Polymorphisms in SLC34A1 and ABCC2 genes are related with altered renal tubular function in HIV patients receiving Tenofovir

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Background

Tenofovir disoproxil fumarate (TDF) is currently one of the most widely prescribed nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) for the treatment of HIV infection, use of which is associated with renal tubular dysfunction and loss of bone density.1,2

Urinary phosphate excretion is an early sign of tubular dysfunction and the chronic consequences of significant loss of phosphate, such as an increased risk of premature osteoporosis and osteomalacia, is of concern.3

There is no consensus about the best parameters to define tubular dysfunction and therefore, the prevalence and characteristics of tubular dysfunction varies between different studies.4

The variability observed in the characteristics and severity of renal dysfunction among TDF exposed patients might be explained in part by host characteristics, including pharmacogenetic factors.5

To date, polymorphisms in the transport proteins MPR2 and MPR4, located in the apical membrane of the tubule, have frequently been associated with kidney tubular dysfunction in patients receiving TDF.6-8

Study Objective

We aimed to examine the association between host single nucleotide polymorphisms (SNPs) and abnormal tubular reabsorption of phosphate (TRP).

Methods

A retrospective case-control study was conducted in HIV-positive patients on TDF-containing therapy.9

Accordingly with TRP value, patients were defined as “cases” when TRP >0.2 and “controls” when TRP >0.8.

Biochemical parameters, HIV related parameters, concomitant medications and comorbidities were obtained from the medical data records.10

Twenty SNPs (minor allele frequencies >5% in Caucasians) were studied in 6 genes coding for transport proteins potentially involved in phosphate reabsorption.11

Tubular reabsorption of phosphate from the urine filtrate: SLC22A11 (SNPs) We dysfunctions apical tubular TDF

The therefore, HIV nucleoside/nucleotide inhibitors.

All SNPs were analyzed by allelic discrimination using TaqMan probes. Haplotypes for individual samples were constructed using PHASE software, version 2.1 (University of Seattle, Washington).

We assessed between-groups differences using t-tests or non-parametric equivalents for quantitative variables and Chi-square test for qualitative variables. Associations between SNPs and abnormal TRP were determined using multivariable logistic regression analyses (SPSS package version 17.0 (SPSS Inc., Chicago, IL).

Results (I)

Patients characteristics

A total of 96 HIV-positive patients were examined: 39 cases and 57 controls.

Baseline characteristics of the patients are detailed in Table 1.

There were no differences between groups according to gender, ethnicity, comorbidities, ARV medication, HIV viral load and CD4 count.

Cases were older and longer exposed to TDF compared to the control group (p=0.01 and p=0.04 respectively).

Table 1. Demographics, comorbidities and HIV related characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal TRP (N=58)</th>
<th>Abnormal TRP (N=39)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>41 (30-44)</td>
<td>46 (39-52)</td>
</tr>
<tr>
<td>Male gender</td>
<td>52 (88)</td>
<td>36 (57)</td>
</tr>
<tr>
<td>Caucasian*</td>
<td>53 (90)</td>
<td>36 (57)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.6 (23.6-23.6)</td>
<td>23.5 (23.5-23.5)</td>
</tr>
<tr>
<td>HCV and/or HIV coinfection*</td>
<td>17 (30)</td>
<td>17 (30)</td>
</tr>
<tr>
<td>Hyperension, Diabetes*</td>
<td>11 (19)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>HIV RNA, log (copies/mL)</td>
<td>1.69</td>
<td>1.69</td>
</tr>
<tr>
<td>CD4+ T-cells (cells/µL)</td>
<td>441 (297-612)</td>
<td>540 (349-782)</td>
</tr>
<tr>
<td>TDF exposure (months)</td>
<td>24 (6-44)</td>
<td>43 (54-64)</td>
</tr>
<tr>
<td>Pi exposure*</td>
<td>30 (53)</td>
<td>16 (41)</td>
</tr>
</tbody>
</table>

*IC: BMI, systolic blood pressure, HCV; hepatitis C virus, HIV; hepatitis B virus, TDF; Tenofovir, Pi, phosphate imibitors.

Genetic polymorphisms associated with abnormal TRP

Figure 1 shows those genes which code for transport proteins that showed differences in the allele/gene frequency among cases and controls (proteins shaded green and blue) as well as all other transport proteins included in the study, that did not show differences between groups (unshaded).

Figure 1. Representation of the transport proteins potentially involved in Tenofovir pharmacokinetics and phosphate tubular reabsorption.

The single SNPs analysis showed a higher percentage of patients with abnormal TRP among the carriers of the allele T in the SLC34A1 gen (rs3812036) (54% vs 30%, p=0.00) and the CC genotype in the ABCC4-669 gen (rs3819449) (46% vs 23%, p=0.053).

Figure 2. Percentage of patients with abnormal TRP according to genotypes.

Results (II)

Variables associated with abnormal TRP

In multivariate analysis, to carry both haplotypes SLC34A1-TG and ABCC2-CGTC time on TDF treatment and presence of comorbidities were independently associated with higher risk of abnormal TRP (OR (95%) 6.1 (1.67-25.36), p=0.007, 1.04 (1.01-1.07), p=0.01 and 3.9 (1.16-13.08), p=0.027 respectively).

Figure 3. Multivariable logistic regression analysis. Adjusted for age, gender, ethnicity and BMI.

Conclusions

Genetic polymorphisms in genes involved in handling of phosphate and protein transporters, along with classical risk factors for renal dysfunction, influence the phosphate wasting in patients exposed to Tenofovir.

Monitoring phosphate wasting and screening for genetic polymorphisms could be a useful tool for early identification of patients at higher risk of developing KTD.

References