Genetic variants of ABCC2 and ABCC10 Are Associated with Tenofovir-induced Proximal Tubular Dysfunction
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BACKGROUND

Tenofovir is an effective and widely used treatment for both HIV and hepatitis B virus infection. However, its use in some patients leads to proximal renal tubular dysfunction (PRTD). The mechanism of TDF induced tubular dysfunction is not fully elucidated. The characteristics and severity of TDF related PRTD vary widely among patients, suggesting an important role of host genetics on susceptibility to kidney damage.

OBJECTIVE

To determine the association between polymorphisms in genes encoding drug transporters and PRTD in Thai patients treated with tenofovir.

METHODOLOGY

PRTD was defined as the presence of at least 2 of the following:
- phosphaturia (total excretion of phosphate >1200 mg per day)
- renal tubular reabsorption of phosphate (TmP/GFR) <2.6 mg/dL
- uricosuria (FE of uric acid <15%)
- non-diabetic glucosuria (urine glucose>100 mg per day or positive urine glucose with plasma glucose <120 mg/dL)

Nine single nucleotide polymorphism (SNPs) in the ABCC2, ABCC4, ABCC10, and SLC2A6 genes were performed in 358 Thais.

Genotypes were determined by allelic discrimination using the Taqman 5′-nuclease assay. Associations between genotypes, subject demographic, disease and treatment characteristics and PRTD were analysed by univariate and backwards stepwise multivariate logistic regression. The baseline model included all covariates with p <0.1 in univariate analysis.

RESULTS

Characteristic of participants (PRTD and non-PRTD) are presented in table 1. Of 358 subjects, 67 (18.7%) patients met the PRTD criteria. In univariate analysis, male gender (OR 1.87, 95%CI 1.08-3.26, p=0.03), age >50 years (OR 1.6, 95%CI 0.78-3.27, p=0.20), BW >55 kg (OR 2.04, 95%CI 1.43-3.4, p=0.02), duration of ART exposure >5 years (OR 1.4, 95%CI 1.2-1.68, p=0.21), indinavir exposure (OR 2.41, 95%CI 1.5-2.32, p=0.03), other PI (OR 1.79, 95%CI 0.88-3.12, p=0.06), CD4 cell count >350 cells/μL (OR 0.70, 95%CI 0.38-1.56, p=0.47), nadir CD4 cell count <100 cells/μL (OR 1.57, 95%CI 0.9-2.74, p=0.11), HIV RNA >50 copies/mL (OR 0.16, 95%CI 0.02-2.1, p=0.08), and hypertension (OR 2.08, 95%CI 1.24-3.4, p=0.04) were significantly associated with PRTD. Using multivariate analysis, the association was still significant for male gender (OR 1.87, 95%CI 1.08-3.26, p=0.03), age >50 years (OR 1.6, 95%CI 0.78-3.27, p=0.20), BW >55 kg (OR 2.04, 95%CI 1.43-3.4, p=0.02), duration of ART exposure >5 years (OR 1.4, 95%CI 1.2-1.68, p=0.21), indinavir exposure (OR 2.41, 95%CI 1.5-2.32, p=0.03), other PI (OR 1.79, 95%CI 0.88-3.12, p=0.06), CD4 cell count >350 cells/μL (OR 0.70, 95%CI 0.38-1.56, p=0.47), nadir CD4 cell count <100 cells/μL (OR 1.57, 95%CI 0.9-2.74, p=0.11), HIV RNA >50 copies/mL (OR 0.16, 95%CI 0.02-2.1, p=0.08), and hypertension (OR 2.08, 95%CI 1.24-3.4, p=0.04) were significantly associated with PRTD.

CONCLUSIONS

We found a significant association between SNPs in the ABCC2 and ABCC10 genes and proximal renal tubular dysfunction in an Asian population. Pharmacogenetic factors may play a role in mediating renal injury in patients treated with TDF. Close monitoring of renal function is warranted in patients with these SNPs who are treated with TDF.

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Table 1: Baseline characteristics of the study population between PRTD and non-PRTD groups.
Continuous covariates are presented as median (IQR), and categorical covariates as n(%).

Table 2: Predictors of PRTD in HIV-1 infected Thai patients in a step-wise multivariate logistic regression model.

Figure 1: Distribution of each SNP between PRTD and non PRTD groups.