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EDITORIAL

The pharmacogenetics of tacrolimus and its implications for personalized therapy in kidney transplant recipients

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Twenty-five years after its approval by the FDA and EMA, tacrolimus remains the cornerstone of immunosuppressive treatment following solid organ transplantation [1,2]. The drug is highly effective in preventing acute rejection but its clinical use still is complicated by its narrow therapeutic range and high inter- and intra-patient pharmacokinetic variability [3,4]. In many transplant centers across the world, the starting dose of tacrolimus is based on a patient's bodyweight, followed by whole-blood tacrolimus concentration measurement (preferably when the drug is in steady state) and dose titration. Therapeutic drug monitoring (TDM) is considered standard of care and limits the time that a patient is under- or overexposed to tacrolimus [1]. However, TDM is a reactive approach and in clinical practice, dosing of tacrolimus remains trial and error. Bodyweight is a poor predictor of an individual's tacrolimus clearance [5,6] and as a result, it may take up to three weeks before a patient has a tacrolimus exposure within the target concentration range [7,8]. In addition, an individual's tacrolimus metabolic phenotype has been associated with transplantation outcomes [9]. A low tacrolimus concentration-to-dose ratio (C/D ratio), which indicates a more rapid tacrolimus clearance, is an independent risk factor for death-censored graft survival [9]. There is an unmet need to personalize tacrolimus treatment and limit the time that transplant recipients are under- or overexposed to tacrolimus in order to limit the risks of acute rejection and tacrolimus-related toxicity, respectively [10].

The inter-individual differences in tacrolimus pharmacokinetics are in large part determined genetically. Single-nucleotide polymorphisms (SNPs) in multiple genes have been associated with tacrolimus dose requirement (for a review see references [11,12]). Especially, SNPs in the cytochrome P450 (CYP) *3A4* and *CYP3A5* genes, which encode the main tacrolimus-metabolizing enzymes, have been strongly linked to an individual's drug metabolizing phenotype [6,13,14]. Carriers of at least one *CYP3A5*1* allele are considered CYP3A5 expressers and require a tacrolimus dose that is at least 1.5 times higher compared to so-called CYP3A5 non-expressers (individuals with the *CYP3A5*3/*3* genotype) [1]. The *CYP3A4*22* SNP has been associated with slower tacrolimus clearance and a lower dose requirement [14–18]. In addition, the *CYP3A4*20* SNP [16,19] and genetic variations in the *ABCB1, POR, PPARA* and NR1I2 genes have all been associated with tacrolimus pharmacokinetics. The effect of these variants seems smaller than that of *CYP3A4* and *CYP3A5* and is probably less clinically relevant [20,21].

It was hoped that pharmacogenetics-guided tacrolimus dosing would improve clinical tacrolimus treatment [22]. In particular, a pharmacogenetics-based approach may lead to a more appropriate tacrolimus starting dose, thereby limiting the time a patient is outside the target concentration range in the critical early post-transplant phase [23]. The efficacy of genotype-based tacrolimus dosing was investigated in three randomized-controlled clinical trials [7,8,24]. In all three trials, the tacrolimus starting dose was based on an individual transplant recipient's *CYP3A5* genotype, being higher in CYP3A5 expressers (carriers of a **1* allele) and lower in non-expressers. In the study by Thervet et al. [8] genotype-guided tacrolimus dosing resulted in significantly more patients being on target at first-steady state (*i.e.* after 5 unaltered tacrolimus doses) compared with the control group who received a standard, bodyweight-based tacrolimus starting dose (43.2% *versus* 29.1%; $p = 0.03$). In the study by Min et al. [24] this approach significantly shortened the time to reach the tacrolimus target concentration range in pediatric solid organ transplant recipients ($n = 53$ patients). However, the absolute difference was small (a median of 3.4 *versus* 4.7 days in the genotype-guided *versus* the standard dose group, respectively). In the trial by Shuker et al. [7] there was no difference in the proportion of living donor kidney transplant recipients that were on target at first steady state measurement. In the standard, bodyweight-based dose tacrolimus group, 37.4% of patients was on target (10–-15 ng/mL) at day three after transplantation, whereas this was 35.6% in the experimental arm in which the tacrolimus starting dose was based on *CYP3A5* genotype. Importantly,

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in none of these three trials any clinical benefit of *CYP3A5*-guided tacrolimus dosing was observed, either in the short- or long-term [7,8,24,25]. The lack of evidence for clinical benefit of genotype-based tacrolimus dosing, is one of the reasons why this strategy has not been widely implemented clinically [26]. The Clinical Pharmacogenetics Implementation Consortium recommends to only use pharmacogenetics-based tacrolimus dosing when an individual's genotype is already available [27].

Not only a patient's genotype but also other factors affect tacrolimus pharmacokinetics, including age, plasma albumin concentration, body surface area, co-medication, ethnicity, and hematocrit [10]. It is reasonable to assume that combining these factors with genetic information in a population pharmacokinetic (popPK) model will allow clinicians to predict a patient's tacrolimus dose requirement with more precision than a prediction based on genotype (or bodyweight) alone, which might increase the clinical benefit. To date, multiple models predicting the tacrolimus starting dose have been developed, both for pediatric, as well as for adult renal transplant recipients [3,28–31]. However, few of these popPK models were externally validated [3,28,29,32,33] and even fewer were tested prospectively [34,35]. The latter is essential before model-based tacrolimus dosing can be implemented clinically. We developed a popPK model for pediatric kidney transplant recipients and validated this model both internally and externally [28]. However, when tested prospectively, the model did not predict a patient's tacrolimus dose requirement sufficiently [34]. Currently, several prospective intervention trials, investigating the efficacy of initial algorithm-based dosing in adult renal allograft recipients are ongoing (https://www.trialregister.nl/trial/7360; NCT03465410; NCT03020589; NCT03527238 see clinicaltrials.gov).

Recent research has mainly focused on the calculation of the tacrolimus starting dose. However, not only the achievement but also the maintenance of the tacrolimus exposure within the target concentration range is a challenge. Patients with a tacrolimus concentration within the therapeutic range at first steady state can have a tacrolimus concentration that lies outside this range on subsequent days. This intra-patient variability is in part explained by post-transplant changes in hematocrit (*e.g.* resulting from blood loss due to surgery or frequent sampling) and albumin concentration (due to, for example, recovery of liver function and co-existing inflammation), and hepatic metabolism (from loss of uremic toxins [36]). Computerized follow-up dosing based on popPK models, may better maintain the targeted tacrolimus exposure and further individualize tacrolimus treatment after transplantation. Størset et al. [37] reported a clinical trial in which standard or high-immunological risk kidney transplant recipients were randomized (after initial bodyweight-based dosing) to undergo either computerized follow-up tacrolimus dosing or conventional tacrolimus dosing by experienced transplant physicians. Computerized dosing, based on several variables (historical tacrolimus dosages, previously measured tacrolimus concentrations, fat-free mass, hematocrit, and time after transplantation), significantly improved the achievement of tacrolimus concentrations within the target range. During the first eight weeks after transplantation, a median of 90% of the patients' tacrolimus concentrations was within the target range following computerized dosing, whereas this was 78% following standard dosing in the standard risk group ($p < 0.001$). Also, in the high-risk group, a significantly higher proportion of the patients' tacrolimus concentrations was within the target range following computerized dosing compared to standard dosing (median 77% *versus* 59%, respectively; $p = 0.04$). In the computer-based dosing group, a lower two-hour plasma glucose concentration was observed following an oral glucose tolerance test, performed eight weeks post-transplantation. This indicates a possible beneficial clinical effect of algorithm-based tacrolimus dosing and the resulting reduced supra-therapeutic exposure in terms of glucose metabolism [37].

Another strategy which may optimize tacrolimus treatment and increase clinical benefit is the monitoring of tacrolimus in a matrix other than whole-blood. Contradictory results have been reported on the correlation between whole-blood tacrolimus exposure and both rejection and drug-related toxicity [38–41]. The tacrolimus concentration at its target site (within lymphocytes) may better correlate with efficacy and clinical outcomes. This hypothesis was supported by the study of Capron et al., in which the tacrolimus concentration within peripheral-blood mononuclear cells correlated significantly with the occurrence and severity of rejection in liver transplant recipients [42]. These findings need to be substantiated in larger studies. Interestingly, the intracellular tacrolimus concentration has been related, although not consistently, to genetic variability in CYP3A4 and CYP3A5 but also to variability in the expression of drug transporter proteins such as ABCB1, which determine the drug's distribution [43–45].

Expert opinion

Although the application of popPK models has the potential to move the field forward, it is clear that current models, which include demographic and genetic patient characteristics, do not explain all inter- and intra-patient variability in tacrolimus pharmacokinetics. Recently, Zimmermann et al. [46] showed that residual variability in drug metabolism may be explained by variation in the human microbiome. Microbiome-encoded enzymes contribute substantially to pre-systemic metabolism of many drugs [46], including tacrolimus [47,48]. Lee et al. [47] demonstrated that the abundance of fecal *Faecalibacterium prausnitzii* is associated with higher tacrolimus requirement in the early post-transplantation phase. We feel that a further exploration of the role of the human microbiome in tacrolimus pharmacokinetics is an important research topic for the years to come and has the potential to improve the performance of future popPK models. Such studies are at present underway (see clinical trials.gov, NCT04207177). Hopefully, the revolutionary findings of Zimmerman et al. and Lee et al. [46,47] will fuel the transplant community to optimize tacrolimus treatment further. We owe this to our patients because tacrolimus will likely remain an essential component of immunosuppressive therapy after transplantation in the decade to come.

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