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신이식환자에서 타크로리무스와 그 대사체의 약력학 및 약동학과 CYP3A4, CYP3A5, MDR-1 유전자 다형성과의 관계

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Pharmacokinetics and Pharmacodynamics of Tacrolimus and its Metabolites in Kidney Transplanted Patients; The Relationship with the CYP3A4, CYP3A5, MDR-1 Genotypes

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Background: The objective of this study was to determine the relationship between the genetic polymorphisms in CYP3A4, CYP3A5 and MDR1 and the pharmacokinetics (PK) and pharmacodynamics (PD) of tacrolimus and its metabolites.

Methods/Materials: The twelve incident kidney transplant recipients receiving tacrolimus were genotyped for CYP3A4*18, CYP3A5*3 and MDR1c3435T, 1236T, 2677T using real-time polymerase chain reaction assays. Dose-adjusted trough levels, PK and PD were determined and correlated with the corresponding genotype.

Results: Does-adjusted concentration (C0) of tacrolimus and its metabolites and AUC0-12 (area under the curve), Cmax (the maximum concentration in blood) were significantly higher in CYP3A5*3/*3 patients (n=7) than in *1/*3 plus *1/*1 patients (n=5) ($p<0.0001$, <0.0001, <0.0001, 0.03, respectively). Co of tacrolimus and metabolites and AUC0-12 of the patients with CYP3A4*1/*18 were significantly lower than those without CYP3A4*1/*1 (p=0.038, 0.001, <0.001, respectively). The patients having MDR1 1236 genotypes with T allele (n=11) showed significantly lower level in Co of metabolites and AUC0-12 compared with those without T allele (p=0.018, 0.029, respectively). And also, Co of tacrolimus in patients having MDR1 2677 with T allele (n=6) was significantly lower compared with those without T allele (p=0.033). In multivariate regression analysis, however, only CYP3A5*3/*3 showed significant relationship with Co of tacrolimus, metabolites and AUC0-12 (p=0.003, 0.033, 0.011, respectively). Among T cell subsets, HLA/DR+ monocyte was mostly correlated with Co and PK of tacrolimus.

Conclusion: This study shows that the CYP3A5*3 gene polymorphisms are significantly associated with the individual difference in PK and PD as well as in Co of tacrolimus and its metabolites.

Key Words: 신이식, 타크로리쿠스, 유전자 다형성
Kidney transplantation, Tacrolimus, Genetic polymorphism