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Influence of single nucleotide polymorphisms on deferasirox C_{trough} levels and effectiveness.

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1. BACKGROUND

Deferasirox (DFX) is the only once-daily oral chelator for first-line therapy of blood transfusion-related chronic iron overload. DFX pharmacokinetic has been related with response to therapy. This drug is metabolized in liver by UDP-glucuronyltransferase (*UGT*) *1A1* and *1A3*, by cytochrome-*P450* (*CYP*) *1A1*, *1A2* and *2D6* enzymes, and it is eliminated via biliary-enteric circulation through multidrug resistance protein 2 (*MRP2*).

2. OBJECTIVES

Our aim was to evaluate DFX plasma concentrations according to single nucleotide polymorphisms (SNPs) in genes involved in this drug metabolism and elimination, in a cohort of non paediatric β-thalassemic patients. Further aim was to define a plasma concentration cut-off value predicting an adequate response to therapy.

FIGURE 1

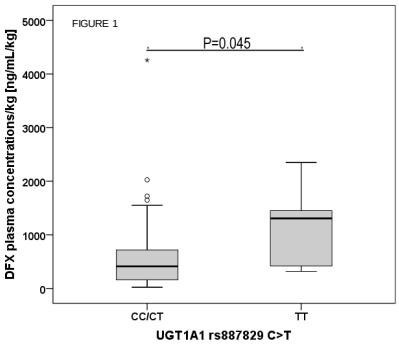
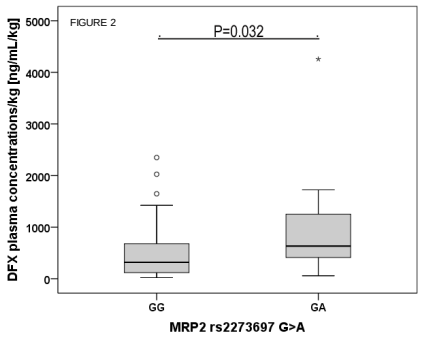


FIGURE 2



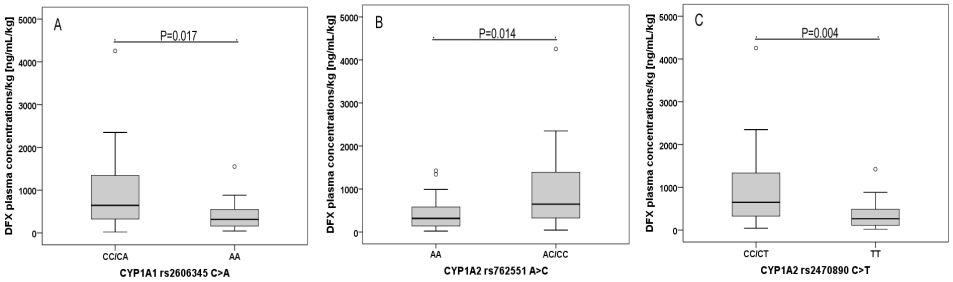
3. MATERIALS & METHODS

DFX concentrations were determined from plasma samples obtained at the end of dosing interval (Ctrough) using an HPLC-UV method (1). Allelic discrimination for SNPs in UGT1A1, UGT1A3, CYP1A1, CYP1A2, CYP2D6, MRP2 and BCRP1 genes was performed by real-time PCR.

4. RESULTS

DFX C_{trough} levels were significantly influenced by *UGT1A1 C>T* (rs887829) [p=0.045] (Fig.1), *MRP2 G>A* (rs2273697) [p=0.032] (Fig.2) and *CYP1A1 C>A* (s2606345) [p=0.017], *1A2 A>C* (rs762551) [p=0.014], *1A2 C>T* (rs2470890) [p=0.004] (Fig.3) SNPs. According to Chirnomas and Galanello efficacy definitions (2,3), a DFX plasma cut-off value of 20,000 ng/mL was identified (ROC curve, p=0.008). A logistic regression analysis was performed to determine factors able to predict this value: both *CYP1A1 C>A* rs2606345 AA (p=0.017) and *CYP1A2 C>T* rs2470890 TT (p=0.037) genotypes may forecast drug concentrations below 20,000 ng/mL, suggesting a negative predictive role of therapy efficacy.

FIGURE 3



5. CONCLUSIONS

Our data, the first obtained in non paediatric patients, suggest the feasibility of a pharmacogenetic-based DFX dose personalization.

	UNIVARIATE			MULTIVARIATE	
	P-VALUE	OR (*odd ratio*)	P-VALUE CORRECTED*	P-VALUE	OR (*odd ratio*)
Age >34.27 Years	**0.114**	0.37 (0.11-1.27)	0.228	0.243	0.42 (0.10-1.82)
Gender	0.365	0.57 (0.17-1.92)	0.465		
BMI at baseline > 22.25 Kg m-2	0.811	1.16 (0.35-3.89)	0.811		
UGT1A1 TT, rs887829	0.213	3 (0.53-16.89)	0.331		
UGT1A1 GG, rs3806596	0.627	1.41 (0.35-5.62)	0.732		
UGT1A3 CT/TT, rs1983023	**0.093**	0.29 (0.07-1.22)	0.326	0.968	1.04 (0.16-6.59)
CYP1A1 AA, rs2606345	**0.007**	0.11 (0.02-0.54)	**0.098**	**0.017**	0.13 (0.02-0.70)
CYP1A1 TT/TC, rs4646903	**0.093**	3.4 (0.82-14.15)	0.260	0.640	1.52 (0.26-8.77)
CYP1A2 AC/CC, rs762551	**0.04**	3.95 (1.07-14.65)	**0.187**	0.966	1.07 (0.04-25.8)
CYP1A2 TT, rs2470890	**0.014**	0.13 (0.03-0.66)	**0.098**	**0.037**	0.17 (0.03-0.90)
CYP 2D6 GG, rs1135840	**0.114**	2.68 (0.79-9.10)	0.266	0.768	1.26 (0.27-5.86)
MRP2 GG/GA, rs2273697	0.780	1.19 (0.35-4.04)	0.840		
BCRP1 GG/GA, rs2231142	**0.193**	0.24 (0.03-2.07)	0.338	0.201	0.21 (0.02-2.27)
BCRP1 CC, rs13120400	0.348	2.19 (0.43-11.21)	0.487		

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