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Comparative clinical trial of the variability factors of the exposure indices used for the drug monitoring of two tacrolimus formulations in kidney transplant recipients

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ABSTRACT

Background: Several studies found differences in tacrolimus whole blood trough levels (C0) or area-under-the curve (AUC) between the twice-daily (Tac-BID) and once-daily (Tac-OD) formulations given to kidney transplant recipients at equal doses. As C0 is widely used as a surrogate of the AUC for individual dose adjustment, this study investigated the correlation and proportionality between C0 and the 24h-AUC, depending on the formulation, time post-transplantation, pharmacogenetics traits and other individual characteristics.

Methods: 45 adult kidney transplant recipients were randomized to receive either Tac OD or Tac BID. On days 8 ± 1 (D8) and 90 ± 3 (month 3, M3), blood samples were collected over 24 h in both groups. Tacrolimus concentrations were determined using HPLC–MS/MS and common *CYP3A5*, *CYP3A4* and *ABCB1* genotypes characterized using allelic discrimination assays. Tacrolimus population pharmacokinetics was studied in the two patient groups using the Iterative Two Stage (ITS) technique, considering a one-compartment model with two gamma laws to describe the absorption phase. Bayesian estimation based on the C0, C1 h and C3 h concentrations was employed to estimate individual Tac $AUC_{0\text{-}12h}$ and $AUC_{12\text{-}24h}$ (for Tac BID), or $AUC_{0\text{–}24h}$ (for Tac OD). Multiple linear regression was used to evaluate the influence of Tac formulation, post-transplantation period, recipient gender, existing glucose metabolism disorders, and *CYP3A5*, *CYP3A4* and *ABCB1* genotypes on C0, $AUC_{0\text{–}24h}$ and the AUC-to-trough concentration ratios.

Results: The Full Analysis Set comprised 22 patients on Tac OD and 20 on Tac BID. Tac exposure indices as well as their time evolution were similar in the two groups. Multi-linear modeling analysis showed

Abbreviations: ABCB1, gene coding the efflux transporter P glycoprotein; AUC, area under the concentration time curve; BPAR, biopsy proven acute rejection; C0, residual whole blood tacrolimus concentration; C24h, whole blood tacrolimus concentration at the end of the 24 h pharmacokinetic profile; Cmax, maximum ('peak') whole blood tacrolimus concentration; CYP3A4, cytochrome P450 3A4; CYP3A5, cytochrome P450 3A5; EC-MPS, enteric coated mycophenolic sodium; EDTA, ethylene diamine tetraacetic acid; GFR, glomerular filtration rate; MDRD, modification of the diet in renal disease; HPLC–MS/MS, high-performance liquid chromatography tandem mass spectroscopy; I.D., internal diameter (of a HPLC column); ITT, intention to treat; MMF, mycophenolate mofetil; NODAT, new onset diabetes after transplantation; Pgp, P-glycoprotein; PK, pharmacokinetics; SAE, serious adverse events; Tac BID, tacrolimus twice daily formulation; Tac OD, tacrolimus prolonged-release once-daily formulation; TDM, therapeutic drug monitoring.

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that the Tac dose was higher with Tac-OD than Tac-BID, on D8 than at M3 and in CYP3A5 expressors ($p < 0.0001$ for all). No such influence was found on C0 or C24 h, while the AUC_{0-24h} was significantly higher on D8 than at M3. The AUC_{0-24h}/C0 ratio was not affected by the drug formulation and the polymorphisms studied, but it was significantly lower on D8 than at M3 ($p = 7.8 \times 10^{-5}$). In contrast, both the post-transplantation period ($p = 1.53 \times 10^{-4}$), and CYP3A5 expression ($p = 0.003$) had a significant influence on the AUC_{0-24h}/C24 h ratio, explaining 19% and 12% of its variability, respectively. Consistently, for both Tac formulations, the AUC_{0-24h} was better correlated with C24 h than C0, and for Tac-BID the AUC_{0-12h} was better correlated with C12 h than C0.

Conclusions: This study confirms that the precisely timed 12h- or 24h-post-dose blood concentration (as opposed to the vaguely defined 'trough level') is a convenient surrogate of the 24h-AUC of tacrolimus for the two TAC formulations over the first 3 months post-transplantation. Still, for a given C24 h value, AUC_{0-24h} was higher on D8 and in CYP3A5 expressors. Bayesian estimation of AUC_{0-12h} for TAC BID and AUC_{0-24h} for TAC OD is feasible using only 3 time points within the first 3 h, thus giving access to the actual overall exposure.

1. Introduction

Tacrolimus is a first-line immunosuppressive drug in the prevention of allograft rejection after solid organ transplantation. As this drug has a narrow therapeutic index with significant inter-individual variability, therapeutic drug monitoring (TDM) is essential to avoid under-or overexposure. A recent review stressed that the more recent tacrolimus prolonged-release, once-daily formulation (Tac OD) formulation Advagraf® had the same efficacy as tacrolimus twice daily formulation (Tac BID) Prograf® in terms of renal function, patient and graft survival at 12 months, and the same safety profile although individual studies found differences, in particular regarding the incidence of infections [1]. An Advagraf® phase II randomized, parallel group study showed that, after kidney transplantation, the 24-h area under the concentration – time curve (AUC_{0-24h}) was comparable to that of Tac BID on days 14 and 42, but on average 30% lower on day 1 with Tac OD [2]. In a non-randomized, parallel-group study, Niioka et al. found that although the AUC_{0-24h} and C0 values were approximately 25% lower with Advagraf® than Prograf® ($p < 0.001$ for all), the dose-adjusted AUC_{0-24h} was not significantly different (43.0 vs. 38.2 ngh/mL per milligram, $p = 0.264$), while the dose-adjusted C_0 only showed a tendency towards lower values (1.2 vs. 1.0 ng/mL/mg, $p = 0.07$) [3]. They also found a rather mediocre correlation between AUC_{0-24h} and C_0 with either Tac BID or Tac OD ($r^2 = 0.575$ and 0.638, respectively). In a retrospective, single-centre, switch study in 284 renal allograft recipients, de Jonge et al. reported that after conversion, C_0 decreased significantly ($-12.7\% \pm 24.4\%$, $p < 0.0001$); as a result, Tac-OD dose was increased in 52.5% patients and despite dose increase, C_0 remained 9% lower on average in the Tac-OD group [4].

Several factors influence tacrolimus pharmacokinetics. We previously showed in a large cohort of renal transplants on TAC BID that dose-standardized exposure to tacrolimus significantly and progressively increased after transplantation from month 1–9 (from 2.33 to 3.44 μg/L/mg for C0/dose, and from 43.1 to 64.2 μg*h/L/mg for AUC/dose) [5]. Also, tacrolimus is a substrate of CYP3A5 and individuals carrying at least one *CYP3A5*1* allele, considered CYP3A5 expressors, had significantly increased oral clearance of Tac BID and Tac OD [6,7] and required 1.5 times higher Prograf® doses than non-expressors (i.e., *CYP3A5*3/*3* homozygotes) to reach the predefined target exposure early after transplantation [8].

In parallel, the *CYP3A4* intron 6 rs35599367 C > T SNP (called *CYP3A4*22*) has been associated with decreased mRNA hepatic expression and enzymatic activity, leading to increased Prograf® dose-adjusted tacrolimus concentrations in kidney transplant recipients [9–11]. Regarding the *ABCB1* gene encoding the P-gp efflux protein, the 2677 Gn > T,A [12] and 3435 C > T polymorphism [13] as well as the haplotype combining these two SNPs [13,14] were associated to different Tac BID dose requirements to reach the same C_0, while the other ABCB1 genotypes tested had no influence [12,15]. For Tac OD, only one study on the influence of ABCB1 polymorphisms was performed, in pediatric renal graft recipients, showing no significant influence of the 3435 C > T SNP [16] (the only one tested).

Finally, circadian variations in the pharmacokinetics of tacrolimus were reported, with a slower and delayed absorption at nighttime as compared to daytime (Cmax = 34.1 ± 12.6 vs. 24.4 ± 9.8 ng/mL, Tmax = 1.6 ± 0.8 vs. 2.7 ± 2.0 h, respectively) [1,17–20].

A single-centre, historical comparison study investigated the influence of some of these factors on TAC BID and TAC OD exposure indices in Japanese transplant recipients, showing: (i) a two-fold increase in C0/dose and AUC_{0-24}/dose between 1 month and 1 year post-transplantation, with both formulations and whatever the *CYP3A5* genotype; (ii) a lower C0/dose for TAC OD than for TAC BID in both CYP3A5 subgroups, while the AUC_{0-24h}/dose was only lower in CYP3A5 expressors; and (iii) an approximately 30% lower C0/dose on Advagraf® than on Prograf®, while the AUC_{0-24h}/dose was not significantly different, which is in favour of a difference between the two formulations in the relationship between C0 and AUC [21].

Finally, in a review article, we emphasized that there is no guarantee that therapeutic drug monitoring strategies applicable to the twice-daily formulation will be equally applicable to the OD formulation, because the correlation between AUC_{0-24} and C_0 is variable and not strong for all formulations, indicating that trough measurements may not always give a good indication of overall drug exposure [22].

As C0 is widely used as a surrogate of the AUC for individual dose adjustment, this study in kidney transplant recipients investigated the correlation and proportionality between tacrolimus AUC_{0-24h} and C0 or C24 h, depending on the drug formulation, *CYP3A5*, *CYP3A4* and *ABCB1* polymorphisms and time post-transplantation in the most critical, early period. We also compared C12 h to C0 as a surrogate of AUC_{0-12h} for tac-BID. For this, we employed state-of-the art pharmacokinetics modeling and multivariate statistical techniques.

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