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ePoster Viewing
Tuberculosis and other mycobacterial infections

Pharmacogenetics of rifampicin: effect of single nucleotide polymorphisms on plasma and intra-PBMC exposure

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Background: Tuberculosis is the second greatest killer worldwide due to a single infectious agent. Rifampicin (RFP) is a first-line drug for tubercolosis treatment. Several studies showed that RFP plasma concentrations are associated with antimicrobial outcomes. Since antibacterial activity relies on appropriate levels also at the site of action (specifically intra-macrophage), intracellular concentrations might be relevant for explaining the variability in response to antitubercular drugs but available data are limited. Furthermore single nucleotide polymorphisms in selected genes have been described to be associated with RFP exposure.

Material/methods: Adult patients with tuberculosis and without HIV-infection, severe malnutrition, liver or kidney failure, treated with RFP (10 mg/kg), were enrolled. Allelic discrimination for ABCB1 3435 C>T (rs1045642), OATP1B1 521 T>C (rs4149056), PXR 63396 C>T (rs2472677), VDR TaqI T>C (rs731236), FokI T>C (rs10735810), BsmI G>A (rs1544410), Cdx2 A>G (rs11568820) and ApaI C>A (rs7975232), CYP24A1 +22776 C>T (rs927650), +3999 T>C (rs2248359) and +8620 A>G (rs2585428), CYP27B1 +2838 C>T (rs4646536) and -1260 G>T (rs10877012) SNPs was performed by real-time PCR. Maximal (Cmax, at the end of three infusions for intravenous and two hours post dose for oral) and trough (Ctrough, at the end of dosing interval) plasma and intra-PBMCs concentrations (IC) were measured at week 2 (intravenous route) and 4 (oral route) using UPLC-MS/MS validated methods. Multivariate linear regression analysis was performed including age, gender, Body Mass Index (BMI), ethnicity and genetic factors (Table 1).

Results: Twenty-four patients (19 males, 11 Caucasians, median age 41.8 years and median BMI 20.6 Kg/m^2) were enrolled. At week 2 median RFP plasma and IC C_{trough} were <limit of detention, LOD (interquartile range, IQR: <LOD-420 ng/mL) and <LOD while median C_{max} were 6652 ng/mL (IQR: 4474-7873 ng/mL) and 7104 ng/mL (IQR: 7104-11124 ng/mL). Concerning week 4, median RFP plasma and IC C_{trough} were <LOD (IQR: <LOD-88 ng/mL) and <LOD whereas median C_{max} were 6606 ng/mL (IQR: 3633-7632 ng/mL) and 7269 ng/mL (IQR: 4953-11823 ng/mL). At week 2, gender and *OATP1B1 521* TT genotype for plasma C_{trough}, *OATP1B1 521* TT and *CYP27B1 +2838* CC/CT considering plasma C_{max}, gender and *ABCB1 3435* TT regarding IC C_{trough} and *BsmI* AA concerning IC C_{max}, remained in linear regression analysis as early predictive factors (Table 1). Concerning week 4, *OATP1B1 521* TT, *FokI* TC/CC, *Cdx2* AG/GG and *CYP24A1 22776* TT genotypes for plasma C_{trough}, *TaqI* TC/CC and *CYP24A1 22776* CT/TT considering plasma C_{max} and BMI regarding IC C_{max}, were retained in final regression model (Table 1).

Conclusions: We here report a significant inter-subject variability in RFP exposure and the effect of single nucleotide polymorphisms in OAT1B1 thus confirming the role of SLCO1B1 in RFP transport. The suggested potential involvement of polymorphisms in vitamin D pathway genes need to be confirmed in other cohorts.