First results of the CYPTAC'H study: influence of CYP3A5 polymorphism of donor and recipient on Tacrolimus exposure in liver transplant recipients.

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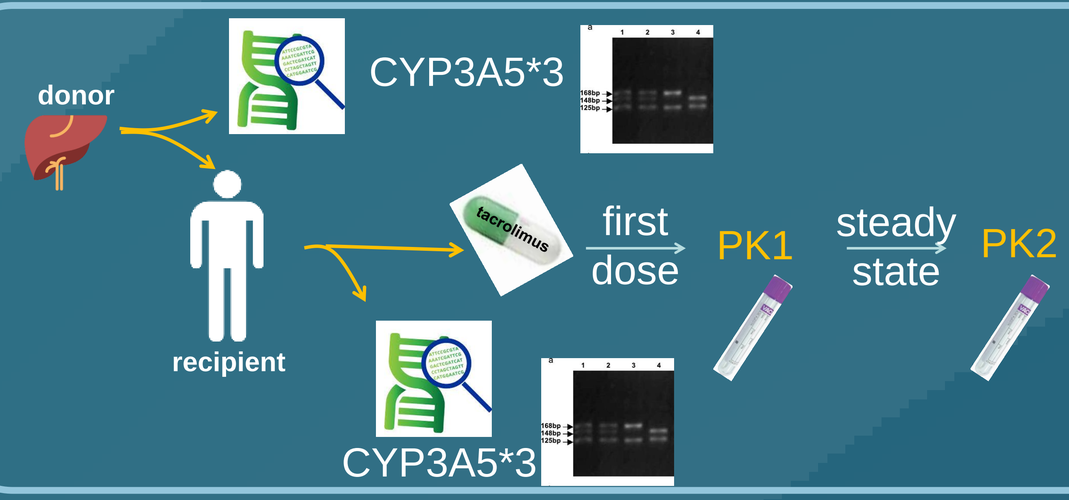
Introduction

There is no longer any mystery about the influence of CYP3A5 polymorphisms on tacrolimus exposure. But, from the donor or the recipient in liver transplantation, who has the highest influence during the immediate post-transplant period? This is the question that the CYPTAC'H study (NCT01388387) attempted to answer, comparing area under the curve (AUC) of tacrolimus after the first dose and at steady-state according to donor and recipient genotypes.

Methods



CYPTAC'H prospective study was conducted in Rennes University Hospital between 2012 and 2018, in adult liver transplant recipients receiving tacrolimus immediately after transplantation. DNA samples were obtained from donors (*via* Etablissement Français du Sang, Rennes) and recipients. Pharmacokinetic samples were collected on two occasions (10 samples each): after the first dose (PK1) and 8 days after transplantation, at steady-state (PK2). CYP3A5 c.6986 A>G (rs776746) polymorphism was determined both in donor and in recipient using PCR-RFLP. CYP3A5*1/*1 and *1/*3 carriers have been grouped together and considered as Cyp3A5 expressors. Tacrolimus exposure was assessed by calculating AUC0-12h of blood concentrations with the trapezoidal rule. Wilcoxon test was used to compare AUC/Dose between genotype groups.

Results

141 patients were included in this study between 2012 and 2018 and 2553 blood tacrolimus concentrations were measured (figure 1). AUC0-12h of tacrolimus was estimated for 140 patients at PK1 and 113 at PK2. Almost 90% of the patients included were men, aged 60 ± 6.6 years (table 1). The first cause of transplantation was hepatocellular carcinoma.

CYP3A5 polymorphisms were distributed as described in table 2 (no significant deviation from Hardy-Weinberg Equilibrium). In the overall study population, the mean dose was not different between PK1 and PK2 (1.75 vs 1.80 mg bid, respectively). Analysis by genotype subgroups reveals a significant increase in dosing in group 1 and in group 2 between PK1 and PK2.

AUC0-12h were significantly different at **PK1** between **recipient *1 carriers and recipient *3 carriers**. Genotype of donor had no effect on tacrolimus exposure. At **PK2**, AUC0-12h were significantly different between **donor *1 carriers and donor *3 carriers**. Genotype of recipient had no effect on tacrolimus exposure (figure 2).

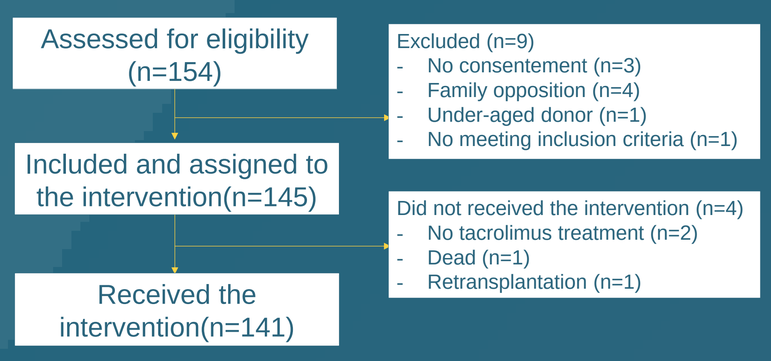


Figure 1 : flow-chart of the clinical trial

Table 2: Genotype frequencies in the studied population (n = 140)

		Donor	
		***1/*3 or *1/*1**	***3/*3**
Recipient	***1/*3 or *1/*1**	group 1 5	group 2 16
	***3/*3**	group 3 14	group 4 105

Table 1: recipients demographics

Parameter		value
About recipient		
Age (year, mean ± sd)		60.0 ± 6.6
Sex (% male)		89.7
Weight (kg)		85.5 ± 16.5
Diabetes before LT (%)		33.8
Arterial hypertension before LT (%)		46.9
Kidney failure before LT (%)		2.1
Indication of transplantation (%)		
	hepatocellular carcinoma / malignant tumor	56.6
	alcoholic cirrhosis	33.1
	HBV or HCV cirrhosis	3.5
	cirrhosis other cause	6.2
	polycystosis	0.7
Graft size parameter		
Type	Whole-liver graft	98.5%
	Split-liver graft	1.5 %
Weight (g, mean ± sd)		1399.5 ± 381.4
About immunosuppressive treatment		
Tacrolimus first dose (mg /day, mean ± sd)		3.5 ± 1.3
Patients treated continuously between the two PKs (%)		70.2
Early discontinuation of treatment (before day 7) (%)		22.7

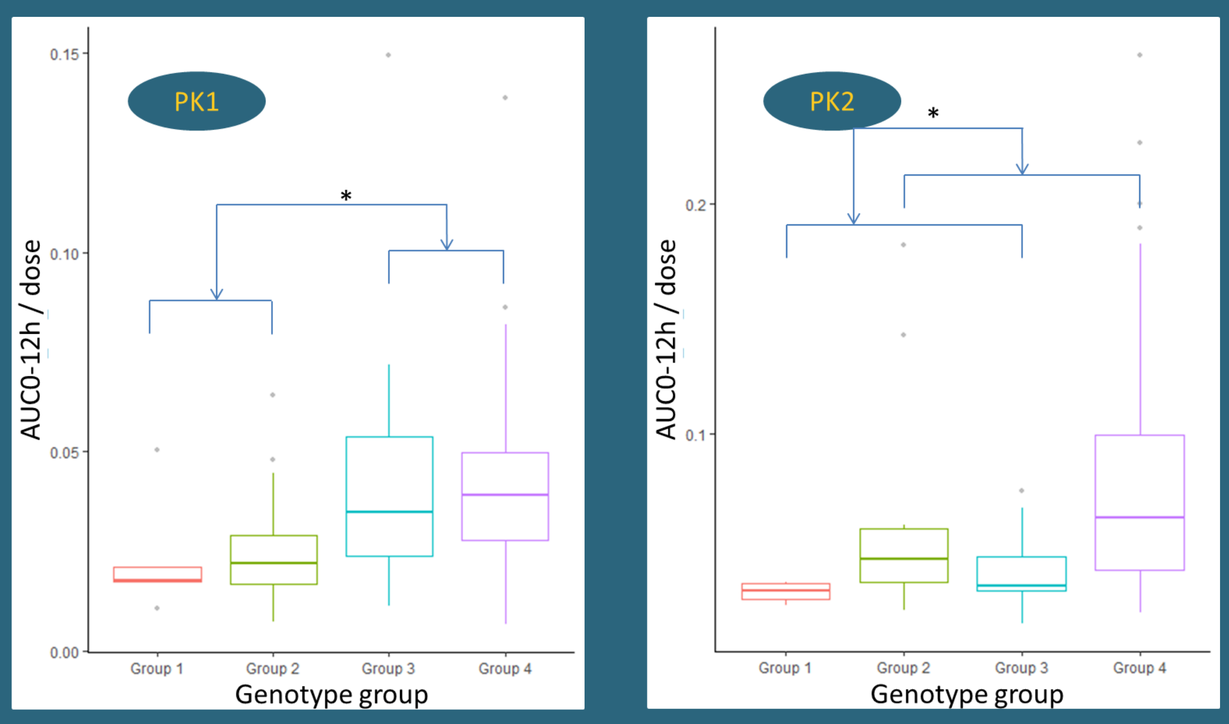


Figure 2: Distribution of AUC/dose ratios according to donor/recipient genotype groups. On the first day of transplantation, the genotype of the recipient has a significant effect on tacrolimus AUC. After 8 days of treatment, it is the donor genotype that has a significant effect on treatment exposure. (* : p<0,05)

Conclusion

These are preliminary results of CYPTAC'H study, obtained by non compartmental analysis and including only the CYP3A5 polymorphisms (CYP3A4*22 and ABCB1 haplotype have been explored but not yet analyzed). However, we can already conclude that recipient genotype of CYP3A5 is the most influential factor in the dose-exposure relationship of tacrolimus immediately after transplantation. Liver function quickly recovers and the intensity of hepatic metabolism becomes more significant than the intestinal pre-systemic metabolism at D8, which could explain the influence of donor genotype on tacrolimus exposure at PK2. The planned PK-pop analysis will provide more precise data on this point.

The confirmation of this information could modify the practice by including CYP3A5 genotyping in pre-transplant check-up, as it is proposed in kidney transplantation with the aim to reduce intra-individual variability and to quickly reach the concentration target. The data from the CYPTAC'H study still holds much information that needs to be analyzed with attention, with the aim of improving the management of liver transplant patients