Sex and Haplotypic Associations with Adverse Effects of Calcineurin Inhibitors Post-Renal Transplant

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ABSTRACT

BACKGROUND: P-glycoprotein (P-gp), an ABC transport protein contributes to the interpatient pharmacokinetic and pharmacodynamic variability of calcineurin inhibitors (CNI), tacrolimus (TAC) and cyclosporine (CYA). ABCB1 encodes P-gp and the single nucleotide polymorphisms (SNP) 1236C>T, 2677T>A, 3435C>T may alter protein expression or function. Our objective was to examine the association of ABCB1 haplotypes, sex and race with chronic CNI adverse effects (AE) in renal transplant recipients (RTX).

METHODS: A meta-analysis of 3 prospective observational studies was completed in 149 stable RTX (49R 51 17 mg/min/1.73m2 ) using identical inclusion and exclusion criteria in 62 African Americans (AA) and 91 Caucasians (C) treated with TCA (tacrolimus 50–150 mg/d) and mycophenolate mofetil or TAC (tacrolimus 5–8 mg/d) and mycophenolate sodium. Each RTX had AE assessed using standardized objective scales by study physicians. A Cumulative AE ratio was determined using 14 AE. Separate gastrointestinal (GI), central nervous system (CNS), and aesthetic adverse effects were also assessed. DNA from peripheral blood mononuclear cells was collected to characterize ABCB1 SNPs completed on 11/15/12. Haplotypic computation and association with AE was completed by THESIAS program on 12/3/12.

RESULTS: All genotype groups in Hardy-Weinberg equilibrium. AA had a greater frequency of the C-G C haplotype (SNPs: 1236-2677-3435) compared to C (71.6% vs. 44.7%, p=0.0001). A gender difference was noted for Cumulative (p=0.004), GI (p=0.046), aesthetic (p=0.0002) and CNS (p=0.051) AE ratios with greater AE rates in females. The Aesthetic AE ratio was associated with haplotype T-T-T-C (p=0.004). Haplotype C-T-T was associated with increased GI AE ratio (p=0.02) though the effect was not significant when sex was included as a covariate (p=0.13). Race had no associations with AE.

CONCLUSION: RTX receiving CNI based immunosuppression within the therapeutic range exhibited interpatient variability in AE with sex of association and ABCB1 haplotypes.

INTRODUCTION

Pharmacologic Immunosuppression

Figure 1: Pharmacologic Immunosuppression

METHODS

Study Design

• Meta-analysis of three observational pharmacokinetic-pharmacodynamic studies

Objectives

• Determine influence of sex and ABCB1 haplotypes on cumulative incidence of adverse effects (AEs) associated with calcineurin inhibitor based maintenance immunosuppression post-renal transplant

Adverse Effects

• Quantified using objective, standardized, nephrologist administered assessment tool

Genomics

• Genomic DNA isolated from 600ml of peripheral blood mononuclear cells (Wizare™ Genomic DNA Purification)

• 10mg of genomic DNA used to characterize SNPs in ABCB1 (1236-2677-3435)

• Taqman™ allelic discrimination assay

• CFX96 Real-Time PCR detection system

• Genotype results for 141 patients utilized for haplotype analysis

• Haplotype frequencies computed by THESIAS®

Stats

• General linear modeling employed for Cumulative, GI, and Aesthetic AE Ratios

• Logistic regression model employed for individual AEs and CNS AE Ratio

• Type of CNI, sex, race, and race X sex interaction as base model grouping variables

• Association of haplotypes with AEs using maximum likelihood estimates with 95% confidence intervals and Chi-Square test for comparison

• Statistical analysis performed with SAS® version 9.3 and THESIAS® version 3.1

RESULTS

Table 1. Adverse Effect Grouping

<table>
<thead>
<tr>
<th>AE Group</th>
<th>AEs Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative</td>
<td>Acne, tremor, myopathy, hirsutism, skin changes, insomnia, headache, vomiting, diarrhea, dyspepsia, PPI, H2RA, gingival hyperplasia, post-transplant diabetes</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>Vomiting, diarrhea, dyspepsia, PPI, H2RA</td>
</tr>
<tr>
<td>Central Nervous System (CNS)</td>
<td>Headache, tremor, insomnia</td>
</tr>
<tr>
<td>Aesthetic</td>
<td>Acne, gingival hyperplasia, alopecia, hirsutism</td>
</tr>
</tbody>
</table>

Table 2. Demographic, Laboratory, and Clinical Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male (n=106)</th>
<th>Female (n=43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC-Myc (mg)</td>
<td>14.5±14.8</td>
<td>10.5±15.8</td>
<td>0.0004</td>
</tr>
<tr>
<td>TAC-CYC (mg)</td>
<td>39±14.5</td>
<td>39±15.8</td>
<td>0.008</td>
</tr>
<tr>
<td>GI Tract</td>
<td>10.3±14.5</td>
<td>10.3±15.8</td>
<td>0.487</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>43/106</td>
<td>43/43</td>
<td>1.000</td>
</tr>
<tr>
<td>Sex (male, n (%)</td>
<td>106/149</td>
<td>43/149</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table 3. Results

<table>
<thead>
<tr>
<th>AE</th>
<th>Male</th>
<th>Female</th>
<th>GI AE Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative</td>
<td>0.0001</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>0.0002</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS CONTINUED

Main effects p value with sex as covariate:

• TTC haplotype: p=0.30 for Cumulative; p=0.02 for Aesthetic

• CTT haplotype: p=0.13 for GI

CONCLUSIONS

• Female sex significantly increases the cumulative incidence of adverse effects associated with calcineurin inhibitor based immunosuppression

• A racial difference in ABCB1 haplotype distribution exists

• The common ABCB1 haplotype TTT, often identified as having decreased P-gp function, is not significantly associated with increased adverse effects

• CTT and TTC haplotypes are associated with increased GI and Aesthetic AEs, respectively

• This association is largely driven by sex as a covariate

FUTURE DIRECTIONS

• Validation of AE assessment tool

• Additional genotyping

• ABC2, CYF34, CYF53, OATP1, UGTs

• Pharmacokinetic analysis