

# CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment

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**Abstract:** Tacrolimus is a commonly used immunosuppressant after kidney transplantation. It has a narrow therapeutic range and demonstrates wide interindividual variability in pharmacokinetics, leading to potential underimmunosuppression or toxicity. Genetic polymorphism in CYP3A5 enzyme expression contributes to differences in tacrolimus bioavailability between individuals. Individuals carrying one or more copies of the wild-type allele \*1 express CYP3A5, which increases tacrolimus clearance. CYP3A5 expressers require 1.5 to 2-fold higher tacrolimus doses compared to usual dosing to achieve therapeutic blood concentrations. Individuals with homozygous \*3/\*3 genotype are CYP3A5 nonexpressers. CYP3A5 nonexpression is the most frequent phenotype in most ethnic populations, except blacks. Differences between CYP3A5 genotypes in tacrolimus disposition have not translated into differences in clinical outcomes, such as acute rejection and graft survival. Therefore, although genotype-based dosing may improve achievement of therapeutic drug concentrations with empiric dosing, its role in clinical practice is unclear. CYP3A5 genotype may predict differences in absorption of extended-release and immediate-release oral formulations of tacrolimus. Two studies found that CYP3A5 expressers require higher doses of tacrolimus in the extended-release formulation compared to immediate release. CYP3A5 genotype plays a role in determining the impact of interacting drugs, such as fluconazole, on tacrolimus pharmacokinetics. Evidence conflicts regarding the impact of CYP3A5 genotype on risk of nephrotoxicity associated with tacrolimus. Further study is required.

**Keywords:** calcineurin inhibitor, graft, pharmacogenomics, kidney, genotype

## Introduction

### Tacrolimus

Tacrolimus (Astellas Pharmaceuticals, Northbrook, IL, USA) is an immunosuppressant of the calcineurin inhibitor class and is considered a cornerstone of maintenance drug therapy after kidney transplantation. Tacrolimus binds to FK506-binding protein 12, which in turn inhibits the action of calcineurin, which is involved in T-cell activation.<sup>1</sup> Tacrolimus was first introduced for clinical use in transplantation in 1989. Initial studies of tacrolimus demonstrated that it reduced 1-year acute rejection rates and improved 6-months graft survival compared to its predecessor, ciclosporin (Novartis Pharmaceuticals, Basel, Switzerland).<sup>2</sup> Over the last 3 decades, use of tacrolimus as the calcineurin inhibitor of choice has grown by large margins. As of 2015, in the United States, tacrolimus is used as part of the immunosuppressant regimen for more than 90% of all kidney transplant recipients.<sup>3</sup> Tacrolimus is available for oral administration in several formulations. The immediate-release capsule is given twice daily, while the

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extended-release capsule or tablet is administered once daily. Oral granules for suspension are available in Europe. It is also available in intravenous form.

Tacrolimus has a narrow therapeutic index. Tacrolimus toxicity occurs at concentrations slightly above or even within its therapeutic range. Toxic effects include nephrotoxicity, infection, hypertension, hyperkalemia, hypomagnesemia, hyperglycemia, diabetes, tremor, and other neurotoxic effects. On the other hand, underdosing can lead to underimmunosuppression and graft rejection. Therefore, therapeutic drug monitoring of tacrolimus is used regularly in clinical practice with the goal of optimizing the fine balance between graft rejection and drug toxicity. Trough blood concentration (C<sub>0</sub>) is the commonly accepted parameter for therapeutic drug monitoring since it predicts risk of both acute rejection and toxicity. C<sub>0</sub> correlates with overall drug exposure as measured by 12-h area under the curve (AUC<sub>0-12h</sub>).<sup>4</sup> There is high interindividual variability in tacrolimus pharmacokinetics. Empiric dosing does not result in predictable systemic drug concentrations.

Tacrolimus is absorbed from the distal segments of gastrointestinal tract with highly variable bioavailability ranging from 5% to 93%.<sup>5</sup> Absorption is rapid, and full absorption occurs in 30–60 minutes after administration of the immediate-release formulation, while the extended-release formulation requires 120 minutes.<sup>6,7</sup> Multiple factors modify its bioavailability such as high dietary fat intake and diabetes, both of which reduce drug absorption. Intestinal enzymes also affect the extent of absorption. Intestinal CYP3A enzymes in the upper small intestine contribute to a first-pass effect in which the drug is metabolized within the gut before it reaches the systemic circulation. Additionally, p-glycoprotein within the gut wall actively pumps drug from the intracellular space of intestinal mucosa cells back into the intestinal lumen. Tacrolimus has a small apparent volume of distribution (V<sub>d</sub> = 1–1.5 L/kg) because it binds extensively (99%) to erythrocytes and blood plasma proteins. Tacrolimus is mainly metabolized in the liver by CYP3A isoenzymes. The key metabolites are demethylhydroxy-tacrolimus and demethyl-tacrolimus, although up to 13 other metabolites have been described. Tacrolimus excretion is primarily via the biliary route, with 97% of radiolabelled tacrolimus recovered in feces. Approximately 3% of tacrolimus is recovered in urine.<sup>8</sup> Tacrolimus half-life is approximately 15.6 hours in adult kidney transplant recipients.<sup>6,7</sup>

## CYP3A subfamily

Tacrolimus pharmacokinetics is heavily influenced by drug-metabolizing enzymes in the CYP3A subfamily. CYP3A is

one of many cytochromes P450, a superfamily of proteins playing a significant role in metabolizing thousands of exogenous and endogenous substances. Individual enzymes within the cytochrome P450 superfamily are categorized by similarities in amino acid sequence. Each enzyme is named according to a family number, a subfamily letter, an individual enzyme number, and an asterisk followed by number for each allelic variant.<sup>9</sup> The cytochromes (CYP) P450 are found in most tissues in the human body and are involved in hormone synthesis and breakdown, vitamin D synthesis, cholesterol synthesis, and metabolism of potential toxic compounds, including drugs. The CYP3A subfamily is especially important in this latter function as an estimated half of all marketed drugs undergo metabolism via these enzymes.<sup>10</sup> In humans, four different CYP3A isoenzymes have been identified: CYP3A4, CYP3A5, CYP3A7, and CYP3A43.<sup>11</sup> In adults, the dominant isoenzyme is CYP3A4, which is expressed in both the gut and the liver. CYP3A5 is likewise present in these tissues, but in addition, it is also present in the prostate and the kidney. CYP3A7 predominates in neonates, but becomes downregulated soon after birth. Its role as a drug-metabolizing isoenzyme is considered negligible in adults. CYP3A43 is less well studied, and so little is known about its functions.

In the case of tacrolimus, the presence of CYP3A4 and CYP3A5 in the intestinal mucosa and in hepatic cells contributes to a first-pass effect as drug molecules are metabolized prior to reaching the systemic circulation. Genetic polymorphism in these 2 enzymes accounts for a significant part of the interindividual variability observed with tacrolimus bioavailability. The best studied genetic variation is in the *CYP3A5* gene.<sup>12</sup>

## CYP3A5 genotypes and their frequencies

Up to 9 different alleles have been identified in the *CYP3A5* gene (Table 1). *CYP3A5* \*1 and \*3 occur frequently and are the most well studied. Genetic assays generally do not test for the other variants that occur more rarely. The distribution of alleles within the population differs depending on ethnicity (Table 2).

The best studied single-nucleotide polymorphism (SNP) is at position 6986 (6986A>G), which is located within intron 3 of the *CYP3A5* gene. Individuals carrying at least 1 copy of the A nucleotide are defined as having the \*1 allele and are known as CYP3A5 expressers. This allele is associated with higher CYP3A5 enzyme expression. Those with homozygous GG nucleotides at position 6986 are known as \*3/\*3 carriers and are considered CYP3A5 nonexpressers.<sup>21</sup> The substitution of G for A generates incorrect mRNA splicing, leading to an

early stop codon that results in a nonfunctional protein. In the seminal study by Kuehl et al,<sup>22</sup> all Caucasian and most African American patients with low concentrations of intestinal or hepatic CYP3A5 (<21 pmol/mg protein) were homozygous for *CYP3A5* \*3. Those with higher CYP3A5 content (between 21 and 204 pmol/mg protein) possessed at least 1 copy of *CYP3A5* \*1. Carriers of the \*1 allele have higher overall CYP3A content by approximately three-fold ( $p=0.001$  for Caucasians,  $p=0.01$  for African Americans). In these patients, CYP3A5 represents at least 50% of the total hepatic CYP3A content.

SNPs usually do not occur independently in a given individual. Rather, one observes linkage disequilibrium, in which two or more SNPs interact because genetic material is passed on to the next generation in blocks of DNA known as haplotypes. Studies show that the *CYP3A5* \*1 wild-type allele is linked to the *CYP3A4* \*1B allele. In one study, 67% of Caucasians and 100% of African Americans possessing *CYP3A4* \*1B also possessed *CYP3A5* \*1.<sup>24</sup> *CYP3A4* \*1B

affects tacrolimus clearance in the same direction. Individuals possessing the *CYP3A4*\*1B allele have lower C<sub>0</sub> by 35% after adjustment for tacrolimus dose compared to wild-type individuals.<sup>25</sup>

## Effect of *CYP3A5* genotype on tacrolimus pharmacokinetics

The wild-type *CYP3A5* \*1 allele is associated with greater production of functional CYP3A5 enzyme, thus leading to higher drug-metabolizing activity by CYP3A overall. The *CYP3A5*\*1/\*1 genotype increases tacrolimus clearance by 2-fold, while the heterozygous *CYP3A5*\*1/\*3 genotype results in approximately 1.7-fold greater clearance compared to the *CYP3A5*\*3/\*3 population.<sup>17,26–27</sup> *CYP3A5* \*3/\*3 has 48% lower oral clearance compared to CYP3A5 expressers<sup>11</sup> (Table 3).

In 2012, Terrazino et al<sup>28</sup> published a meta-analysis to estimate the effect of *CYP3A5* 6986A>G polymorphism on tacrolimus dose-adjusted trough concentration in kidney transplant patients. Nineteen studies involving 2,028 patients were included in the meta-analysis. Overall, patients with the \*3/\*3 genotype had significantly higher dose-adjusted trough concentrations (weighted mean difference: 63.57 ng/mL per mg/kg, 95% confidence interval [CI]: 50.85–76.30) compared with the combined group of \*1/\*3 and \*1/\*1 patients. This effect was maintained when stratified by ethnic group (Caucasian and Asian) and by time since transplant (≤1 month, 3–6 months, 12–24 months). The authors additionally compared the effect of \*1/\*1 genotype versus \*1/\*3 genotype in 10 studies. The difference in dose-adjusted trough concentration was smaller at 19.83 ng/mL per mg/kg (95% CI: 13.86–25.80).

**Table 1** CYP3A5 alleles

Allele	Nucleotide variation	Effect on CYP3A5 protein <sup>a</sup>
*1	Wild type	Normal function
*2	27289G>T	Limited/no data
*3	6986T>C	Loss of function
*4	14665T>C	Limited/no data
*5	12952A>G	Limited/no data
*6	14690C>T	Loss of function
*7	27131_27132insA	Loss of function
*8	3699G>A	Limited/no data
*9	19386C>T 6986T>C	Limited no data

**Notes:** <sup>a</sup>Note that “normal” function is not indicative of the most common phenotype within the general population. In most ethnic groups, absence of functional CYP3A5 is most frequent. Adapted from Birdwell et al.<sup>13</sup> For any updates to this table or CPIC guideline see: <https://cpicpgx.org/guidelines/guideline-for-tacrolimus-and-cyp3a5/>.

**Table 2** Frequency of CYP3A5 alleles in different ethnic populations

Ethnic population	Frequency of CYP3A5 allele		
	CYP3A5 *1/*1 (%)	CYP3A5 *1/*3 (%)	CYP3A5 *3/*3 (%)
Caucasian	1	13–17	82–86
Black	37–45	40–54	9–15
Indian	2.5–11	38–57	32–60
Chinese	7.7	44.8	47.4

**Notes:** Data from Barry and Levine,<sup>11</sup> Rojas et al,<sup>14</sup> Tang et al,<sup>15</sup> Chen et al,<sup>16</sup> Boughton et al,<sup>17</sup> Niioka et al,<sup>18</sup> Chandel et al,<sup>19</sup> and Satoh et al.<sup>20</sup>

**Table 3** Key terminology and definitions

Patient profile	Allele	SNP	Effect	Tacrolimus trough level	Tacrolimus dose requirement
CYP3A5 expressers	*1/*1	rs6986 AA	mRNA splices correctly, leading to greater	↓	↑
	*1/*3	rs6986 AG	quantity of CYP3A5 enzyme	↓	↑
CYP3A5 nonexpressers	*3/*3	rs6986 GG	Incorrect mRNA splicing leading to nonfunctional CYP3A5 protein	↑	↓

**Abbreviation:** SNP, single-nucleotide polymorphism.

Another meta-analysis was completed in 2015 by Rojas et al<sup>14</sup> that included 37 observational studies looking at outcomes of tacrolimus dose-adjusted trough concentration, acute rejection, acute nephrotoxicity, and chronic nephrotoxicity among kidney transplant patients. Of the 37 studies, 31 reported tacrolimus trough concentration-to-dose ratio. Rojas' study<sup>14</sup> showed similar findings as the previous meta-analysis. Tacrolimus dose-adjusted trough concentrations were significantly lower in CYP3A5 expressers with a standardized mean difference of 42.46 (95% CI: 31.12–53.8) ng/mL per mg/kg/d at 1 week, 56.49 (95% CI: 40.94–72.03) ng/mL per mg/kg/d at 2 weeks, 50.73 (95% CI: 38.01–63.45) at 1 month, 70.45 (95% CI: 56.34–84.56) ng/mL per mg/kg/d at 3 months, 63.66 (95% CI: 49.16–78.16) ng/mL per mg/kg/d at 6 months, and 61.26 (95% CI: 45.99–76.53) ng/mL per mg/kg/d at 12 months.

Age does not appear to be a significant modifier of CYP3A5 genotypic differences in tacrolimus clearance. In one pediatric study of 48 patients, prepubertal children (age <12 years) showed significantly higher weight-adjusted tacrolimus dose requirement by approximately two-fold compared to those older than 12 years. This was observed among both the CYP3A5 nonexpresser and the CYP3A5 expresser groups. Additionally, patients with CYP3A5 \*1/\*3 genotype demonstrated higher tacrolimus dose requirement compared with CYP3A5 \*3/\*3 genotype, independent of age.<sup>29</sup>

In terms of intraindividual variability in tacrolimus concentrations, the evidence is conflicting. Yong et al<sup>30</sup> found that in a small group of healthy volunteers (n=29), nonexpressers had greater variability. The authors attributed this to the fact that nonexpressers are more reliant on CYP3A4 metabolism, which is more prone to enzyme inhibition or induction effects. However, another study compared the degree of variability in tacrolimus concentrations in 118 renal transplant recipients (37 expressers, 81 nonexpressers) and found that both groups had approximately 14% intraindividual variability, with no difference between the two groups.<sup>31</sup>

The effect of CYP3A5 polymorphism on clearance appears to be drug specific. The other calcineurin inhibitor commonly used in renal transplantation, ciclosporin, undergoes similar metabolic pathways as tacrolimus. Surprisingly, studies show conflicting results with respect to influence of CYP3A5 polymorphism on ciclosporin metabolism.<sup>23</sup> In a large study of 147 Chinese renal transplant recipients, carriers of the CYP3A5 \*1 allele in fact had lower dose-normalized trough ciclosporin concentrations compared to CYP3A5 \*3/\*3 individuals.<sup>32</sup> Two other studies had findings in the opposite direction, with those having CYP3A5 \*1 allele demonstrating higher trough concentration-to-dose ratio.<sup>33,34</sup>

Four additional studies found no difference between CYP3A5 expressers versus nonexpressers.<sup>35–38</sup> The differing effect of the polymorphism on the two drugs may be due to the lesser contribution of CYP3A5 to ciclosporin metabolism compared to tacrolimus.<sup>39</sup>

There is limited evidence regarding the effect of other CYP3A5 genetic variants on tacrolimus metabolism. In a genome-wide study 197 African American kidney or kidney–pancreas transplant recipients, CYP3A5\*6 and CYP3A5\*7 were associated with reduced tacrolimus clearance.<sup>26</sup> These two alleles lead to loss of protein function, similar to \*3, and is presumed to affect tacrolimus clearance to a similar degree. In this study, CYP3A5 polymorphism explained 34.1% of the variance in tacrolimus dose. Niioka et al<sup>18</sup> looked at the predictive value of CYP3A5 genotype on tacrolimus dose requirement in the first month posttransplant. Of 9 clinical or pharmacogenetic factors examined, only CYP3A5 genotype, weight, hematocrit, and total clearance of tacrolimus during continuous intravenous infusion were correlated with tacrolimus dose. The contribution of CYP3A5 genotype to tacrolimus dosing increased over the course of the first month posttransplant, accounting for 7.2% at day 14 and 20.4% by day 28. In another study, Wang et al<sup>40</sup> screened 768 SNPs in genes affecting the metabolism, transport, and calcineurin inhibition pathways of tacrolimus in a group of 96 renal transplant patients. In addition to 6986A>G, two additional CYP3A5 SNPs (*rs4646457*, *rs15524*) were identified to be significantly correlated with tacrolimus dose requirement.

## Genotype-based dosing

The effect of CYP3A5 \*1 and \*3 alleles on tacrolimus pharmacokinetics is consistently and extensively documented across a multitude of studies over the past 15 years.<sup>14,28</sup> These findings have led to strong interest in using CYP3A5 genotype to guide empiric tacrolimus dosing. The goal of genotype-based dosing is to provide empiric dosing that allows rapid achievement of therapeutic drug concentrations, particularly in the initial days after transplant. In one retrospective study, an empiric weight-based starting dose of 0.1 mg/kg was used to target a therapeutic range of 4–8 mcg/mL.<sup>16</sup> Among CYP3A5 nonexpressers (CYP3A5\*3/\*3), 50% of patients achieved C0 within the target range by day 3 of therapy. Among CYP3A5 expressers (CYP3A5\*1/\*3 or \*1/\*1), however, only 35.3% of patients achieved trough concentrations within the therapeutic range by day 3. Use of therapeutic drug monitoring did allow for rapid dosing correction. By day 7, 64.2% of expressers, compared to 55.4% of nonexpressers, achieved therapeutic trough concentrations.

These results suggest that *CYP3A5* genotyping is likely more useful if available before kidney transplant.

A prospective randomized controlled trial of *CYP3A5* genotype-based dosing was performed by Thervet et al.<sup>41</sup> Investigators enrolled 280 de novo renal transplant recipients from 12 sites. Half of the study population was randomized to standard dosing 0.2 mg/kg/d and the other half was randomized to genotype-based dosing 0.3 mg/kg/d for *CYP3A5* expressers and 0.15 mg/kg/d for nonexpressers. The proportion of patients with *CYP3A5* \*3/\*3 was high at 78.8%, with only 16.9% of patients being heterozygous for *CYP3A5* \*1/\*3 and 4.2% of patients being homozygous with *CYP3A5* \*1/\*1. These proportions were expected given the predominantly Caucasian population (89.9%). There was no difference between the standard and genotype-based dosing groups in the frequency of alleles. At day 3 after drug initiation, significantly more patients in the genotype-based dosing group achieved tacrolimus drug concentrations within the therapeutic range (43.2%) compared with the standard dosing group (29.1%,  $p=0.03$ ). The genotype-based dosing group also required fewer dose modifications, and the median days to achieve target therapeutic range was fewer. There were no differences observed in clinical outcomes including patient and graft survival, incidence of delayed graft function, acute rejection, biopsy-proven acute rejection, new-onset diabetes, or adverse events in the 3 months follow-up period. However, the study was underpowered to detect differences in these outcomes. Findings from Thervet et al<sup>42</sup> were not replicated in a more recent randomized controlled trial of similar design. In this second study, 240 patients living donor kidney recipients received either genotype-based dosing or weight-based dosing of tacrolimus immediately after transplant. The investigators found no difference between the two groups in proportion of patients within target therapeutic range at day 3 after transplant (37.4% weight-based dosing versus 35.6% genotype-based dosing,  $p=0.79$ ). The authors propose the discrepancy in findings compared to Thervet's study<sup>42</sup> may be related to differences in patient populations. In the Thervet study,<sup>42</sup> deceased donor kidney recipients started tacrolimus up to 7 days posttransplant, while in the other study all patients initiated tacrolimus immediately posttransplant. Interindividual differences due to gastrointestinal motility or corticosteroid dose in the first week after transplant may overshadow the effect of *CYP3A5* genotype.

The Clinical Pharmacogenetics Implementation Consortium published guidelines in 2015 with recommendations for *CYP3A5* genotype-based dosing of tacrolimus.<sup>13,43</sup> It

should be noted that these guidelines do not recommend for or against performing genotyping for tacrolimus dosing, given a lack of clear clinical benefit. Rather, the Clinical Pharmacogenetics Implementation Consortium is an international group with interest in facilitating clinical utility of pharmacogenetic testing if results are available.

## Which genotype is relevant: recipient or donor?

As it is *CYP3A5* intestinal and hepatic content that mediates differences in tacrolimus bioavailability, it is the kidney transplant recipient – rather than donor – genotype that exerts the influence on drug pharmacokinetics.<sup>44</sup> On the other hand, donor genotype dictates *CYP3A5* expression within the kidney. In the kidney, *CYP3A5* is the predominant *CYP3A* isoenzyme present. In one study of 21 kidney donors, the *CYP3A5*\*1/\*3 genotype was associated with 8-fold higher microsomal *CYP3A5* content in renal tissue, as well as 18-fold higher *CYP3A* catalytic activity ( $p=0.0001$  and  $0.0137$ , respectively).<sup>45</sup> One may hypothesize that *CYP3A5* genetic polymorphisms affect intrarenal metabolism of tacrolimus and potentially mediate renal effects of the drug.

Calcineurin inhibitors mediate nephrotoxicity via a vasoconstrictive mechanism at the afferent glomerular arteriole, resulting in decreased renal blood flow and decreased glomerular filtration rate.<sup>46</sup> In one case report, a kidney transplant recipient presented with severe tacrolimus-induced nephrotoxicity on renal biopsy despite low serum concentrations of tacrolimus.<sup>47</sup> The authors hypothesized that this phenomenon is explained by mismatch between the recipient and donor *CYP3A5* genotype. In this case, the recipient genotype was *CYP3A5* \*1/\*3, indicating “fast” metabolism mediated by expression of *CYP3A5* enzyme. This was observed, whereby the recipient had tacrolimus concentrations below the target range despite doubling of the tacrolimus dose over the course of 1 month. On postoperative day 31, renal biopsy performed for persistent delayed graft function showed prominent isometric vacuolization suggestive of calcineurin inhibitor toxicity. The donor genotype was *CYP3A5* \*3/\*3, representing low enzyme expression locally in the kidney graft. Potentially, this may contribute to higher tacrolimus concentrations in the kidney despite low serum concentrations, leading to nephrotoxicity.

Other authors have tested this hypothesis in kidney and other solid organ transplant recipients, with conflicting results. The study of calcineurin inhibitor nephrotoxicity is challenged by lack of a clear clinical phenotype to define the endpoint. In the largest of these studies, Kuypers et al<sup>48</sup>



examined the association between calcineurin inhibitor toxicity and tacrolimus C0, AUC0-12h, dose, and *CYP3A5* genotype. Calcineurin inhibitor toxicity was defined as de novo arteriolar hyalinization on biopsy histology. Three hundred four participants were included. As expected, the *CYP3A5* expressers showed a trend for higher tacrolimus dose requirement compared to nonexpressers. Higher tacrolimus dose requirement predicted occurrence of calcineurin inhibitor (CNI) toxicity, with 25% of patients on >0.2 mg/kg/d exhibiting toxicity, versus 16.2% of patients on 0.1–0.2 mg/kg/d and only 4.5% of those requiring <0.1 mg/kg/d ( $p<0.0001$ ). Systemic tacrolimus exposure, as measured by C0 and AUC, was not predictive of CNI toxicity risk. Rather, presence of a *CYP3A5*\*1 allele was associated with higher risk of CNI toxicity (32.4% versus 15.2%,  $p=0.01$ ) compared to those homozygous for *CYP3A5*\*3/\*3. The authors raise the possibility that the higher intrarenal metabolism of tacrolimus in *CYP3A5*\*1 individuals increases tacrolimus metabolite content in the kidney. However, it is unclear if and how tacrolimus metabolites cause CNI toxicity.

In two other studies, one with cardiac recipients and one with renal recipients, there was no correlation between *CYP3A5* genotype and nephrotoxicity.<sup>49,50</sup> Two other small studies of liver and kidney allograft recipients found the opposite and that the *CYP3A5* \*1 allele was protective against CNI nephrotoxicity.<sup>51,52</sup> A meta-analysis of 5 studies ( $n=867$ ) evaluating effect of *CYP3A5* genotype on chronic nephrotoxicity was inconclusive.<sup>14</sup> It neither demonstrated nor excluded an effect of genetic polymorphism on the risk chronic nephrotoxicity (odds ratio [OR]: 1.81, 95% CI: 0.89–3.68). The same authors also pooled results from 3 studies ( $n=363$ ) assessing risk of acute nephrotoxicity and determined that *CYP3A5* polymorphism had no impact (OR: 0.9, 95% CI: 0.45–1.83).<sup>14</sup>

In a small study of 25 African American healthy volunteers, *CYP3A5* genotype was correlated with blood pressure, with the *CYP3A5*\*1/\*1 genotype having a mean blood pressure 19.3 mmHg higher than those with *CYP3A5* \*3/\*3 genotype.<sup>45</sup> In a study of renal transplant recipients, the *CYP3A5* \*1 allele carriers likewise had higher adjusted systolic and diastolic blood pressure at 6 months and 24 months posttransplant compared to noncarriers, although the difference was not statistically significant.<sup>53</sup> There was also a trend for a higher number of antihypertensives used among the *CYP3A5* \*1 allele carriers, although this was not statistically significant either.

## Differences in tacrolimus clearance due to drug formulation

Tacrolimus is available in two oral formulations, either immediate-release tacrolimus (IR-Tac), administered twice daily, or extended-release tacrolimus (ER-Tac), administered once daily. The drug manufacturer (Astellas, Tokyo, Japan) recommends that stable patients can be converted between the two different formulations using 1:1 ratio.<sup>7</sup> The two formulations demonstrated similar rates of acute rejection, patient survival, and graft survival up to 12 months posttransplant.<sup>54</sup> Some evidence suggest that there may be differences between the formulations with regard to the effect of *CYP3A5* genotype on drug clearance.

In one study, Fan et al<sup>55</sup> found that in a cohort of 106 newly transplanted patients (ER-Tac  $n=45$ , IR-Tac  $n=61$ ), those taking the ER-Tac formulation required a higher total daily dose to achieve target trough concentrations in the first 21 days compared to those on IR-Tac.<sup>55</sup> This effect was particularly pronounced in the 40 patients who had a *CYP3A5* \*3/\*3 genotype. The mean daily dose of ER-Tac was greater than mean daily dose of IR-Tac in the cohort of *CYP3A5* nonexpressers at day 14, 21, and 28. In the high-expressor group, the difference in dose requirement was less pronounced. Another study demonstrated the opposite finding among 56 renal transplant recipients who took either ER-Tac ( $n=24$ ) or IR-Tac ( $n=32$ ) and underwent 24-h pharmacokinetic monitoring pretransplant, 1 month, and 1 year posttransplant.<sup>56</sup> In *CYP3A5* expressers, the AUC0-24h was 25% lower if ER-Tac was used compared to IR-Tac.

In another study at a Canadian transplant center, investigators examined the relationship between *CYP3A5* genotype and dose requirement in 60 stable renal transplant recipients (mean time posttransplant 7.4 years) who converted from IR-Tac to ER-Tac.<sup>57</sup> Patients were converted using 1:1 ratio initially, with therapeutic drug monitoring performed after conversion to determine subsequent dose adjustment. There were 43 (71.6%) patients who were nonexpressers (*CYP3A5*\*3/\*3) and 17 patients who were expressers (*CYP3A5* \*1/\*3 and \*1/\*1). A greater proportion of those who were *CYP3A5* expressers required a dose increase after switching to ER-Tac (69% versus 47%,  $p=0.004$ ). In addition, the expressers also required a greater degree of dose increase than the *CYP3A5* nonexpressers (45.3% versus 26.6% increase in dose,  $p=0.003$ ). One proposed mechanism is that the extended-release formulation increases gut transit time, thereby exposing the drug molecule to *CYP3A5* enzymes in the proximal small intestines for a longer duration. This

allows interindividual enzyme expression differences to exert greater influence on bioavailability.

## Role of *CYP3A5* polymorphism in tacrolimus drug interactions

It is well known that tacrolimus disposition is affected by numerous drug interactions, especially if concomitant medications can induce or inhibit either CYP3A enzyme activity or p-glycoprotein activity. However, not all patients are affected to the same degree by such interactions. Wide interindividual variation is observed both clinically and in pharmacokinetic studies.<sup>58,59</sup>

In one study, genetic polymorphism in *CYP3A5* partially explained interindividual variability in response to a tacrolimus–fluconazole drug interaction.<sup>60</sup> Fluconazole is an antifungal drug with known inhibitory activity on CYP3A enzymes, and therefore effects increased tacrolimus concentrations in renal transplant patients. In this retrospective study, 29 transplant recipients who had tacrolimus concentrations monitored while taking fluconazole 50–400 mg/d for median duration of 17 days received genotyping. Among the *CYP3A5*\*1/\*3 carriers, dose-corrected tacrolimus trough concentrations did not change significantly from baseline ( $1.26 \pm 1.23$  fold). The *CYP3A5*\*3/\*3 homozygotes, however, saw a  $3.28 \pm 2.34$  fold increase in dose-corrected tacrolimus trough concentrations, which was statistically significantly different from the heterozygous patients ( $p=0.04$ ). As a result, the CYP3A5 nonexpressers were at greater risk of supratherapeutic tacrolimus concentrations with 73.9% of patients having tacrolimus concentration  $>15$  ng/mL, while only 16.7% of CYP3A5 expressers experienced the same. In vitro studies have found that the fluconazole inhibits CYP3A4 activity to a far greater degree than CYP3A5.<sup>61</sup> The results of this study may be explained by the fact that CYP3A5 expressers can rely on an “escape pathway” in the form of CYP3A5 when fluconazole exerts inhibitory action on CYP3A4.

In a pediatric study of 48 patients, higher dose of methylprednisolone was correlated with higher dosing requirement for tacrolimus to achieve concentrations within the therapeutic range, regardless of *CYP3A5* genotype.<sup>29</sup> Higher dose of methylprednisolone was also associated with lower dose-normalized tacrolimus concentration independent of *CYP3A5* genotype. This suggests that the effect of *CYP3A5* genotype on drug interaction interindividual variability is drug specific. This may be related to the mechanism of drug

interaction, in which methylprednisolone causes enzyme induction while fluconazole causes enzyme inhibition.

## Effect of *CYP3A5* polymorphism on graft outcomes

In one of the earliest studies reporting clinical outcomes, MacPhee et al<sup>27</sup> found that in their cohort of 178 patients, those expressing CYP3A5 enzyme were significantly more likely to be below the target therapeutic range (39.6% of patients) compared to *CYP3A5*\*3/\*3 genotypes (8.8% of patients) in the first week posttransplant. Despite use of therapeutic drug monitoring, a significant segment of the *CYP3A5*\*1/\*1 or \*1/\*3 populations (17% of patients) continued to have blood concentrations below the therapeutic range in the second week after transplant. Only 4% of patients with the *CYP3A5*\*3/\*3 genotype had subtherapeutic tacrolimus concentrations in the second week. The difference in achieving therapeutic drug concentrations did not translate into any observed differences in rejection rates. However, the authors did note that CYP3A5 expressers had earlier rejection compared to nonexpressers (median 7 versus 13 days,  $p=0.005$ ). Tacrolimus target concentrations in this study were high (15–20 ng/μL in the first week, 10–15 ng/μL in the second week) when compared to contemporary practice. Moreover, immunosuppression therapy consisted of dual therapy only without antibody induction. The overall rejection rate was high at 42.7%. In the modern era, use of antibody induction is much more prevalent and may blunt the deleterious effect of subtherapeutic tacrolimus concentrations.

In a more recent study, *CYP3A5* polymorphism had no impact on renal function as measured by estimated glomerular filtration rate, acute rejection rates, or tacrolimus toxicity (nephrotoxicity and neurotoxicity).<sup>62</sup> This study involved only 103 renal transplant recipients. A larger study of 209 kidney transplant recipients similarly demonstrated no relationship between *CYP3A5* genotype and renal function, biopsy-proven acute rejection rates, delayed graft function, or tacrolimus toxicity on biopsy.<sup>44</sup> A third study from Thailand enrolled 164 patients in the first 3 months posttransplant. The rate of biopsy-proven acute rejection and median time to first rejection episode was similar in both CYP3A5 expressers and nonexpressers.<sup>63</sup> Recently, Flahault et al<sup>64</sup> published the largest observational study of 577 patients followed for up to 5 years. There was no association of *CYP3A5* genotype with biopsy result, renal function, biopsy-proven acute rejection, or graft survival.

In a meta-analysis of 10 studies (1,246 patients), Terrazzino et al<sup>28</sup> found that there was no difference in acute rejection rate between CYP3A5 expressers and nonexpressers (OR: 0.763, 95% CI: 0.532–1.094). On the other hand, in a newer and larger meta-analysis of 21 studies (n=2,185), Rojas reported the pooled estimate showed a higher likelihood of acute rejection in patients who are CYP3A5 expressers (OR: 1.32, 95% CI: 1.02–1.71) compared to nonexpressers.<sup>14</sup> The majority of studies (15 of 21) used renal biopsy for diagnosis of acute rejection, while the remaining studies used clinical criteria or a combination of clinical criteria and biopsy. When limited to only studies with biopsy-proven acute rejection, the difference between CYP3A5 expressers versus nonexpressers no longer existed (OR: 1.25, 95% CI: 0.96–1.62).

Overall, the evidence suggests little correlation between *CYP3A5* genotype and clinically important outcomes. This observation may be explained by several reasons. First, deviations outside the therapeutic range due to genetic polymorphisms appear to play a role early posttransplant when the patient is first initiated on a weight-based tacrolimus dose. The use of therapeutic drug monitoring can easily correct sub- or suprathreshold drug exposure quickly. Second, tacrolimus concentration is one of many contributing factors to acute rejection risk or graft function. Multiple other factors play a role. Existing studies may lack sufficient power to detect small differences in rejection risk related to *CYP3A5* genotype solely. Third, in the early period posttransplant, concomitant immunosuppression in the form of antibody induction therapy, mycophenolate, and high dose corticosteroid is prevalent. Any negative impact of tacrolimus underdosing is mitigated by use of these other medications.

## Beyond CYP3A5: multivariable prediction of tacrolimus pharmacokinetics

There is evidence that accounting for multiple genetic polymorphisms predicts tacrolimus clearance better than use of *CYP3A5* genotype alone. In one study, Gervasini et al<sup>62</sup> examined the relationship between both clinical outcomes and tacrolimus pharmacokinetics with *CYP3A4\*1B*, *CYP3A5\*3*, *CYP2C8\*3*, *CYP2J2\*7*, and *ABCB1* genes. The authors found that *CYP3A4\*1B* status additionally predicted tacrolimus pharmacokinetics on top of *CYP3A5* genotype. A recent analysis used both *CYP3A4\*22* and *CYP3A5\*3* genotypes to categorize patients as poor, intermediate, or extensive metabolizers of tacrolimus.<sup>65</sup> The combination of both genotypes was used to define optimal starting doses

for each category of metabolizer. Another larger study looked at tacrolimus trough concentrations from 695 renal transplant recipients analyzed against a broad panel of more than 700 genetic variants. Although *CYP3A5* was found to be the most important genetic variant, six additional variants were also found to each explain up to 2%–6% of the dosing variability in tacrolimus.<sup>12</sup> The authors suggest that dosing algorithms based on multiple clinical and genetic factors work better than dosing based on *CYP3A5* genotype alone. In a Han Chinese population, analysis of 10 SNPs covering 4 genes demonstrated that the *CYP3A5* gene played the predominant role in determining dose-adjusted tacrolimus trough concentrations.<sup>66</sup> However, in CYP3A5 nonexpressers only, additional SNPs in the genes coding for *CYP3A4*, *MDR1*, *NR1I2* also predicted tacrolimus trough concentrations.

*CYP3A5* genotype has been included as a parameter in pharmacokinetic modeling to predict tacrolimus dose requirement. In one externally validated model, the authors used the assumption that tacrolimus clearance was 30% higher (95% CI: 13%–46%) and bioavailability 18% lower (95% CI: 2%–29%) in CYP3A5 expressers compared with nonexpressers.<sup>67</sup> A dosing strategy based on Bayesian dose adjustment with this model successfully led to 65% of patients achieving mean tacrolimus concentrations within an acceptable target range, compared to 32% using a weight-based strategy. Not all dosing algorithms have been successful when applied to an external population. When the dosing algorithm published by Passey et al<sup>17,68</sup> was implemented in an independent cohort, the algorithm was found to be poorly predictive of tacrolimus clearance. In this cohort of 255 patients, the correlation of dose-normalized whole blood trough concentrations had low correlation with clearance predicted by the equation from the algorithm.

Genetic variation in proteins associated with CYP activity may also impact tacrolimus disposition. Cytochrome P450 oxidoreductase (POR) is a protein that interacts with CYP through electron donation and is considered essential for CYP-mediated drug biotransformation. One SNP in particular, *POR\*28* (*rs1057868*; C>T), increases in vivo CYP3A activity.<sup>21</sup> In one study of 71 healthy volunteers, *POR\*28* carriers who were CYP3A5 expressers had 40% lower tacrolimus exposure compared to CYP3A5 expressers with wild type *POR*.<sup>69</sup> Interestingly, the population of CYP3A5 nonexpressers did not demonstrate any effect by *POR* SNP. In this case, drug metabolism is wholly dependent on CYP3A4, which does not interact in the same manner with POR.



## Conclusion and future directions

Over the past two decades, the role of *CYP3A5* genetic polymorphism in influencing tacrolimus dose requirement has been extensively documented. The best studied polymorphism is the SNP 6986A>G. The mutant variant bearing G nucleotide is denoted by \*3 allele. In most ethnic populations, except blacks, homozygous \*3/\*3 is the most frequent genotype and is associated with *CYP3A5* nonexpression. Tacrolimus clearance is approximately two-fold lower in nonexpressers, and dose-adjusted trough concentrations are higher. The wild-type variant bearing A nucleotide is denoted by \*1 allele and is associated with *CYP3A5* enzyme expression. *CYP3A5* expressing individuals have lower tacrolimus trough concentrations by 40%–50% when provided the standard weight-based dose. These individuals should be provided empiric doses 1.5–2 times higher than the usual starting dose. Nevertheless, clinical use of genotype-based dosing for tacrolimus has not been widely adopted. To date, majority of studies have not demonstrated benefit in clinically important outcomes such as acute rejection, risk of nephrotoxicity, or graft survival with using genotype-based dosing. *CYP3A5* genotype has been noted to impact patient response to drug interaction with fluconazole and differential absorption of drug formulations.

There is a lack of studies measuring clinical outcomes associated with use of multivariable dosing algorithms compared to weight-based dosing. Further studies are needed to clarify the effect of renal *CYP3A5* genotype on risk of tacrolimus-induced nephrotoxicity. Currently available studies report conflicting results. Preliminary evidence suggests that epigenetic changes affect *CYP3A4* and *3A5* expression, but these have not been studied in human trials.<sup>70</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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