Determination of the most influential sources of variability of tacrolimus trough blood levels in adult liver transplant patients: a bottom-up approach

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Introduction and objectives

Tacrolimus (TAC), an immunosuppressant drug used for the prevention of graft rejection after liver transplantation, presents a large pharmacokinetic variability and blood concentration of TAC must be monitored. Most part of the interindividual variability remains unexplained. The objective was to identify predictive factors influencing TAC trough concentrations using a bottom-up approach.

Patients & Method

A physiologically-based pharmacokinetic (PBPK) model of TAC was proposed **(figure 1)**, taking into account the body weight (BW), the proportion of adipose tissue, hematocrit, lipid fraction of organs, liver function, CYP3A5 genotype of patient and concomitant drugs (CYP3A4 inhibitors). A saturation of binding to red blood cells was accounted for. TAC concentration profiles were simulated in a virtual population defined by a set of covariate values similar to those from a real population of 66 transplanted patients included in a multicentric PK study. Correlations between covariates were accounted for. For the validation of the PBPK model, trough blood concentrations were compared with those observed in the clinical study. Then, the impact of each covariate has been tested on trough TAC concentration in order to identify the most influential ones.

Results

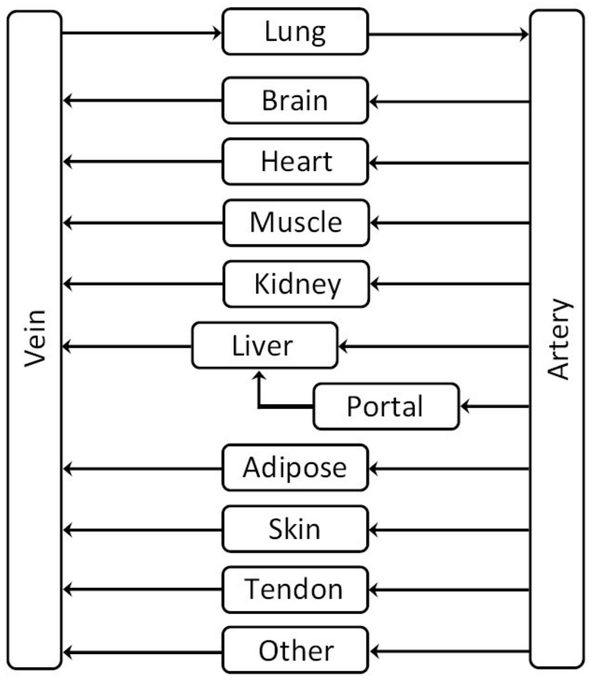

Figure 1. PBPK model of TAC

For CYP3A5 *3/*3 genotype of liver donor and three levels of drug-drug interaction (without inhibition, low and moderate inhibition of CYP3A4), means were 7.84 vs 7.87, 8.22 vs 8.35 and 10.3 vs 10.1 ng/ml for observed vs simulated trough blood concentrations of TAC **(figure 2).**

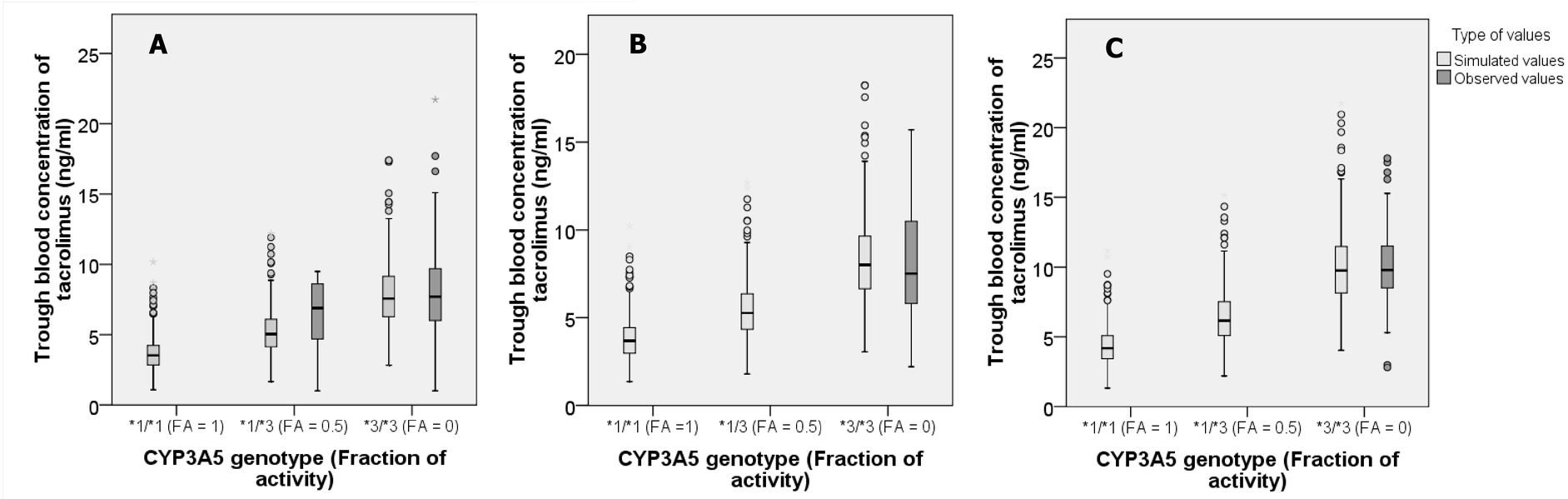

Figure 2. Trough blood concentration of TAC A : without interaction. B : with low inhibition of CYP3A4. With moderate inhibition of CYP3A4

With a dosage regimen of 0.03 mg/kg every 12 hours, a significant increase of the mean trough concentration of TAC (5.09 to 13.1 ng/mL) has been found when BW increases (50 to 100 kg) **(figure 3).**

For the severity of cirrhosis (Child Pugh score of A to C), hematocrit (0.19 to 0.43), proportion of adipose tissue (0.10 to 0.30), the same trend in trough concentration was found: means of 12.8 to 37.5, 4.93 to 12.0 and 6.03 to 8.97 ng/mL, respectively **(figures 4, 5 and 6).**

Without drug-drug interaction, mean simulated trough concentrations for the three genotypes of CYP3A5 were 3.73, 5.25, and 7.87 for *1/*1 (fraction activity (FA) of 1), *1/*3 and *3/*3 (no protein activity), respectively **(figure 2A).**

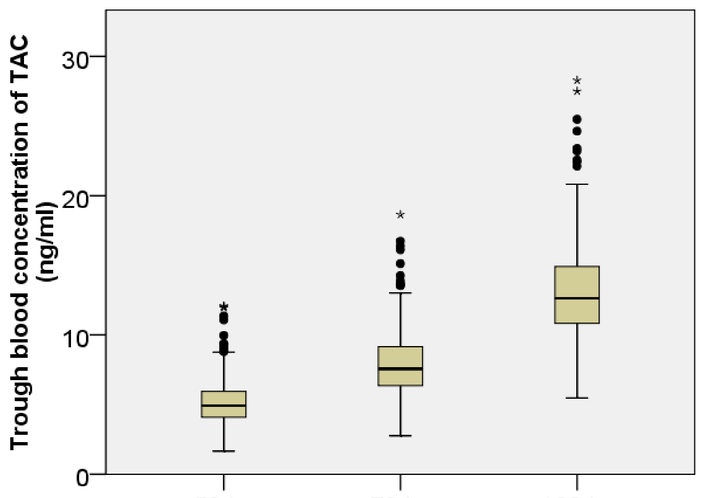

Figure 3. Effect of BW on trough blood concentration of TAC

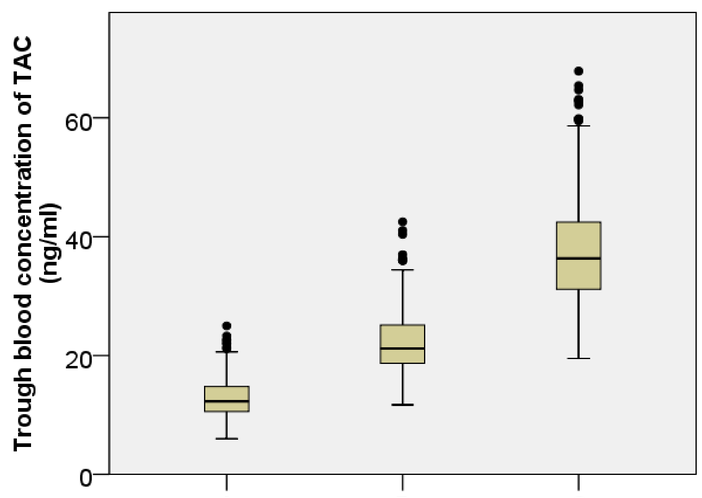

Figure 4. Effect of the 3 levels of severity of cirrhosis on trough blood concentration of TAC

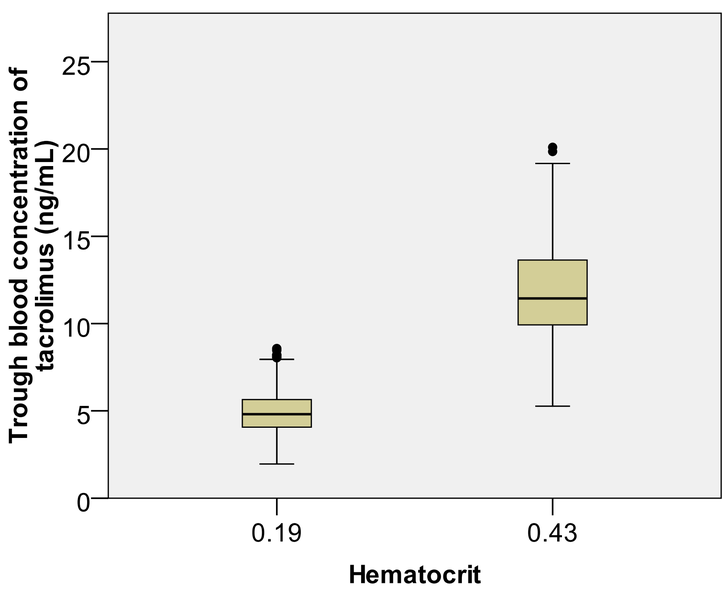

Figure 5. Effect of hematocrit on trough blood concentration of TAC

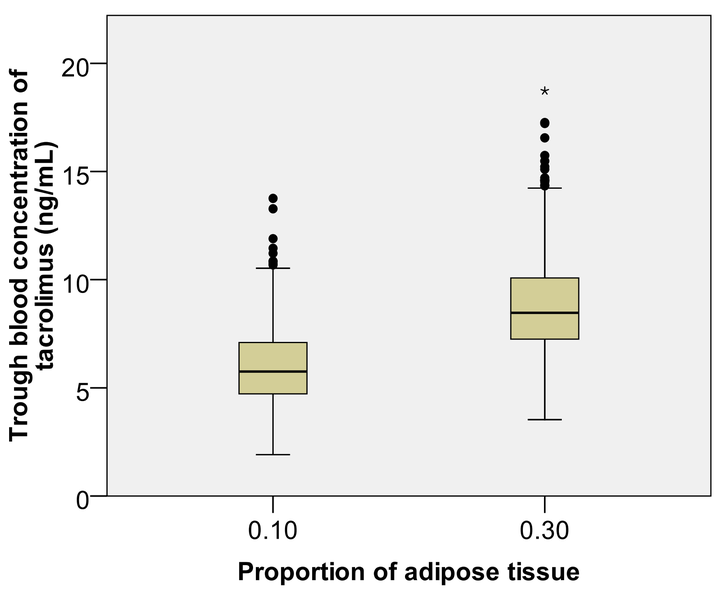

Figure 6. Effect of proportion of adipose tissue on trough blood concentration of TAC

Conclusion and perspectives

Bottom up approach allowed taking into account the influence of relevant covariates on trough blood concentration of TAC. The most influential covariate were BW, hematocrit, liver function and CYP3A5 genotype of the liver donor. These covariates must therefore be taken into account to help the clinician to choose the initial dosage regimen according to the characteristics of the transplant recipient patient.