Genetic polymorphisms at the Pregnane X Receptor (PXR) and CYP3A5 loci influence the pharmacokinetics of tacrolimus in renal transplant patients

(125 characters including spaces; limitation is 150 characters including spaces)

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BACKGROUND: Tacrolimus is an immunosuppressive drug used to treat organ rejection following allogenic transplant. Proper dosing of tacrolimus can be a complicated process due to wide interpatient variability of tacrolimus pharmacokinetics (PK). An understanding of genetic factors behind this wide variability will improve the outcome for patients receiving tacrolimus therapy.

METHODS: Blood samples were obtained from 35 renal transplant patients after oral administration of tacrolimus (15 time points each, NCT01889758). Tacrolimus concentration was quantitated by LC-MS/MS assay, and PK parameters were determined using WinNonlin software. Genomic DNA isolated from whole blood was used for qPCR-based genotyping of SNPs in CYP3A4, CYP3A5, and PXR. We investigated the relationship between patient genotype and dose-normalized PK parameters at steady state using JMP software.

RESULTS: Dose-normalized trough concentration (C_{trough}/dose) showed the highest correlation with individual SNPs. The C_{trough}/dose was significantly lower in CYP3A5 expressors compared to CYP3A5 non-expressors ($P = 0.0008$). In CYP3A5 non-expressors, the "T" allele of the rs2472677 SNP in PXR was correlated with C_{trough}/dose. The T/T genotype showed considerably higher C_{trough}/dose compared to the C/T genotypes, followed by C/C genotype ($P = 0.0083$).

CONCLUSION: This study shows the significant correlation of the rs2472677 SNP in PXR to the C_{trough}/dose of tacrolimus in CYP3A5 non-expressors. This finding indicates that the CYP3A4 abundance, regulated by PXR, could be an important determinant of the PK variability of tacrolimus when considered in combination with CYP3A5 expression. Genotyping for PXR and CYP3A5 will improve tacrolimus dosing in renal transplant patients.