases through a standardized questionnaire. **PTN was defined by neutrophil count below 2000/mm³ at any time during the year following kidney transplant.** Patients who developed PTN (PTN+) were compared to patients who did not (PTN-), using Wilcoxon tests for quantitative variables, and Chi2 tests for qualitative variables.

RESULTS

93 patients included



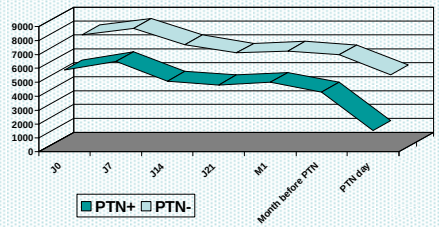
• 4 PTN+ episodes were excluded because neutropenia was deemed to be due to CMV syndrom => **68 PTN+ analyzed**

• No significant difference was found in demographics caracteristics between PTN+ and PTN- patients

Neutrophil count	Patients (n, %)
1500 – 1999 / mm³	16 (23.5%)
1000 – 1499 / mm³	18 (26.5%)
500 – 999 / mm³	21 (30.9%)
< 500 / mm³	13 (19.1%)

Median delay between transplant and PTN	94 days (36 – 365)
Median delay between V-GCV introduction and PTN	89 days (32 – 356)
Median delay from PTN onset to neutrophil nadir	5 days (0 – 102)
Median duration of neutropenia	21 days (1 – 368)

Neutrophil count evolution from transplantation to PTN



• PTN+ patients had lower neutrophil count before V-GCV was introduced, during the first week post-transplant, with a median of 5900/mm3 [2150-17860] versus 7710/mm3 [4460-12250] in PTN- (P<0.05).

• After V-GCV was introduced, neutrophil counts gradually decreased at the same rate in both groups.

Predictive value of neutrophil counts for the risk of PTN during the following month		
Neutrophil count	Sensitivity	Specificity
3 665 / mm³	20%	99%
4 170 / mm³	48%	90%

Treatments

☆**Mycophenolic Acid** (MPA)	PTN+	PTN-	p
Mycofenolate mofetil	63 (92.6%)	16 (76.2%)	0.05
Sodic mycofenolate	5 (7.4%)	3 (14.3%)	0.39
None	0 (0.0%)	2 (9.5%)	0.05

No significant differences in terms of daily or total dose of MPA between both groups

MPA AUC for 34 PTN+ patients and 11 PTN- patients:

- Higher first determination of AUC for PTN+ patients : **AUC > 60 h.mg/l : 45.5% of PTN+ patients vs 14.7% of PTN- patients (p<0,05)**
- But no significant difference during the month preceeding PTN onset

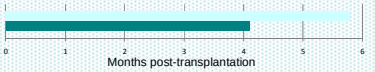
☆**Valganciclovir** (V-GCV): all patients

No significant differences in terms of daily or total dose of V-GCV between both groups

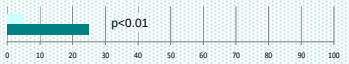
Dosage adapted to glomerular filtration rate	PTN+	PTN-	p
When introduced	25 (36.8%)	9 (42.8%)	0.59
When PTN occured	27 (39.7%)	10 (47.6%)	0.52

Neutropenia consequences

Total duration of V-GCV treatment



CMV viremia in the 3 months following V-GCV stop



Bacterial infection in the month following neutropenia

Acute rejection

5 PTN+ patients in the 3 months following neutropenia (median delay, 37 days) *vs* no PTN- patient (during the same time)

Conclusions

- **PTN occurs in > 75% of CMV D+/R- kidney transplants receiving prophylactic V-GCV**

- **Although most probably drug-related, no significant association with V-GCV or MPA dose**

-**The risk of PTN is mostly related to the neutrophil count before V-GCV introduction**

- **A neutrophil count below 4000/mm³ has a sensivity of 48%, and a specificity of 90%, to predict the risk of neutropenia onset during the following month**

- **A prospective, interventional study is requested to determine if early adaptation of V-GCV based on neutrophil count could reduce the risk of PTN and improve patients pronostic.**