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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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Background : 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, which has the most influence in the immediate post-transplant period? This is the question that the CYPTAC'H study attempted to answer.

Methods: CYPTAC'H study (NCT01388387) was conducted in Rennes University Hospital on adult liver transplant recipients receiving tacrolimus immediately after transplantation. 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. Tacrolimus exposure was assessed by calculating area under the curve (AUC0-12h) of blood concentrations with the trapezoidal rule. Wilcoxon test was used to compare AUC/Dose between genotype groups.

Results: 141 patients aged of 60.0±6.6 years old, were included in this study between 2012 and 2018 and 2553 blood tacrolimus concentrations were measured. AUC0-12h of tacrolimus was estimated on 140 patients at PK1 and 113 at PK2. CYP3A5 polymorphisms were distributed this way: 104 patients were donor and recipient *3/*3; 13 patients were donor *1/*3 or *1/*1 (*1 carrier) and recipient *3/*3; 16 patients were donor *3/*3 and recipient *1 carrier; 5 patients were donor and recipient *1 carrier. AUC/dose ratio was significantly higher in *3/*3 recipients than in *1 carrier recipients at PK1, regardless the donor genotype. Conversely, once steady-state was reached the AUC/dose ratio was significantly higher in *3/*3 donors than in *1 carrier donors, regardless the recipient genotype.

Conclusions: these are preliminary results obtained by non compartmental analysis and including only the CYP3A5 polymorphisms. However we can already conclude that recipient genotype of CYP3A5 is the most influential in the dose-concentration relationship of tacrolimus immediately after transplantation. The confirmation of this information could modify the practice by including CYP3A5 genotyping in pre-transplant check-up, as is done for kidney transplantation. The data from the CYPTAC'H study still holds much information that needs to be analysed with attention, with the aim of improving the management of liver transplant patients.

Keywords: liver transplant, CYP3A5 polymorphism, tacrolimus exposure