Identification of influence of CYP3A5 genetic polymorphism in tacrolimus pharmacokinetics assessed from routine TDM data using mixed effect modeling

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Purpose: To identify and quantify the contribution of the genetic polymorphism of CYP3A5 and environmental factors on tacrolimus dispoition by population pharmacokinetic(PK) approach

Method: The genetic variants of CYP3A5 gene was determined by PCR and DdeI restriction analysis in 114 Korean patients who had received renal transplantation.

We analyzed population PK of tacrolimus with genotype of CYP3A5 as a covariate using NONMEM in the patients who had monitored the tacrolimus level by routine TDM. Other covariates such as age, sex, body weight, comedication, laboratory results were also included and the significance was evaluated.

Result: The frequency of the homozygous wild-type (*1/*1) of CYP3A5 was 10% (12/114), the heterozygous (*1/*3) was 30.7%(35/114). and the homozygous mutant-type(*3/*3) was 58.8%(67/114) in the TPL patients population. Tacrolimus was used to 3(15%: *1/*1 wild-type), 4(20%: *1/*3 heteromutant) and 13(65%: *3/*3 homomutant) patients. The population PK for tacrolimus disposition was best fitted to one compartment model with first order absorption and elimination. The clearance(CL) and volume of distribution(Vd) of the final model were as flows: CL= 14.7*(1 (if *1/*1 wild-type, *1/*3 heteromutant) or 0.57(if *3/*3 homomutant)) L/hr ; Vd = 0.68 L/kg, the coefficient of variation(CV) of CL was estimated to 29% , that of Vd was 148%. Other covariates did not show significant influence on CL of tacrolimus.

Conclusion: The allele frequencies of CYP3A5 *1, *3 in Korean were similar to those of other Asian ethnic group. The population PK approach result suggest that tacrolimus disposition is influenced by CYP3A5 *3/*3 allele. The homozygous mutant patients had decreased clearance which was 57% of clearance in patient with at lease one *1 allele.