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Impact of CYP3A5 Polymorphism on Tacrolimus to Predict the Optimal Initial Dose Requirements in South Indian Renal Transplant Recipients

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Abstract : Background: Tacrolimus is a potent immunosuppressant clinically used for the long term treatment of antirejection of transplanted organs in liver and kidney transplant recipients though dose optimization is poorly managed. However, So far no study has been carried out on the South Indian kidney transplant patients. The objective of this study is to evaluate the potential influence of a functional polymorphism in CYP3A5*3 gene on tacrolimus physiological availability/dose ratio in South Indian renal transplant patients. Materials and Methods: Twenty five renal transplant recipients receiving tacrolimus were enrolled in this study. Their body weight, drug dosage, and therapeutic concentration of Tacrolimus were observed. All patients were on standard immunosuppressive regime of Tacrolimus-Mycophenolate mofetil along with steroids on a starting dose of Tac 0.1 mg/kg/day. CYP3A5 genotyping was performed by PCR followed with RFLP. Conformation of RFLP analysis and variation in the nucleotide sequence of CYP3A5*3 gene were determined by direct sequencing using a validated automated generic analyzer. Results: A significant association was found between tacrolimus per dose/kg/d and CYP3A5 gene (A6986G) polymorphism in the study population. The CYP3A5 *1/*1, *1/*3 and *3/*3 genotypes were detected in 5 (20 %), 5 (20 %) and 15 (60 %) of the 25 graft recipients, respectively. CYP3A5*3 genotypes were found to be a good predictor of tacrolimus Concentration/Dose ratio in kidney transplant recipients. Significantly higher L/D was observed among non-expressors 9.483 ng/mL(4.5- 14.1) as compared with the expressors 5.154 ng/mL (4.42-6.5) of CYP3A5. Acute rejection episodes were significantly higher for CYP3A5*1 homozygotes compared to patients with CYP3A5*1/*3 and CYP3A5*3/*3 genotypes (40 % versus 20 % and 13 %, respectively). The dose normalized TAC concentration (ng/ml/mg/kg) was significantly lower in patients having CYP3A5*1/*3 polymorphism. Conclusion: This is the first study to extensively determine the effect of CYP3A5*3 genetic polymorphism on tacrolimus pharmacokinetics in South Indian renal transplant recipients and also shows that majority of our patients carry mutant allele A6986G in CYP3A5*3 gene. Identification of CYP3A5 polymorphism prior to transplantation could contribute to evaluate the appropriate initial dosage of tacrolimus for each patient.

Keywords : kidney transplant patients, CYP3A5 genotype, tacrolimus, RFLP
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