Population pharmacokinetic model for intracellular and whole blood tacrolimus in liver transplant recipients

Franck B[1,2], De Quélen M[1], Tron C[1,2], Bellissant E[1,2], Verdier M-C[1,2], Comets E[1] and Lemaitre F[1,2,3]
[1]University of Rennes, Centre Hospitalier Universitaire Rennes, École des Hautes Études en Santé Publique, IRSET (Institut de Recherche en Santé, Environnement et Travail), UMR S 1085, Rennes, France. [2]Department of Clinical and Biological Pharmacology and Pharmacovigilance, Clinical Investigation Center CIC-P 1414, Rennes, France. [3]FHU SUPORT, Rennes

Background
Tacrolimus is the cornerstone of current immunosuppressive strategies in liver transplant recipients. The drug showed large intra- and inter-individual variabilities and a narrow therapeutic index. Thus, therapeutic drug monitoring is routinely performed based on the determination of trough blood concentrations. However, the variability of the clinical response remains high and need to be better described, especially by deciphering the relationship between tacrolimus and biomarkers such as calcineurin activity. The objectives of this study were to develop a population pharmacokinetic model (POPPK) of whole-blood and intracellular tacrolimus in liver transplant recipients and to describe the relationship between tacrolimus exposure (whole blood and intracellular) and calcineurin activity.

Methods
Data from two clinical studies were collected. The first clinical study provided complete whole blood, intracellular and calcineurin activity profiles at day 7 after liver transplantation. The second clinical study provided trough concentrations (whole blood, intracellular and calcineurin activity) up to 6 months after liver transplantation. The POPPK analysis was performed using a nonlinear mixed effects modeling approach with Monolix®. Demographic, genetic, biological and clinical covariates were tested. The model was internally evaluated using visual predictive check.

Results
A total of 32 patients from the first study were included and contributed to 315 whole blood concentrations, 257 intracellular concentrations and 225 calcineurin activity measurements. The median/range patient weight and dose administered before PK profile were 97kg [50-121] and 1.5mg [0.5-3.5], respectively. A total of 94 patients from the second study were included (28 patients in common with the first study) and contributed to 1028 whole-blood concentrations, 859 intracellular concentrations and 815 calcineurin activity measurements. The median/range weight and dose administered were 80.7kg [42.8-126.3] and 2.0mg [0.35-6.5], respectively. A 2-compartment model with first-order absorption and linear elimination best described the data. The intracellular concentrations were proportional to blood concentrations. A high interoccasion variability of intracellular distribution of tacrolimus was observed during the 6 months follow-up.

Conclusions
This POPPK model well described whole blood and intracellular concentrations and have shown a decrease of intracellular tacrolimus distribution over the months after transplantation.

Keywords
Tacrolimus, peripheral blood monoculear cells, transplantation, population pharmacokinetic