EFFECT OF *CYP3A4*22* ON ORAL RILPIVIRINE PLASMA CONCENTRATIONS

Rana Abutaima[1]; Marta Boffito[2]; Andrea Calcagno[3]; Jessica Cusato[3]; Antonio D'Avolio[3]; Laura Else[1]; Chris Higgs[2]; Saye Khoo[1]; Marco Siccardi[1]; Andrew Owen[1].

[1]University of Liverpool, Liverpool, UK, [2]St Stephen's AIDS Trust, Chelsea and Westminster Hospital, UK, [3]Unit of Infectious Diseases, University of Turin, Department of Medical Sciences, Amedeo di Savoia Hospital, Turin, Italy.

Correspondence: rana.abutaima@liverpool.ac.uk

UNIVERSITY OF LIVERPOOL

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Introduction

- Rilpivirne (RPV) is a second-generation nucleoside reverse transcriptase inhibitor (NNRTI) that is used in combination with other antiretroviral (cART) backbone therapies.
- RPV is mainly metabolized by phase I metabolic enzymes, notably, CYP3A4, CYP3A5 and CYP2C19 and is a substrate for the SLC22A1 uptake transporter. However, little is known about the role of other drug transporters in RPV disposition. Also, many metabolic enzymes and drug transporters are transcriptionally regulated by PXR (NR1I2).
- Interindividual variability in drug disposition can occur because of genetic polymorphisms such as single nucleotide polymorphisms (SNPs).
- Some of the SNPs that are expressed in the genes encoding metabolic enzymes, drug transporters and nuclear receptors are functional and might result in decreased or increased protein expression or activity, consequently, altered drug pharmacokinetics.

Objective

- In this study, we sought to determine associations between genetic variants within the genes coding for these proteins and RPV plasma concentrations.

Study population

- Patients were recruited in Amedeo di Savoia Hospital, Turin, Italy and St Stephen's AIDS Trust, Chelsea and Westminster Hospital, London, UK
- 112 were on RPV with emtricitabine (FTC), tenofovir (TDF), 35 on RPV with ritonavir boosted darunavir (DRV/rtv) and 3 on RPV with abacavir (ABC), lamivudine (3TC).
- Blood samples were collected from 150 patients after ethical approval. 12 hours post RPV dose (C_{12})

Sample analysis

- Plasma samples were quantified for RPV concentration using a validated LC-MS/MS method.
- DNA was extracted from patients' blood or plasma samples using a DNA extraction kit.
- DNA was genotyped by allelic discrimination using real time PCR for selected functional SNPs using TaqMan assays.

Statistical analysis

- Samples were tested for compliance with Hardy-Weinberg equilibrium using Chi square test.
- Univariate linear regression was performed for each variable against RPV C_{12} after it was log transformed.
- Variables that had a p-value ≤0.2 were included in the multivariate linear regression and a p-value of ≤0.05 was considered statistically significant.

Results

- 150 patients were genotyped for the selected SNPs, and all were in Hardy-Weinberg equilibrium with p-value> 0.05 in Chi-square test.
- The association test between RPV C_{12} and independent variables was carried out after log transformation. However, data in (table 3) are presented as RPV C_{12} with an overall mean ±SD of 170.1ng.ml^{-1} and carrier/non-carrier analyses were applied in the linear regression.
- In the univariate analysis, patients' **height** was significantly associated with RPV C_{12} with p-value = 0.01.
- ***CYP3A4*22*** (rs35599367) T allele was significantly associated with higher RPV $\log_{10}C_{12}$ by 7.8%. While the percentage difference in RPV $\log_{10}C_{12}$ associated with the **backbone therapies** was 1.3% higher with TDF/FTC, 3.2% less with DRV/rtv and 6.5% less with ABC/3TC. On the other hand, ***SLCO2B1* rs1789693** T allele contributed to 2.26 less RPV $\log_{10}C_{12}$ compared to non-carriers, however, we could not show statistical significance with the available sample size (p-value = 0.09) (figure1).

SNP	Minor Allele Frequency (%)	
*CYP3A4*22* (rs35599367) c.522-191C>T	T: 4.03	C: 95.97
*CYP2C19*2* (rs4244285) c.681G>A	A: 10.67	G: 89.33
*CYP2C19*3* (rs4986893) c.636G>A	A: 0.34	G: 99.66
*CYP2C19*17* (rs12248560) g-806 C>T	T: 21.77	C: 78.23
*CYP3A5*3* (rs776746) c.-253-1G>A	A: 6.04	G: 93.96
NR1I2 (rs2472677) c.96-7659C>T	T: 54.67	C: 45.33
SLC22A1 (rs628031) c.1222A>G	G: 63	A: 37
SLC22A1 (rs72552763) c.1260_1262delGAT	Del: 16.33	Non: 83.67
SLC22A1 (rs622342) c.1386-2964C>A	A: 71.33	C: 28.67
SLC22A1 (rs683369) c.480G>C	C: 84.33	G: 15.67
SLCO2B1 (rs1789693) c.540+3551T>A	A: 63.67	T: 36.33
SLCO2B1 (rs1077858) c.643+2318G>A	A; 63.33	G: 36.67
SLCO2B1 (rs12422149) c.503G>A	A: 10.33	G: 89.67
SLCO2B1 (rs35199625) c.169G>A	0.68	G: 99.32
SLCO2B1 (rs2712807) c.-546G>A	A: 86.67	G: 13.33
SLCO2B1 (rs2851069) c.-71T>C	C: 60	T: 40
Characteristics	n=150	
Age (years)	42.7 (20.4-74.5)	
Height (cm)	173.5 (145-191)	
Weight (kg)	72.3 (45-112.2)	
Ethnicity		
Gender	Male 86% Female 14%	
Backbone therapy	Tenofovir Emtricitabine 74.7% Darunavir/ritonavir 23.3% Abacavir , lamivudine 2%	

Table 1: Characteristics of patients population and minor allele frequency. Data shown as mean (minimum and maximum value) and percentage.

Univariate analysis				
Variables	β	95% Confidence interval (CI)		P value
Gender	0.074	-0.032	0.181	0.169
Age	0.000	-0.003	0.004	0.868
Caucasian	-0.082	-0.348	0.183	0.540
Height	-0.006	-0.010	-0.001	0.01
Weight	-0.002	-0.006	-0.001	0.11
*CYP3A4*22* (rs35599367)	-0.165	-0.296	-0.033	0.014
*CYP2C19*2* (rs4244285)	-0.052	-0.142	0.039	0.262
*CYP2C19*3* (rs4986893)	-0.27	-0.715	0.175	0.233
*CYP2C19*17* (rs12248560)	0.014	-0.062	0.089	0.724
*CYP3A5*3* (rs776746)	0.035	-0.77	0.15	0.54
NR1I2 (rs2472677)	0.007	-0.073	0.088	0.860
SLC22A1 (rs628031)	-0.018	-0.094	0.057	0.632
SLC22A1 (rs72552763)	0.006	-0.075	0.087	0.884
SLC22A1 (rs622342)	-0.027	-0.101	0.047	0.473
SLC22A1 (rs683369)	-0.034	-0.116	0.048	0.414
SLCO2B1 (rs1789693)	0.055	-0.021	0.131	0.153
SLCO2B1 (rs1077858)	0.017	-0.059	0.092	0.664
SLCO2B1 (rs12422149)	-0.018	-0.113	0.076	0.700
SLCO2B1 (rs35199625)	-0.123	-0.448	0.202	0.457
SLCO2B1 (rs2712807)	-0.035	-0.122	0.051	0.422
SLCO2B1 (rs2851069)	0.046	-0.031	0.122	0.240
Concomitant drugs	-0.096	-0.171	-0.022	0.012

Table 2: Univariate analysis results of log RPV C_{12} against other dependent variables shown in the table

Variable	Mean C_{12} value (ng. mL^{-1}) (SD)	Multivariate linear regression (Backward method)			
		β	95% CI		P value
Height		-0.004	-0.01	0.001	0.07
TDF/FTC	182.3 (93.9)	-0.09	-0.16	-0.01	0.02
DRV/r	140.2 (62)				
ABC/3TC	171.4 (89.9)				
*CYP3A4*22* T allele carrier	221.2 (50.6)	-0.17	-0.30	-0.03	0.02
*CYP3A4*22* Non-carrier	167.98 (89.9)				
SLCO2B1 rs1789693 T allele carrier	163.43 (82.5)	0.06	-0.01	0.14	0.09
SLCO2B1 rs1789693 Non-carrier	183.59 (97.4)				

Table 3: Association between C_{12} and patients' characteristics after multivariate linear regression.

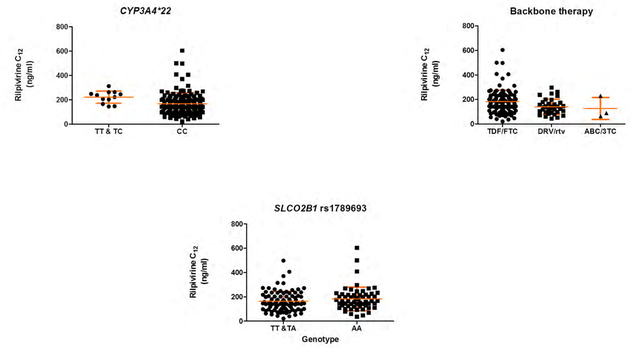


Figure 1: Association between $\log_{10}$RPV C_{12} and *CYP3A4*22* A allele carrier, *SLCO2B1* (rs1789693) T allele carrier and backbone therapies.

Conclusion

- These results indicate that ***CYP3A4*22*** (c.522-191 C>T; rs35599367) is associated with RPV pharmacokinetics but further studies are required to confirm this association. While the impact of CYP3A4*22 on C_{12} was relatively minor, a more marked effect may be expected after administration of the RPV long-acting depot and this warrants further investigation.
- RPV is a drug of wide therapeutic index so the effect of backbone therapy might be negligible in terms of adverse events. However, RPV concentration monitoring is required to avoid suboptimal exposure and subsequent development of resistance.
- Further investigation of RPV substrate specificity to SLCO2B1 is warranted.