The effect of tacrolimus formulation (prolonged-release vs. immediate-release) and pharmacogenetics on its susceptibility to drug-drug interactions with St. John´s Wort

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Introduction

Tacrolimus, an often-used immunosuppressant, is metabolized by cytochrome P450 3A (CYP3A) and is susceptible to interaction with the CYP3A4 and P-glycoprotein inducer St. John's Wort (SJW) [1]. CYP3A enzymes are predominantly expressed in the small intestine and liver. Prolonged-release tacrolimus (PR-Tac) formulations are absorbed in more distal intestinal sections [2], thereby potentially bypassing intestinal first-pass metabolism. Envarsus®, a tacrolimus formulation that is absorbed largely in the colon, is considerably less susceptible to CYP3A inhibition by voriconazole [3].

We aimed to analyze the effect of SJW on tacrolimus pharmacokinetics after immediate release (IR-Tac; Prograf®) and PR-Tac (Envarsus®) formulations and to evaluate whether CYP3A4 activity (estimated with a midazolam microdose) and CYP3A5 genotype correlate with these changes.

Participants and Methods

We included 18 healthy volunteers (including 8 females; 7 CYP3A5 expressors) in this randomized, cross-over, phase I clinical trial (EudraCT 2020-002569-33) who received a single oral tacrolimus dose (IR-Tac or PR-Tac, 5 mg each) alone or during SJW (300 mg TID starting 10 days before tacrolimus and continued for 3 more days), with a washout period of at least 14 days between tacrolimus administrations. Concentrations were quantified using UPLC-MS/MS methods and pharmacokinetics were analyzed by non-compartmental methods and mixed model ANOVA. The CYP3A4 phenotype was quantified by measuring midazolam metabolism with an oral microdosing procedure. Pharmacokinetic parameter ratios are reported as geometric mean and 90 % confidence intervals, a *P* value < 0.05 was considered statistically significant.

Results

SJW decreased IR-Tac exposure (AUC) 0.73-fold (90% CI 0.60–0.88) and maximum concentration (C_{max}) 0.61-fold (0.52-0.73). With PR-Tac, the decrease in AUC was 0.67-fold (0.55–0.81) and C_{max} 0.69-fold (0.58-0.82), with no statistical difference between the two formulations (*P*=0.60). The extent of interaction appeared to be less pronounced in volunteers with higher baseline CYP3A4 activity and in CYP3A5 expressors; exposure after PR-Tac was decreased 0.57-fold (0.45-0.73) in CYP3A5 nonexpressors and only 0.87-fold (0.64-1.17) in expressors (*P*=0.08), while after IR-Tac exposure was decreased 0.69-fold (0.54-0.88) in nonexpressors and 0.79-fold (0.59-1.07) in expressors (*P*=0.54). The decrease in exposure after PR-Tac was less pronounced, 0.76-fold (0.59-0.98), in participants with high CYP3A4 baseline activity than in those with low CYP3A4 activity whose exposure decreased 0.60-fold (0.46-0.77) (*P*=0.26). After IR-Tac, tacrolimus exposure decreased 0.93-fold (0.72-1.2) in volunteers with high activity and 0.57-fold (0.44-0.73) in those with low activity (*P*=0.03). No serious or severe adverse events were observed.

Table 1: Relative change in tacrolimus pharmacokinetics after induction with St. John´s Wort in 18 healthy volunteers

	IR-Tac	PR-Tac	*P*
$AUC_{0-\infty}$	0.73 (0.60-0.88)	0.67 (0.55-0.81)	0.60
AUC_{0-48}	0.75 (0.61-0.91)	0.69 (0.57-0.84)	0.62
AUC_{0-24}	0.75 (0.62-0.91)	0.71 (0.59-0.87)	0.75
C_{max}	0.61 (0.52-0.73)	0.69 (0.58-0.82)	0.42
t_{max}	1.23 (0.97-1.55)	1.02 (0.81-1.29)	0.34
$t_{1/2}$	0.93 (0.88-0.98)	0.98 (0.93-1.04)	0.16
Cl_F	1.37 (1.13-1.67)	1.49 (1.12-1.80)	0.60

Table 1: Data are shown as geometric mean ratio (fold-change) and 90 % confidence interval. $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-48}, area under the plasma concentration-time curve from time 0 to 48 hours; C_{max}, maximum concentration; Cl_F, apparent clearance; IR-Tac, immediate-release tacrolimus; PR-Tac, prolonged-release tacrolimus; t_{max}, time to maximum concentration; $t_{1/2}$, half-life.

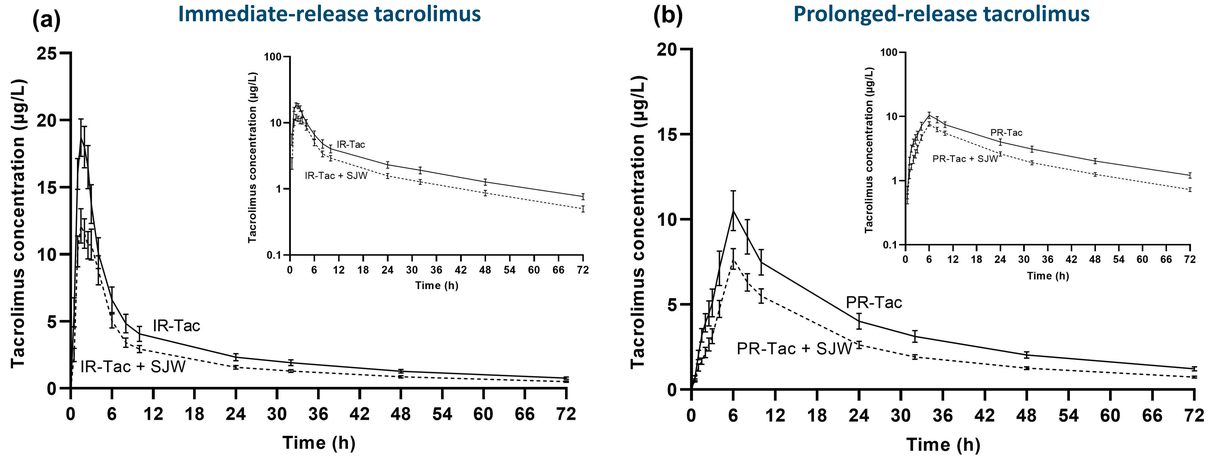

Fig. 1: Tacrolimus concentrations (mean ± standard error of the mean) after (a) a single oral 5-mg dose of immediate-release tacrolimus (IR-Tac) or (b) a single oral 5-mg dose of prolonged-release tacrolimus (PR-Tac) alone (solid line) and after induction with St. John´s Wort (SJW) (dashed line) in 18 healthy volunteers. IR-Tac, immediate-release tacrolimus; PR-Tac, prolonged-release tacrolimus; SJW, St. John´s Wort.

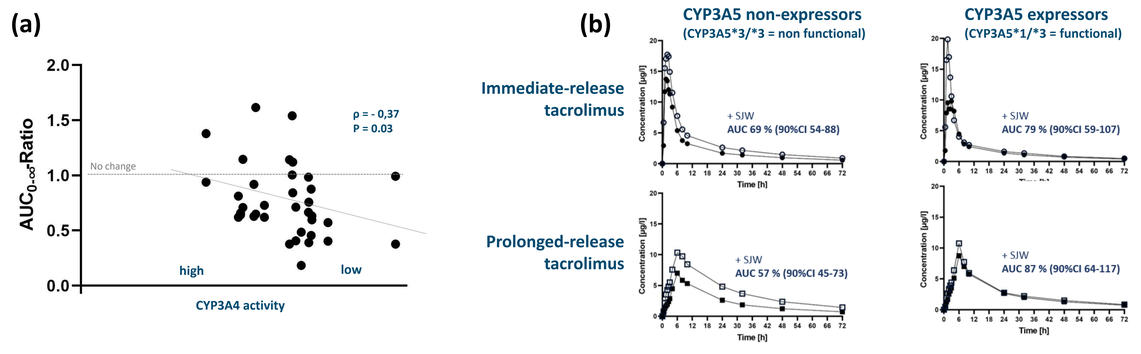

Fig. 2: Change in tacrolimus exposure by SJW (combined data from both tacrolimus formulations) in relation to CYP3A4 activity, as determined by a midazolam microdose (a). Tacrolimus concentrations after a single oral 5-mg dose of immediate-release tacrolimus (IR-Tac) or prolonged-release tacrolimus (PR-Tac) alone and after induction with St. John´s Wort (SJW) in 18 healthy volunteers according to CYP3A5 genotype (b).

Conclusion

In contrast to CYP3A inhibition, CYP3A4 induction by SJW showed a similar extent of interaction with both tacrolimus formulations, possibly due to higher colonic tacrolimus metabolism than previously assumed. A higher metabolic capacity, i.e. CYP3A5 expressors and volunteers with high CYP3A4 activity, appeared to attenuate the extent of induction by SJW, possibly due to presystemic SJW metabolism or limited inducibility in individuals with already high metabolic capacity. Finally, it can be stated that patients taking tacrolimus are not protected from drug-drug interactions by SJW irrespective of drug formulation.

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References

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Acknowledgements

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