EV0138 26th ECCMID

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

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BACKGROUND

Tuberculosis (TB) 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 antiTB drugs but available data are limited. Furthermore single nucleotide polymorphisms (SNPSs) in selected genes have been described to be associated with RFP exposure.

An high frequency of vitamin D deficiency in TB patients has been reported; Vitamin D is able to increase phagocythosis through activation of macrophages and subsequently to limit intracellular growth of *M. tuberculosis*; in addition, SNPs on its receptor (VDR) seem to play an important role on treatment outcome (1,2).

Our aim was to retrospectively evaluate pharmacogenetic role of SNPs involved in RFP transport (*SLCO1B1*, *MDR1* and *PXR* genes), vitamin D (*VDR*, *CYP24A1* and *CYP27B1* genes) metabolism and activity on drug plasma and intracellular (IC) concentrations.

MATERIAL AND METHODS

Adult patients with tuberculosis and without HIV-infection, severe malnutrition, liver or kidney failure, treated with RFP (10 mg/kg), were included. 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 (C_{max}, at the end of three infusions for intravenous and two hours post dose for oral) and trough (C_{trough}, at the end of dosing interval) plasma and IC concentrations were measured at week 2 (intravenous route) and 4 (oral route) using UPLC-MS/MS validated methods (3). For IC pharmacokinetic evaluation we used peripheral blood mononuclear cells (PBMCs), as tissue macrophages seem to be the target of antitubercular drugs.Multivariate linear regression analysis was performed including age, gender, Body Mass Index (BMI), ethnicity and genetic factors (Table).

WEEK	Concentration	FACTOR	*p**	β	IC95%	
2	Plasma C_{trough}	Gender	0.025	0.401	126.147	1655.176
		OATP1B1 521 T>C	0.044	0.345	6.458	1313.556
	Plasma C_{max}	*OATP1B1 521* T>C	0.019	0.432	452.896	4571.040
		CYP27B1 +2838 CC/CT	0.024	0.416	469.172	5857.279
	Intra-PBMCs C_{trough}	Gender	0.029	0.374	105.007	1798.840
		ABCB1 3435 TT	0.016	0.411	197.851	1721.987
	Intra-PBMCs C_{max}	*BsmI* AA	0.006	0.547	2414.805	12519.590
4	Plasma C_{trough}	*OATP1B1 521* T>C	0.010	0.340	63.126	409.738
		FoKI TC/CC	0.009	-0.341	-535.759	-86-109
		Cdx2 AG/GG	**<0.001**	-0.497	-675.700	-230.415
		CYP24A1 22776 TT	0.027	0.299	34.232	510.262
	Plasma C_{max}	*TaqI TC/CC*	0.043	0.359	98.898	5711.512
		CYP24A1 22776 CT/TT	0.036	0.384	240.434	6502.709
	Intra-PBMCs C_{max}	BMI	0.015	0.488	203.270	1733.442

Table . Factors retained in multivariate linear regression analyses (*p*<0.05), able to predict RFP plasma and IC levels, at week 2 and 4, considering both C_{trough} and C_{max}. **p*: *p-value*; β: β coefficient; IC 95%: interval of confidence at 95%. Considering *OATP1B1 521* no patients with CC genotype were present in our cohort. Results with a p-value > 0.05 had not been reported.

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 (Table), 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.

Considering week 4 (Table), *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 .

CONCLUSIONS

Pharmacogenomics and TDM could contribute to enhance anti-TB therapy optimization on the basis of interindividual genetic variability. Different studies suggest that inheritance plays a significant role in anti-TB treatment, particularly regarding RFP.

This study confirms the role of *SLCO1B1* gene and reveals, for the first time, the involvement of vitamin D pathway gene polymorphisms on RFP PK.

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