Title: Effect of the *POR*28* and *CYP3A5*1* genotype on the blood concentration of tacrolimus in renal transplant recipients

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Background: The P450 oxidoreductase (POR) is an important factor affecting the activity of cytochrome P450 (CYP), drug metabolizing enzymes. It has been reported that carrying *POR*28*, a single nucleotide polymorphisms (SNPs) on *POR*, increased in the activity of CYP3A. Since tacrolimus (TAC) is metabolized by intestinal and hepatic CYP3A4/5, *POR*28* might affect TAC clearance (CL/F) in addition to *CYP3A5* genotype. We investigated the different effects of *POR*28* on the blood TAC between in patients with and without *CYP3A5*1* in renal transplantation.

Methods: Fifty nine renal transplant recipients (male/female: 43/16, 45±11 yrs.) receiving once a daily formulation of oral TAC (46–110 μg/kg/days) were enrolled for the study. Blood TAC concentration was monitored for 1-4 weeks after transplantation. The CL/F for TAC were estimated as follows: CL/F = dosing rate (μg/kg/hr) / steady state concentration (μg/L), and were compared between the patients with and without *CYP3A5*1* and *POR*28*. The study was approved by the local ethics committee of University of Tsukuba Hospital.

Results: Blood TAC concentration were maintained 5–10 ng/mL for both genotypes, *CYP3A5*1* carriers (n=21) and non-carriers (n=38) (7.1±1.8 vs. 9.0±2.0 ng/mL) and *POR*28* carriers (n=43) and non-carriers (n=16) (8.4±2.3 vs. 8.2±1.8 ng/mL), at week 3–4 after starting TAC administration. The mean CL/F of TAC for *CYP3A5*1* carriers were significantly higher than those for the non-carriers (1.07±0.40 vs. 0.49±0.19 L/hr/kg, $P<0.0001$). No difference in CL/F of TAC was observed between *POR*28* carriers and non-carriers (0.73±0.44 vs. 0.62±0.24 L/hr/kg). In the patients with *CYP3A5*1* the mean CL/F of TAC for *POR*28* carriers (n=15) were significantly higher than those for the non-carriers (n=6) (1.16±0.44 vs. 0.84±0.15 L/hr/kg, $P<0.05$). No difference was observed in the CL/F of TAC between the *POR*28* carriers (n=28) and non-carriers (n=10) in *CYP3A5*1* non-carrier patients (0.49±0.19 vs. 0.50±0.19 L/hr/kg).

Conclusions: It was confirmed that *POR*28* allele is associated with a higher TAC CL/F in kidney transplant recipients carrying *CYP3A5*1*, whose CYP3A5 enzyme responsible for TAC metabolism.

Key Words: tacrolimus clearance, CYP3A5, POR, polymorphism