Factors influencing pharmacokinetics of tacrolimus during the early liver post-transplantation period: a population analysis

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Introduction and objectives

Tacrolimus (TAC) is an immunosuppressive agent used for the prevention of acute rejection after liver transplantation. Clearance and bioavailability of TAC are controlled by the activity of P-glycoprotein (P-gp) and CYP3A5 in the gut and the liver. P-gp and CYP3A5 are polymorphic, and the genotype of the donor and the recipient may differ.

The objective was to investigate the population pharmacokinetics (PK) of TAC during the first 15 days post-transplantation and identify recipient and donor characteristics that influence PK parameters.

Methods

This was a prospective multicentric study (3 sites). 65 adult patients receiving oral TAC after liver transplantation were included. For each patient, at least 3 blood samples were taken at 3 occasions D2, D7 and D14. Patients characteristics collected and tested were: age, body weight, total plasmatic proteins, albumin concentration, coagulation factor V, prothrombin time, total and conjugated bilirubin, alkaline phosphatase (AP), Gamma Glutamyl Transferase (GGT), ALAT, ASAT, serum creatinine concentration (SCR), red blood cell count and haematocrit. Genetic factors were also collected for each donor and transplant recipient: CYP3A5 (intron 3) and P-gp (3435C_T in exon 26 in MDR1 gene) genotypes. PK analysis was carried out by using Monolix V3.1.

Results

Table I. Characteristics of the 65 patients

	n	Mean ± SD	Median	(min , max)
Age (y)	65	52.9 ± 10.1	55	(27 , 67)
Body weight (kg)	48	70.8 ± 13.4	70	(45 , 107)
Total plasmatic proteins (g/L)	65	52.1 ± 10.8	52	(26 , 97)
Albumin concentration (g/L)	44	24.2 ± 11.0	21	(11 , 87)
Coagulation factor V (%)	57	97.9 ± 40.6	93	(17 , 196)
Prothrombin time (%)	65	76.6 ± 22.0	75	(1.9 , 180)
Total bilirubin (mg/L)	65	70.1 ± 96.8	34	(6 , 631)
Conjugated bilirubin (mg/L)	65	50.0 ± 73.7	22	(3 , 487)
AP (UI/L)	65	196 ± 153	148	(9 , 1120)
GGT (UI/L)	65	232 ± 186	190	(4 , 1670)
ALAT (UI/L)	65	366 ± 680	172	(10 , 12337)
ASAT (UI/L)	65	246 ± 712	61	(10 , 9391)
SCR (µmol/L)	65	94.0 ± 51.0	82	(11 , 525)
Red blood cell count (T/L)	65	3.20 ± 0.49	3,15	(1.98 , 4.58)
Hématocrit (%)	65	29.0 ± 4.18	28.4	(18.5 , 41.5)
Dosage regimen (mg/kg/day)	48	0.09 ± 0.07	0.07	(0.01 , 0.36)

Mean patient age and body weight were 52.9 ± 10.1 years and 70.8 ± 13.4 kg, respectively. Mean dosage regimen of TAC was 0.087 ± 0.067 mg/kg per day **(table I).**

A one-compartment model with first order absorption and elimination adequately described the data. Typical population estimates (relative standard error) of absorption rate constant, apparent distribution volume and apparent clearance (CL) were 0.91 h-1 (216%), 486 L (21%) and 11.7 L/h (14%), respectively.

Five covariates were found relevant: AP, ASAT, SCR, CYP3A5 genotype of the donnor, P-gp genotype of the recipient. CL of TAC was negatively related to AP, ASAT and SCR **(figure 1).**

Regarding CYP3A5, mean CL was lower when the donor was CYP3A5*3/*3 homozygote rather than carrying at least one CYP3A5*1 allele: 12.6 ± 4.6 (n=31) *vs* 24.8 ± 3.1 L/h (n=8) (p<0.005 with Mann-Whitney test) **(figure 2).**

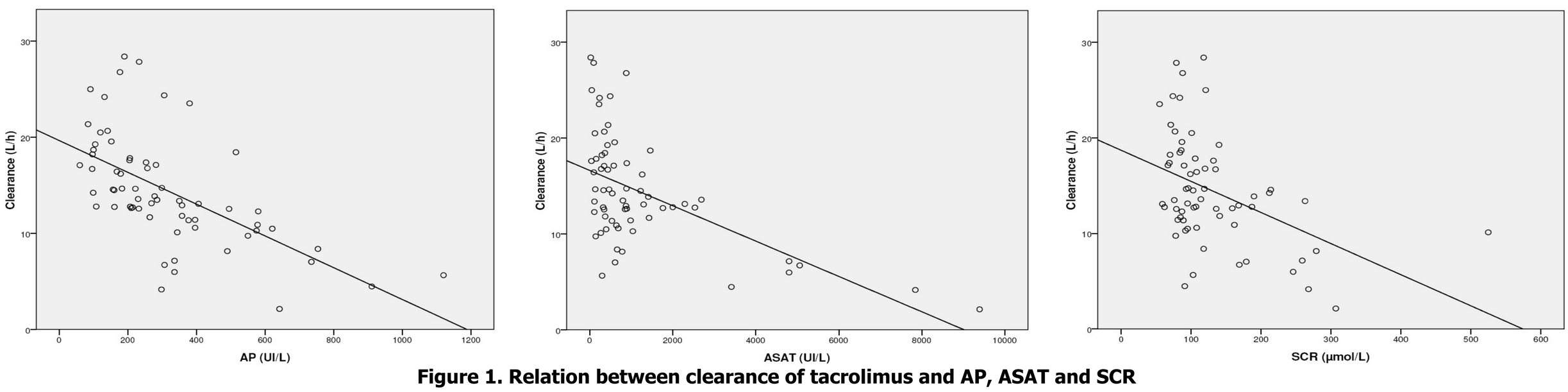

Figure 1. Relation between clearance of tacrolimus and AP, ASAT and SCR

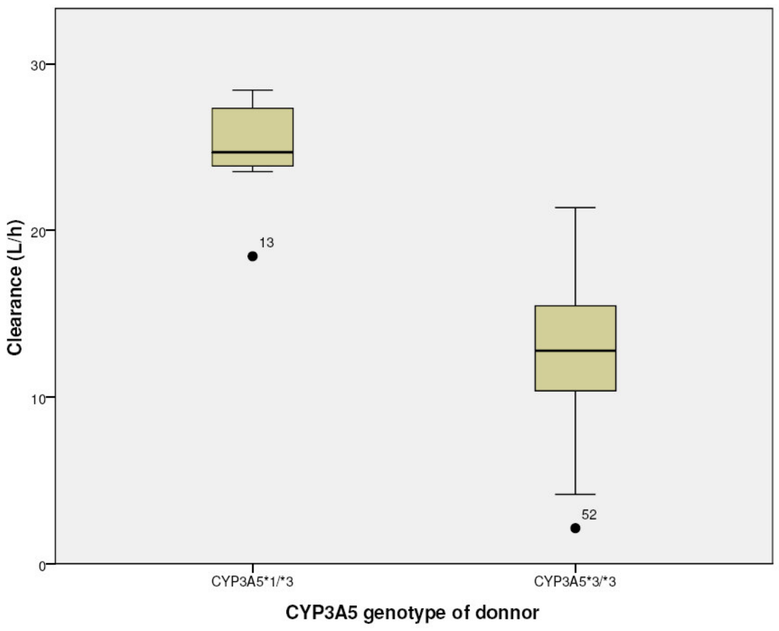

Figure 2. Effect of CYP3A5 genotype on clearance of tacrolimus

For P-gp, there was a significant difference between the mean CL of the 3 types of patients : 13.7±6.1 L/h for T/T homozygotes ("mutant" alleles, n=14); 14.2±4.6 L/h for C/T heterozgygotes (n=17) and 18.5±5.3 L/h for C/C homozygotes (n=17) (p< 0.05 with Kruskal-Wallis test) **(figure 3).** This result is consistent to a previous study in liver transplant recipients that have demonstrated that patients with strongly expressed MDR1 (C/C homozygotes) required higher tacrolimus doses to achieve trough concentrations similar to those of patients with weak expression (T/T homozygotes) [1].

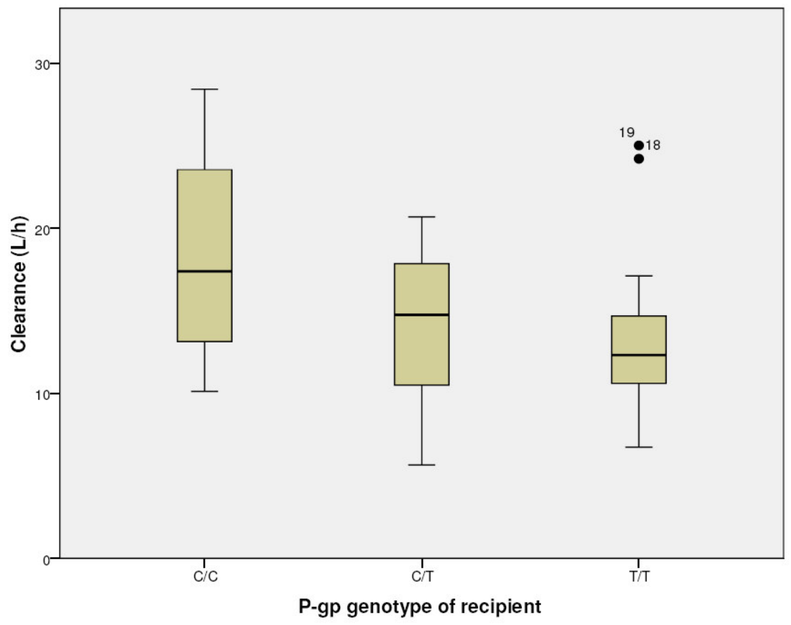

Figure 3. Effect of CYP3A5 genotype on clearance of tacrolimus

Conclusion

During the early post-transplant period, some biological parameters but especially CYP3A5 and P-gp genotypes, should be taken into account because of their effect on the CL and consequently on the initial dosing regimen of TAC.

[1] T. Hashida, S. Masuda, S. Uemoto, H. Saito, K. Tanaka, and K. Inui. Pharmacokinetic and prognostic significance of intestinal MDR1 expression in recipients of living-donor liver transplantation. Clin Pharmacol Ther. 69:308-316 (2001).