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

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Background・Objectives

The P450 oxidoreductase (POR) is an important enzyme 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 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 renal transplant recipients with and without *CYP3A5*1* , being associated with expression of CYP3A5.

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/day) were enrolled for the study(Table 1). Blood TAC concentration was monitored for 1–4 weeks after transplantation. The CL/F for TAC were estimated as follows:

CL/F = TAC dosing rate (μg/kg/hr)
/ steady state TAC concentration (μg/L),

and were compared between the recipients 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 and non-carriers (7.1±1.8 vs. 9.0±2.0 ng/mL), and *POR*28* carriers and non-carriers (8.4±2.3 vs. 8.2±1.8 ng/mL), at week 3–4 after starting TAC administration (Fig. 1A). No difference was observed in kidney function (serum creatinine levels) (Fig. 1B) and liver function (Alanine aminotransferase) between the recipients carrying and non-carrying *CYP3A5*1* allele.

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, $P < 0.0001$) (Fig. 2A). 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) (Fig. 2B).

In the recipients with *CYP3A5*1* carrier, the mean CL/F of TAC for *POR*28* carriers were significantly higher than those for the non-carriers (1.16±0.44 vs. 0.84±0.15 L/hr/kg, $P < 0.05$) (Fig .2C).
In the recipients with *CYP3A5*1* non-carrier, no difference was observed in the CL/F of TAC between the *POR*28* carriers and non-carriers (0.49±0.19 vs. 0.50±0.19 L/hr/kg) (Fig. 2D).

Table 1. Characteristics of kidney transplant recipients.

N (male/female)	59	(43/16)
Age (years)	44	(21–68)
Body weight (kg)	67.2	(41.8–88.8)
Donor type (Living/Deceased)		52/7
Initial dose of TAC(μg/kg/day)	78	(46–110)
*CYP3A5*1* carrier(*n*)	21	
*POR*28* carrier(*n*)	43	

Data presented as median(range).

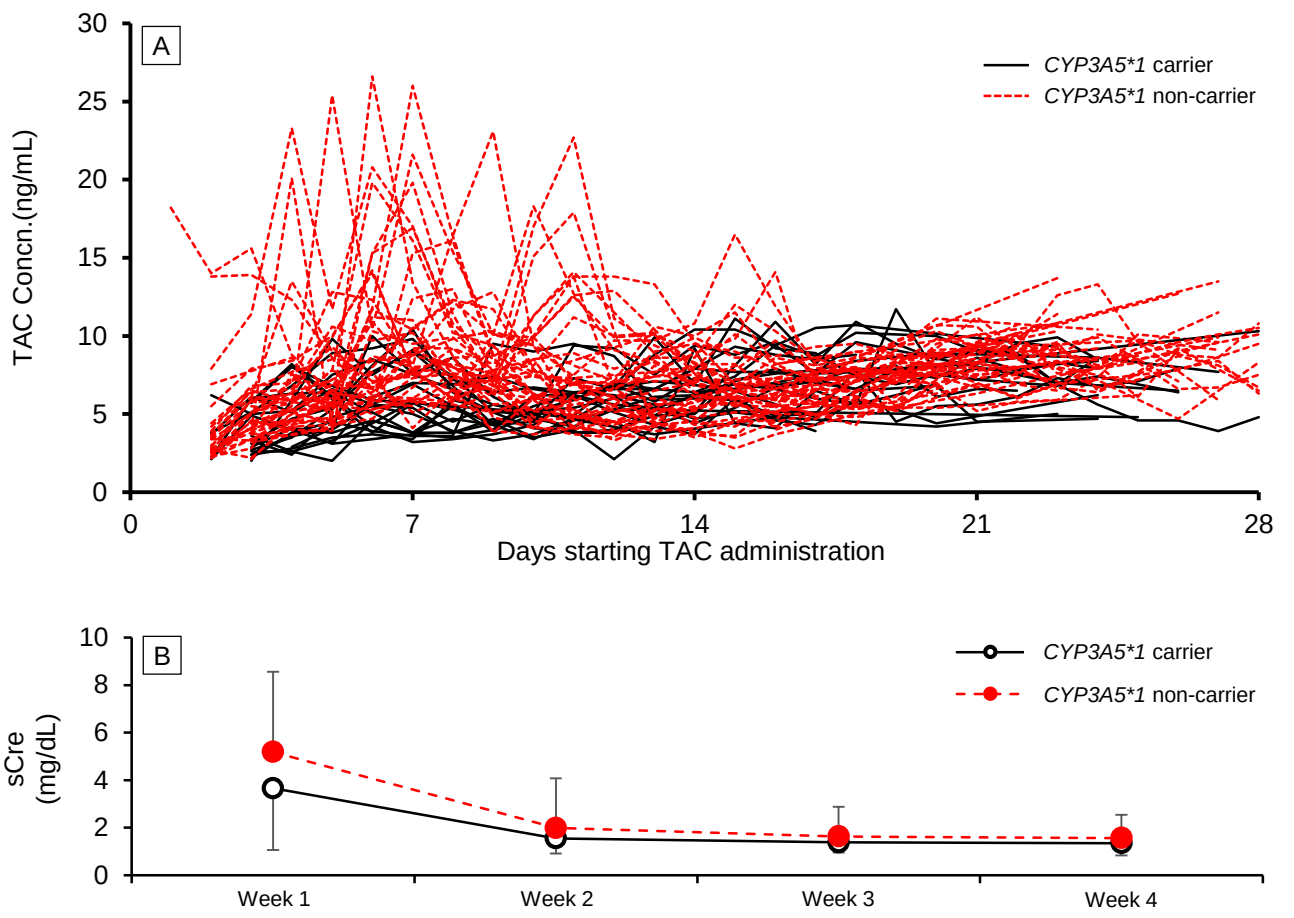

Figure 1. TAC concentration(A), and serum creatinine(B) after kidney transplantation.
Solid line(black) indicates *CYP3A5*1* carrier and dotted line(red) indicates *CYP3A5*1* non-carrier.

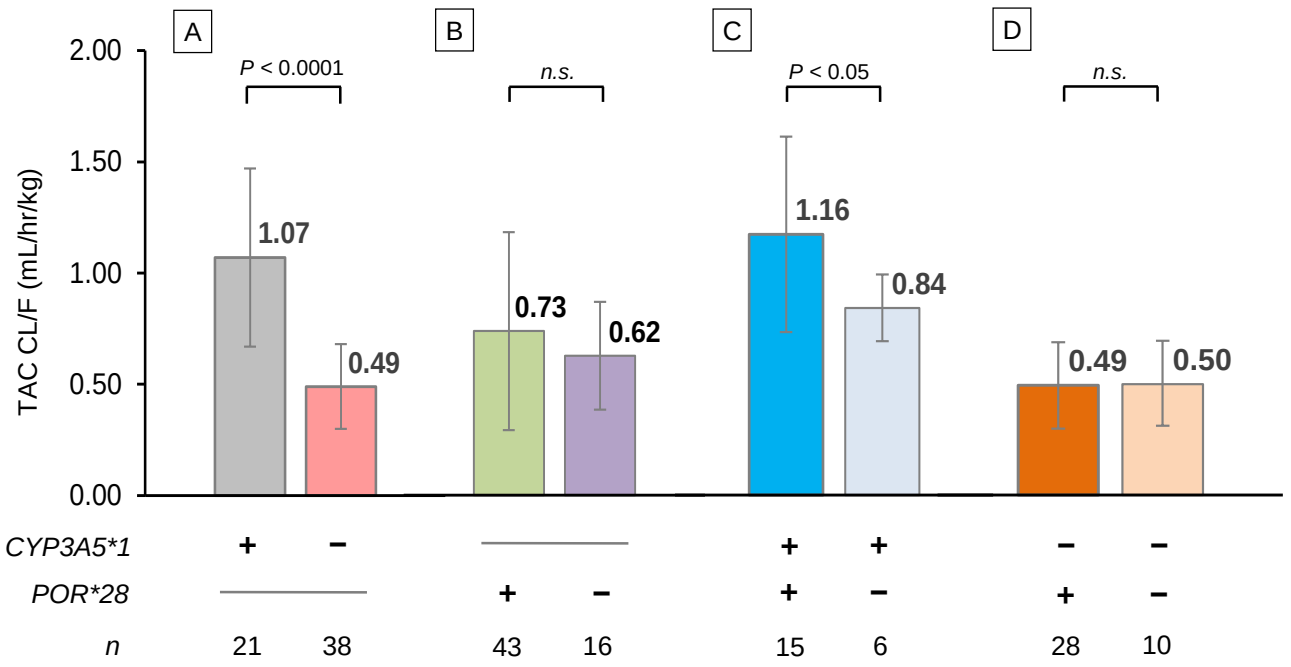

Figure 2. TAC clearance 3–4 weeks after transplantation in recipients with and without carrying *CYP3A5*1* and *POR*28* allele.
A, recipients with(+)/without(-) *CYP3A5*1* allele.
B, recipients with(+)/without(-) *POR*28* allele.
C, *CYP3A5*1* carrier recipients with(+)/without(-) *POR*28* allele.
D, *CYP3A5*1* non-carrier recipients with(+)/without(-) *POR*28* allele.

Conclusion

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.

The authors have no conflicts of interest relevant to the content of this presentation.