UGT1A1 and PPARA as genetic predictors of liver abnormalities in HIV infected patients on atazanavir treatment

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Abnormalities in liver enzymes are described in HIV patients treated with protease inhibitor-containing antiretroviral drug combinations, independently of the coinfection with hepatitis viruses (Akhtar et al., 2008). Patients treated with ritonavir boosted atazanavir (ATV/r) frequently show increased indirect bilirubin plasma concentrations, due to ATV-inhibition of UDP-glucuronosyl transferase (UGT) 1A1 gene (Cleijsen et al., 2007). ATV/r is metabolised mainly by cytochrome P450 3A (CYP3A) enzymes. Variability of CYP3A activity may have a genetic basis and variant alleles into CYP3A or peroxisome proliferator-activated receptor alpha (PPARA) genes may be responsible for altered ATV/r metabolism (Kathrin et al., 2012). Thus, high drugs blood levels could affect ATV/r related adverse events. Here, we investigated the role of functional SNPs involved in ATV/r metabolism on liver enzymes.
129 HIV-patients treated with atazanavir/ritonavir (ATV/r 300/100) and presenting abnormal serum bilirubin values were consecutively included in the study. Genomic DNA was isolated from peripheral blood cells. Genotypes were determined by Real-Time PCR using LightSNiP (TIB-MolBiol). Genetic associations were assessed using a multivariate model adjusted for age, sex, BMI, HCV coinfection and alcohol intake. Polymorphisms associated with liver enzyme levels (gamma-glutamyltransferase and alanine aminotransferase) with a p-value inferior to 0.1, entered in a multivariate analysis to evaluate their overall effect. The study enrolled 104 males and 25 females. The mean age was 45 years (± 10.7 SD). Variant alleles UGT1A1*28 were present in heterozygosis in 52 (40.3%) patients and in homozygosis in 28 (21.7%), respectively. CYP3A4 *22 were present in 9 (7%) and 1 (0.8%) of cases in heterozygosis and homozygosis, respectively. The heterozygosity and homozygosity status of CYP3A5*3 was observed in 18 (14%) and 108 (83.7%) patients. PPAR rs4253728 SNP is present in 50 (38.8%) patients in heterozygosis and in 8 (6.2%) in homozygosis.
By multivariate analysis, total bilirubin was associated with UGT1A1*28 (p=0.0008), the mean values were 2.1, 2.4, 3.9 mg/dl in *1/*1, *1/*28, *28/*28 respectively. Individuals carrying the PPARA rs4253728 variant alleles were associated to higher gamma-glutamyltransferase levels (43 vs 27 U/L, p=0.013). UGT1A1*28 was confirmed to be associated with increased bilirubinaemia. Carriers of PPARA rs4253728 variant alleles, a genetic regulator of CYP3A4 activity, showed significantly higher gamma-glutamyltransferase levels. Further investigations are needed to confirm these data and to assess the clinical significance of this finding.