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EDITORIAL

# Role of pharmacogenetics and tacrolimus dosing in liver transplantation

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After liver transplantation (LT), long-term immunosuppression is required to prevent allograft rejection. Tacrolimus (TAC), a macrolide antibiotic and calcineurin inhibitor, is the primary immunosuppressive agent after LT. After absorption, TAC forms a complex with the FK-binding protein, with subsequent competitive binding and inhibition of calcineurin, ultimately leading to a decrease in interleukin-2 (IL-2) transcriptional activity and reduced T-cell proliferation. Due to its narrow therapeutic window, monitoring of TAC whole-blood trough concentrations is essential to ensure adequate drug levels and to avoid toxicity. Two formulations of TAC are currently available. The immediate-release TAC (IR-TAC) is given twice daily, whereas the prolong-released TAC (PR-TAC) is given once daily, thereby potentially improving patient adherence. In clinical practice, the switch from IR-TAC to PR-TAC is performed primarily to increase patient compliance. In a phase III trial of de novo LT recipients, the efficacy and safety profiles were found to be similar between PR-TAC and IR-TAC [1]. The conversion from IR-TAC to PR-TAC is relatively straight forward using the same daily-dose requirement, although significant variation in calcineurin activity may occur during the early post-transplant period [2].

In fact, it is well established that there is high inter- and intra-patient variability in the pharmacokinetics of TAC, which is metabolized by enzymes in the cytochrome P450 (CYP) 3A family. Both CYP3A4 and CYP3A5 are clinically important isoforms, with high sequence homology and substrate overlap. The poor oral bioavailability of TAC is due to the pre-systemic elimination and first-pass metabolism by intestinal CYP3A and hepatic CYP3A respectively, with subsequent systemic clearance via biliary excretion of its metabolites. Single nucleotide polymorphisms (SNP) in the CYP3A5 gene can alter enzyme expression, with higher expression leading to more extensive metabolism, and vice versa. One of the best studied SNP in CYP3A5 is the A6986G transition within intron 3 (CYP3A5*3) which is associated with reduced function as a result of alternative splicing, with production of a truncated protein [3]. Homozygous carriers of CYP3A5*3 gene (*3/*3) have no CYP3A5 activity, and therefore have a higher dose-normalized trough TAC concentration compared to CYP3A*1 carriers. Another essential component of CYP-mediated drug oxidation is CYP P450 oxidoreductase (POR), which acts as an electron donor through transfer from NADPH to CYP. Polymorphisms in the POR gene therefore can also affect CYP function, with POR*28 being one of the best studied polymorphisms. The presence of POR*28 with A503V mutation alters the reactivity of POR binding site with CYP, potentially enhancing TAC metabolism with increased CYP activation.

In LT, the situation becomes even more complex as it is necessary to consider both the donor hepatic and recipient intestinal CYP3A status when assessing TAC pharmacokinetics. For instance, the CYP3A5 genotype of the donor liver may be different to the CYP3A5 genotype residing in the recipient intestine. Furthermore, the relative influence of donor and recipient genotypes remains unclear, and it is possible that this interplay may not be static and may change over the post-transplant period, with donor genotype expression being delayed. In addition, there is influence of other enzymes in the CYP3A family, including CYP3A4 and CYP3A7. In a recent study of LT recipients, CYP3A7, CYP3A4, and CYP3A5*3 polymorphisms in the recipients and not the donors were associated with tacrolimus C0/D in the early post-transplant period [4].

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Apart from the CYP3A enzyme system, membrane transporters are also important in determining the pharmacokinetics of TAC. These transporters allow TAC to be absorbed into the systemic circulation and into the hepatocytes to be metabolized, and can also influence the intracellular concentration of TAC in target cells, thereby affect the therapeutic efficacy. The two main types of transporters include the ATP-binding cassette transporters (ABC) and the solute carrier transporters (SLC). Once TAC is metabolized by CYP3A, it is transported out of cells via the P-glycoprotein (ABCB1) transporter, which is encoded by the multidrug resistance-1 (MDR1) gene. Although numerous polymorphisms exist for the ABCB1 gene, data to date are inconsistent, with lack of clear association between ABCB1 genotypes and TAC whole blood concentrations [5]. It is possible that these transporters have greater influence on intracellular concentrations of TAC rather than whole blood concentrations. Another transporter is the multidrug resistance-associated protein 2 (MRP2) coded by the ABCC2 gene. Again, the results have not been conclusive in showing definite relationships between SNP in the ABCC2 gene and TAC pharmacokinetics, with almost all studies performed on renal transplant patients [6]. The most studied SNPs for ABCC2 include the – 24C > T, 1249G > A, and 3972C > T, giving rise to the following haplotypes: H1 (wildtype), H2 (1249G > A) with increased expression, and H9 (3972C > T) and H12 (– 24C > T and 3972C/T) with decreased expression [7].

In the current study by Park et al. [8], the authors investigated the effects of SNPs for CYP3A5, MDR1 (1236C > T, 2677G > T/A, and 3435C > T), ABCC2 (– 24C > T, 1249G > A, and 3972C > T), and POR*28 in donors and recipients on TAC dose-adjusted trough levels in LT recipients after switching from IR-TAC to once daily PR-TAC. This is a small single-center retrospective study of 87 patients who underwent living-donor LT at least 1 month before switching to PR-TAC. Donors for each recipient were also included. The study divided the patients into 2 groups: those with < 30% decrease in C0/dose (group 1) and those with ≥ 30% decrease in C0/dose (group 2) following switching to PR-TAC. The study showed that recipient CYP3A5 *1/*3 and *3/*3 were more frequent in group 1 compared to group 2, whereas CYP3A5 *1/*1 was more frequent in group 2 ($p = 0.016$). These findings are consistent with what we know already with regard to CYP3A5 genotypes. However, they did not find any significant differences in donor CYP3A5 variants between the two groups. The discrepancy between recipient and donor findings may highlight the differences between hepatic and intestinal CYP3A influences, and the effect of time after LT on the function and the relative influence of these two enzymes, with those in group 2 having an earlier switching time ($p = 0.025$).

The ABCC2 SNP findings in the current study were consistent with previous studies of renal transplant recipients, with higher AA and AG genotypes in group 2 than in group 1 ($p = 0.042$). The donor high-activity ABCC2 genotype (H1/H2 and H2/H2) was significantly more frequent in group 2 than in group 1, while the low-activity genotype (H1/H9, H1/H10, H1/H12, H9/H12, and H12/H12) was more frequent in group 1 than in group 2 (0 vs. 14.3%; 36.8 vs. 20.4%; $p = 0.013$). With regard to the other SNPs in MDR1 and POR*28, no significant differences were observed between the two groups and with TAC C0/dose in the current study.

Although the current study by Park et al. [8] does shed some light onto the potential effects of SNPs in TAC pharmacokinetics when switching to PR-TAC, this is a small retrospective study, and the TAC measurements following switching had a wide range from 5 to 102 days. Furthermore, the switching time was significantly different between the two groups and not controlled, and after adjusting for switching time, no factors were found to be associated with a reduction in TAC C0/dose. The significantly higher TAC trough levels before switching in group 2 may be due to the shorter switching time and may also impact the results. Therefore, it is difficult to draw any firm conclusions from the current study, and further prospective studies controlling the exact timing of drug intake, time of switching from LT, and fixed time points of TAC measurement are required to confirm these results. However, the study has highlighted the role of pharmacogenetics when switching between different formulations of tacrolimus.

For the conversion from IM-TAC to PR-TAC, determination of specific SNPs in donors and recipients is unlikely to have any practical clinical application on its own given the complex interplay between enzymes and transporters in different organs and cellular compartments. In addition, other factors, such as age, ethnicity, body surface area, hematocrit, drug–drug interactions, and liver function, may also alter TAC metabolism and excretion. Therefore, the clinical utility of studying these pharmacogenetic alterations may be limited. This is highlighted by the discordant results from previous studies, despite much research over many years. However, it is important for clinicians to be aware of the role of these SNPs, and that they can account for wide variations in the pharmacokinetics of TAC even with a simple one-to-one conversion. Close monitoring of drug levels must be performed after switching to PR-TAC for timely dose adjustments to avoid rejection and drug toxicity with insufficient and inadvertent high levels respectively. It is important to note that the toxicity effect of TAC is bimodal, with early onset adverse events including acute nephrotoxicity and neurotoxicity occurring as a result of local drug accumulation that may not be reflected in therapeutic drug levels. Therefore, whole blood trough levels are only a surrogate

measurement for intracellular drug concentrations, of which the latter may be more indicative of the amount of drug available for target interaction. Indeed, studies of tacrolimus concentration inside peripheral blood mononuclear cells (PBMCs) have shown poor correlation with whole blood concentration [9, 10]. Finally, although determination of SNPs may help guide TAC dosing, there is to date no direct evidence that this will ultimately lead to an improved clinical outcome. A large prospective study, inclusive of models that consider and integrate the complex interplay between multiple factors including the various SNPs and their relative influences are required to determine the exact utility of TAC pharmacogenetics in clinical practice. Until then, personalized prescriptions of TAC based on pharmacogenetic analysis remain in theory only, and not ready for prime time.

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## Declarations

**Conflict of interest** James Fung declares that there is no conflict of interest.

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