Category: Pharmacometrics

EFFECT OF ANTIBIOTICS-MEDIATED MICROBIOTA DEPLETION ON TACROLIMUS PHARMACOKINETICS IN MICE

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Figure 1a.

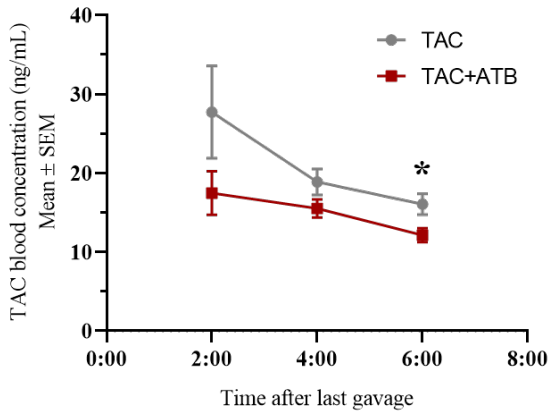

Figure 1b.

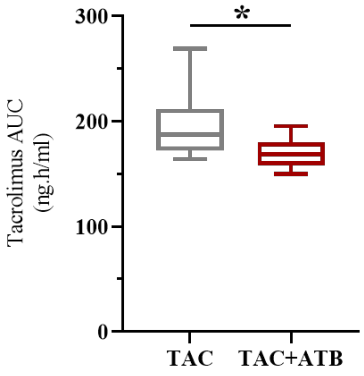

Figure 1a. Tacrolimus exposure in mice treated with an antibiotic cocktail (red) or vehicle (grey) in the drinking water. **Figure 1b.** Comparison between the two groups of tacrolimus median AUC derived from the PK model.

Background: Considerable progress has been achieved to enhance transplant survival by understanding the pharmacogenetics factors influencing tacrolimus (TAC) pharmacokinetics (PK), which explain inter-patient variability. However, these genetics factors cannot explain the high intra-patient variability observed. Over the last decade, pharmacomicrobiomics has emerged as a new field of pharmacology, focusing on the effect of microbes on drug action, disposition, and toxicity. Several clues suggest the involvement of the gut microbiota in the modulation of TAC PK[1]. In this project, we investigated the role of gut microbiota on TAC PK in mice.

Methods: 1st experiment: 10 mice were treated with different TAC doses (from 0.1 to 10 mg/kg of body weight) to determine the best dose for future experiments. At steady-state, blood concentrations were determined at T0h and T2h using HPLC-MS/MS. 2nd experiment: a kinetic curve covering 6 time points [0, 1, 2, 3, 4 & 6h] was performed at steady-state at the selected dose (3.0mg/kg_{BW} /day for 5 consecutive days) to decide on the best sample strategy for the 3rd experiment (n = 24 mice ; n = 72 PK data). 3rd experiment: mice were treated with TAC +/- an antibiotic (ATB) cocktail that ensure microbial depletion (2,6 log_{10} reduction). Blood levels were determined at 2, 4 and 6h and compared among groups (n = 10 mice/group). All generated data (at 3mg/kg dose level only, n = 54 mice, n = 171 PK data) were used to build a population PK model, using the NONMEM software. We estimate PK parameters and derive AUC and T½.

Results: The dose of 3.0mg/kg_{BW} was further selected. Primary PK parameters were estimated with the use of PK model (Median [IC95%]): Cl/F = 0.326 l/h [0.290 – 0.362]; V = 2.1 l [1.747 – 2.453]; ka = 1.22 h^{-1} [0.57 – 1.87]. Median $AUC_{0\text{-}24h}$ and T½, derived from primary PK parameters, were respectively 220.1 ng.h/ml and 3.69 h. TAC exposure under ATB treatment (Figure 1a.) showed an almost significant trend of reduction (2-way ANOVA with repeated measures, p = 0.071). When looking at the median AUC calculated for each group based on the PK model (Figure 1b.), we observed a significant reduction in total AUC under ATB supplementation (168.8 versus 187.4 ng.h/ml; Wilcoxon-Mann-Whitney test, p = 0.023).

Conclusions: Our results demonstrate that effective ATB-mediated microbial depletion decreases TAC exposure. This observation suggests that the gut microbiota influences TAC metabolism. If confirmed in humans, this information can be of importance for explaining inter- but also intra-individual variability in TAC exposure.

[1] Guo Y, Crnkovic CM, Won KJ, et al. Commensal Gut Bacteria Convert the Immunosuppressant Tacrolimus to Less Potent Metabolites. Drug Metab Dispos. 2019;47:194-202

Keywords: Tacrolimus, Gut microbiota, Pharmacokinetics, Inter- and intra-individual PK variability, Mouse model.