Impact of pharmacogenetic markers of vitamin D pathway on deferasirox pharmacokinetics in children.

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***Aims*:** β-thalassemia major patients had extremely low vitamin D levels, due to reduced intestinal absorption, subicteric tint and/or iron induced higher pigmentation, interfering with vitamin skin synthesis and liver function. Moreover it has been revealed a negative correlation between 25(OH)D3 and serum ferritin, higher in these subjects. We reports our preliminary experience on the potential use of vitamin D pharmacogenetic to understand DFX interindividual variability in a children cohort.

***Material and methods*:** β-thalassemic children received a the recommended DFX dose of 20 mg/Kg/day. Drug plasma concentrations at the end of dosing interval (C_{trough}) and after 0, 2, 4, 6 and 24 hours drug administration were measured by an HPLC-UV method[1]. Analyzed single nucleotide polymorphisms (SNPs) were *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)* and *GC 1296 T>G (rs7041).* Kruskal-Wallis and Mann-Whitney tests have been used to compare pharmacokinetic parameters and SNPs, considering the level of statistical significance. Any predictive power of the considered variables was finally evaluated through univariate and multivariate linear regression analyses.

Results: Data required to calculate AUC parameters were available only for 9 of 18 enrolled subjects. DFX dose (mg/Kg/day) (p=0.003; β=0.612), *CYP24A1 8620 AG/GG* (p=0.012; β=-0.420) and *ApaI AA* (p=0.025; β=-0.392) were retained in linear regression model as C_{trough} predictor factors. AUC resulted significantly influenced by *CYP24A1 3999 TC/CC* genotype (p=0.040) and in regression analyses *FokI CC* (p=0.008; β=0.645) and *ApaI AA* (p=0.007; β=-0.626) resulted statistically significant. *CYP24A1 3999 TC/CC* and *FokI CC* genotypes influenced $t_{1/2}$ with a p value of 0.040 and 0.020; *FokI TC/CC* (p=0.003; β=-0.604), with BMI (p=0.027; β=0.380) and AST levels (p=0.010; β=-0.464), was retained in linear regression model. *CYP27B1 2838 C>T* (p=0.040) and *-1260 G>T* (p=0.040)*, ApaI AA* (p=0.027) and *BsmI G>A* (p=0.039) SNPs showed an influence on C_{min}; only AST levels remained as C_{min} predictive factor in multivariate regression analysis (p=0.009; β=-0.803). C_{max} was influenced by *TaqI TC/CC* (p=0.040) and it was retained also in regression analysis (p=0.004; β=-0.666) with *FokI CC* (p=0.010; β=0.544). No factors significantly influenced T_{max}; whereas in linear regression model *GC 1296 TG/GG* (p=0.033; β=-0.707) was retained. *CYP24A1 3999 TC/CC* and *FokI CC* significantly influenced Vd (p=0.040 and p=0.020, respectively); creatinine levels (p=0.005; β=0.655) and *FokI TC/CC* (p=0.011; β=-0.544) had significant p values in linear regression model.

***Conclusions*:** To our knowledge, this is the first study to date that focus on role of vitamin D pharmacogenetics and iron chelating in children; larger studies, incorporating vitamin D serum levels, are warranted. In our opinion, the genetic factors should be taken in consideration in the routine clinical practice for the optimization of drug therapies.

1. De Francia S, Massano D, Piccione Fm *et al*. A new HPLC UV validated method for therapeutic monitoring of deferasirox in thalassaemic patients. *J Chromatogr B Analyt Technol Biomed Life Sci* 893-894 127-133 (2012).