

Influence of CYP3A5 and ABCB1 Genotypes on Pharmacokinetics of Immediate and Prolonged Release Tacrolimus Preparations

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Background. Tacrolimus is available in two formulations, immediate-release, (Prograf®) and prolonged -release formulation of tacrolimus (Advagraf®). Tacrolimus has a narrow therapeutic index with wide variation between- and within individuals. It is mainly metabolized by CYP3A4/5 and is transported by P-glycoprotein (P-gp). Expression of CYP3A decreases and expression of P-gp increases along the length of the gut.

Objective. We aimed to determine whether the CYP3A5*3 and ABCB1 genotypes influence the pharmacokinetics of prolonged-release tacrolimus in the same way as is well established for the immediate release preparation, in stable renal transplant recipients.

Methods. A total of sixty-four stable renal transplant recipients treated with twice daily tacrolimus (Prograf®) were switched to the same total daily dose of Advagraf® with 24 hour pharmacokinetic profiles before and two weeks after the change. Patients were divided into 4 genotype categories based on expression of CYP3A5 (*1/*1 or *1/*3), CYP3A5 non-expressers (*3/*3), high expressers of P-gp (ABCB1; CC) or low expressers of P-gp (ABCB1; CT or TT).

Results. ABCB1 polymorphisms contributed to significant changes in tacrolimus pharmacokinetic parameters and dose requirements only in CYP3A5*1 allele carriers. Dose-normalized pharmacokinetic parameters were significantly lower in CYP3A5 expressers than in CYP3A5 non-expressers for both preparations (Table). The influence of the CYP3A5 and ABCB1 genotype on tacrolimus exposure was the same for the prolonged release preparation Advagraf® as for the immediate release preparation, Prograf®.

Genotype		n	Twice daily tacrolimus				Advagraf®			
CYP3A5	ABCB1		AUC ₀₋₂₄	C _{max}	CO	Dose	AUC ₀₋₂₄	C _{max}	CO	Dose
Expressers	High	12	179	17.2	5.2	9.2	166	14.1	4.7	9.3
Expressers	Low	18	254	22.0	8.5	7.0	261	20.8	8.0	6.9
Non-expressers	High	4	536	41.8	17.7	3.5	419	31.6	11.7	3.5
Non-expressers	Low	30	471	35.0	16.4	3.7	440	31.1	13.9	3.6

Conclusion. Pharmacogenetic dosing strategies based on these genotypes are likely to be equally applicable to prescribing the once daily tacrolimus formulation, Advagraf®, as to twice daily formulations.