

## ABCB1 haplotypes enhances the effect of CYP3A5 polymorphism on tacrolimus pharmacokinetics after kidney transplantation.

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**Introduction:** Tacrolimus (TAC) is widely used to prevent acute rejection following solid-organ transplantation and it's known to be substrate of cytochrome P450 (CYP) 3A5 and P-glycoprotein (ABCB1). Studies have shown that genetic polymorphisms (SNPs) of CYP3A5 proteins are highly associated with variations in TAC pharmacokinetics with controversial results regarding the ABCB1 polymorphisms. Some works have showed a strong linkage disequilibrium among the highly frequent ABCB1 polymorphisms 1236C>T (rs1128503), 2677G>A/T (rs2032582) and 3435C>T (rs1045642) but no study has assessed the linkage between CYP3A5 and the ABCB1 polymorphisms so far. **Objective:** Study the linkage disequilibrium among ABCB1 and CYP3A5 polymorphisms and the influence of ABCB1 haplotypes and CYP3A5 polymorphisms on TAC Co/Dose ratio. **Methods:** Patients receiving TAC for at least 12 months (n=108) were genotyped (real-time PCR) for CYP3A5\*3 (rs776746) and for ABCB1 1236C>T (rs1128503), 2677G>T/A (rs2032582) and 3435C>T (rs1045642) polymorphisms. ABCB1 gene haplotypes were statistically inferred using PHASE software (version 2.1) and EH program was used to perform a linkage analysis between each pairwise combination of variants. TAC dose-normalized predose concentrations (Co/dose; ng/mL per mg/day per kg body weight) was retrieved from medical records up to 01 year after transplantation. Data are represented as median and interquartile range and p value <0.05 was considered statistically significant. **Results:** No deviation from Hardy-Weinberg equilibrium was observed in our study population. ABCB1 haplotype frequencies were 49% 2677G-3435C-1236C and 30% 2677T-3435T-1236T. Linkage studies revealed that 1236C>T, 2677G>A/T and 3435C>T are genetically associated with each other and also there is a linkage disequilibrium between 1236C>T and CYP3A5 ( $D'=0,46$ ). Individuals homozygous for the variant CYP3A5 allele or for the variant ABCB1 haplotype (TTT) showed higher Co/dose ratio (130.2 (175.4-97.55) vs. 71.3 (109.0-45.6),  $p<0.001$  and 151.8 (205.6-112.1) vs. 109.6 (120.6-53.4.5),  $p=0.07$ , respectively). When compared only in the variant group for the CYP3A5, ABCB1 variant haplotype (TTT) also showed higher Co/dose ratio compared to the wild type haplotype (167.8 (218.0-130.4) vs. 114.9 (140.0-91.1),  $p=0.001$ ). **Conclusion:** This work shows linkage disequilibrium among the ABCB1 genotypes and between ABCB1 1236C>T and CYP3A5\*3 and our data suggest that mutations on ABCB1 and CYP3A5 gene have a synergistic and independent effect on TAC bioavailability.

**Keywords:** pharmacogenetics, kidney transplantation, cytochrome P450, tacrolimus pharmacokinetics, ABCB1.

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