### Title

Higher number of tacrolimus dose adjustments in kidney transplant recipients who are extensive and intermediate CYP3A5 metabolizers.




### Journal

Clinical Transplantation, 37(4)



### Authors

Reininger, Kevin
Onyeaghala, Guillaume
Anderson-Haag, Teresa
et al.



### Publication Date

2023-04-01

### DOI

10.1111/ctr.14893

Peer reviewed

HHS Public Access

Author manuscript

*Clin Transplant*. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

*Clin Transplant*. 2023 April ; 37(4): e14893. doi:10.1111/ctr.14893.

# Higher number of tacrolimus dose adjustments in kidney transplant recipients who are extensive and intermediate CYP3A5 metabolizers

**Kevin A. Reininger**[*,1], **Guillaume Onyeaghala**[*,2,3], **Teresa Anderson-Haag**[1], **David Schladt**[2], **Baolin Wu**[4], **Weihua Guan**[4], **Casey R. Dorr**[2,3], **Rory Remmel**[5], **Roslyn Mannon**[6], **Arthur Matas**[7], **William S. Oetting**[8], **Paul Stahler**[9], **Ajay Israni**[3,10], **Pamala A. Jacobson**[8]

[1]Department of Pharmacy, Hennepin County Medical Center, Minneapolis, Minnesota

[2]Hennepin Healthcare Research Institute, Minneapolis, Minnesota

[3]Division of Nephrology, Hennepin Healthcare, University of Minnesota, Minneapolis, Minnesota

[4]Department of Biostatistics, University of Minnesota, Minneapolis, Minnesota

[5]Department of Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota

[6]Division of Nephrology, University of Nebraska, Omaha, Nebraska

[7]Department of Surgery, University of Minnesota, Minneapolis, Minnesota

[8]Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, Minnesota

[9]Division of Surgery, Hennepin Healthcare, Minneapolis, Minnesota

[10]Department of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota

## Abstract

Kidney transplant recipients carrying the CYP3A5*1 allele have lower tacrolimus troughs, and higher dose requirements compared to those with the CYP3A5*3/*3 genotype. However, data on the effect of CYP3A5 alleles on post-transplant tacrolimus management are lacking.

Corresponding Author: Pamala Jacobson, jacob117@umn.edu, Address: 7-151 Weaver-Densford Hall, 308 Harvard St. SE, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, Phone: 612-624-6118.

*these authors equally contributed to the research

**Authorship.** Kevin A. Reininger: Participated in research design, participated in the writing of the paper, participated in the performance of the research, participated in data analysis. Guillaume Onyeaghala: Participated in research design, participated in the writing of the paper, participated in data analysis. Teresa Anderson-Haag: Participated in research design. David Schaldt: Participated in research design, participated in data analysis. Baolin Wu: Participated in research design, participated in data analysis. Weihua Guan: Participated in research design, participated in data analysis. Casey R. Dorr: Participated in research design. Rory Remmel: Participated in research design. Roslyn Mannon: Participated in research design. Arthur Matas: Participated in research design. William S. Oetting: Participated in research design. Ajay Israni: Participated in research design, participated in the performance of the research. Paul Stahler: Participated in research design. Pamala A. Jacobson: Participated in research design, participated in the writing of the paper, participated in the performance of the research

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by Transplantation.

The effect of CYP3A5 metabolism phenotypes on the number of tacrolimus dose adjustments and troughs in the first six months post-transplant was evaluated in 78 recipients (64% Caucasians). Time to first therapeutic concentration, percentage of time in therapeutic range (TTR), and estimated glomerular filtration rate were also evaluated.

Fifty-five kidney transplant recipients were CYP3A5 poor metabolizers (PM), 17 were intermediate metabolizers (IM), and 6 were extensive metabolizers (EM). Compared to PMs, EMs/IMs had significantly more dose adjustments (6.1 vs 8.1, p=0.015). Overall, 33.82% of trough measurements resulted in a dose change. There was no difference in the number of tacrolimus trough measurements between PMs and EM/IMs. The total daily tacrolimus dose requirements were higher in EMs and IMs compared to PMs (<0.001). TTR was ~50% in the PMs and EMs/IMs groups.

CYP3A5 EM/IM metabolizers have more tacrolimus dose changes and higher dose requirements which increases clinical management complexity. Larger studies are needed to assess the cost and benefits of including genotyping data to improve clinical management.

**Keywords**

Kidney transplants; CYP3A5; clinical management; tacrolimus

## 1. Introduction

Tacrolimus-based regimens are standard of care for maintenance immunosuppression for nearly every organ including the kidney. Use of tacrolimus is complex due to its narrow therapeutic index and high inter- and intra-patient variability as well as time varying exposure levels that necessitates therapeutic drug monitoring to ensure appropriate trough blood concentrations. Low concentrations increase the risk of rejection and high concentrations increase the risk of toxicity. In recent years, high intra-patient variability has been associated in some studies with a greater risk of adverse graft outcomes[1–5].

Variability in tacrolimus trough concentrations among patients is associated with non-adherence; interactions with food, other drugs, disease; and genetic variation[6]. Tacrolimus is extensively metabolized by the cytochrome P450 (CYP) 3A5 enzyme which is a highly polymorphic gene. Common CYP3A5 variant alleles such as CYP3A5*3, *6, and *7 are loss of function (LoF) alleles encoding for a nonfunctional protein. Most Caucasians carry one or two CYP3A5*3 alleles. African Americans are much less likely to carry CYP3A5 LoF alleles and as a result have significantly greater clearance of tacrolimus, lower trough concentrations, and higher dose requirements than Caucasians[7–10]. While CYP3A5 genotype has reliably demonstrated effect on metabolism and dose requirements of tacrolimus, it has inconsistently been associated with estimated glomerular filtration rate (eGFR), acute rejection, and graft survival[11–13]. Given the strong association between genetic variation and dose the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines for tacrolimus dosing based on CYP3A5 phenotypes[14].

The impact of CYP3A5 phenotype on clinical management of tacrolimus (such as utilization of healthcare resources) has been poorly studied. The primary objectives of this study

were to evaluate if CYP3A5 metabolism phenotypes were associated with the number of tacrolimus trough concentrations measured and dose adjustments made to achieve trough concentrations in the therapeutic range in the first 6 months posttransplant.

## 2. Material and Methods

### 2.1 Study Population

Study participants were kidney transplant patients enrolled from Hennepin Healthcare in the National Institutes of Health funded Genomics of Transplantation (GEN03) multi-center, prospective, observational, genome wide association study (GWAS) between 2013 and 2016[8,15–17]. Participants for the current study were selected from the GEN03 participants and were included if they received *de novo* immediate release tacrolimus-based maintenance immunosuppression and had CYP3A5 genetic information available from the GWAS. Patients were excluded if they were age < 18 years at time of enrollment into GEN03, were switched from tacrolimus to alternative therapy within 6 months of transplant, had incomplete genotype data available for the CYP3A5 alleles *3, *6, and *7, or had incomplete 6-month follow-up data within the electronic medical record (EMR). This study was approved by the local institutional review board (IRB #12–3506).

### 2.2 Data Collection

Data were obtained from the GEN03 study database with supplemental data collected from the EMR for the first 6 months post-transplant. Data obtained prospectively through the GEN03 GWAS study database included demographics, CYP3A5 genotypes, acute rejection, and serum creatinine at 1, 3, and 6 months post-transplant. Supplemental data collected to evaluate effect on clinical management included all measured tacrolimus trough blood concentrations, dose at time of trough measurement, if dose adjustments were made, timing of trough concentration relative to dose, and goal trough range. Due to the difficulty in consistently identifying longitudinal drug-drug interactions through review of medical records, concomitant drug-drug interactions were not recorded.

### 2.3 Genotype Data

Three common CYP3A5 LoF genetic variants [CYP3A5*3 (rs776746), CYP3A5*6 (rs10264272), and CYP3A5*7 (rs41303343)] were taken from the GWAS chip for each participant and used in this analysis[15]. Genotype data were then used to create CYP3A5 metabolism phenotypes which were assigned based on the CPIC guidelines for CYP3A5 genotype and tacrolimus dosing[7]. Patients with any two LoF alleles were designated poor metabolizers (PM), with any one LoF allele were designated intermediate metabolizers (IM), and with no LoF alleles were designated extensive metabolizers (EM).

### 2.4 Immunosuppression Management

Patients received maintenance immunosuppression of tacrolimus, mycophenolate mofetil, and corticosteroids tapered to a maintenance dose of prednisone 5 mg daily over 14 to 90 days. Patients at high risk for rejection were initiated at a dose of tacrolimus 0.15 mg/kg/day based on ideal body weight with a tacrolimus trough concentration target of 8–12 ng/mL for the first three months followed by 5–10 ng/mL lifelong thereafter. High risk determination

was based on at least two of the following risk factors: complete 6 antigen HLA mismatch, cytotoxic panel reactive antibody >20%, African American race, age < 40 years, donor specific antibody (DSA) deemed clinically relevant, and re-transplantation. Patients with standard or low risk of rejection were initiated at a dose of tacrolimus 0.1 mg/kg/day based on ideal body weight with a lifelong tacrolimus trough concentration target of 4–8 ng/mL. Antibody induction was antithymocyte globulin or basiliximab, depending on rejection risk.

### 2.5 Outcomes and Statistical Analysis

Participant baseline characteristics and clinical outcomes were summarized descriptively in Table 1 using means for continuous variables and frequency counts with percentage for categorical variables. The primary analysis was the association of CYP3A5 metabolism phenotypes with number of tacrolimus trough concentrations measured and number of tacrolimus dose adjustments for any reason made in the first 6 months posttransplant. The number of tacrolimus trough measurements was defined as the total number of trough concentrations reported in the EMR and determined to be appropriately obtained (within 11–13 hours of previous dose with a documented collection time). The number of tacrolimus dose adjustments was defined as all dose increases or decreases, and was determined through review of pharmacy records in the EMR. Secondary endpoints were time to first therapeutic trough concentration, percentage of time in therapeutic range (TTR), and eGFR at 6 months. Time to first therapeutic trough concentration was defined as first trough measurement within goal range from the time of kidney transplant. TTR was calculated using the Rosendaal method[18]. Trough measurements reported as < 2 ng/mL were imputed as 1.99 ng/mL. eGFR was estimated using Modification of Diet in Renal Disease (MDRD) equation[19]. The association between our primary endpoints (number of tacrolimus trough concentrations and number of tacrolimus dose adjustments) and CYP3A5 metabolism phenotypes was evaluated using quasi-likelihood based Poisson regression adjusted for age at transplant, gender, body mass index (BMI) at baseline, history of diabetes at baseline and initial tacrolimus dose. The EM and IM phenotype groups were combined and compared to the PM group.

For our secondary endpoints, the association between TTR and eGFR with CYP3A5 metabolism phenotypes was evaluated using multivariable linear regression analysis with TTR and eGFR modeled as continuous variables. The association between time to first therapeutic trough and CYP3A5 metabolism phenotype was evaluated using a Cox regression analysis. Co-variates for the linear and Cox regression models were the same as those used in the primary analysis. The association between dose normalized trough concentrations [tacrolimus trough (ng/mL) / total daily dose (mg)] over time and CYP3A5 metabolism phenotypes was evaluated using mixed effect regression model. To account for the change in trough concentrations over time in our mixed effect regression model, we included time in an interaction term with the binary phenotype (EM/IM compared to PMs) and as a random coefficient. All analyses were performed using STATA 14.

## 3. Results

Ninety-three patients were enrolled into the GEN03 GWAS study at Hennepin Healthcare and evaluated for inclusion. Five patients were excluded because they received a *de novo* cyclosporine-based regimen, eight were excluded for incomplete genotype information, and two were excluded for incomplete follow-up. A total of 78 patients were included in this analysis.

Baseline characteristics are described in Table 1. Fifty-five patients (70.5%) were PMs, seventeen patients (21.8%) were IMs, and six patients (7.7%) were EMs. Multiple tacrolimus trough measurements were collected per recipient and a total of 1533 were identified in the 6 months after kidney transplant. After excluding trough measurements without documented collection time after previous dose or where the previous dose was not taken 11–13 hours prior to sampling, 1425 troughs (93%) were available for evaluation (mean of 18.2 troughs per individual).

The number of trough measurements and dose adjustments by metabolism phenotype and association analyses are shown in Table 2. Overall 33.82% (482/1425) of trough measurements resulted in a dose change. Patients with the CYP3A5 EM/IM phenotypes had 1.28 times (95% CI: 1.05; 1.56, p=0.015) more tacrolimus dose adjustments when compared to PMs. EM/IM and PM phenotypes had on average 8.1 and 6.1 dose adjustments, respectively. Patients with CYP3A5 EM/IM phenotypes did not have more tacrolimus trough measurements compared to PMs (p=0.66).

For our secondary outcomes, we found that CYP3A5 metabolism phenotypes were not associated with time to first therapeutic trough, TTR, and eGFR at 6 months (Table 2). The time to first therapeutic trough was not different between CYP3A5 EM/IM and PM phenotypes [hazard ratio (HR) = 0.86 (0.49; 1.49, p=0.59)]. Both CYP3A5 metabolism phenotype groups had ~50% TTR and there was no difference between the groups (51.4% vs 49.7%, p=0.72). The eGFR at 6 months was not different between the EM/IM and PMs groups (p=0.81). Trough concentrations were not different across the phenotypes (Supplemental Table 1). EM and IMs had significantly higher dose requirements and lower dose-normalized troughs relative to the PMs (Supplemental Table 1 and 2).

## 4. Discussion

This study identified that the number of tacrolimus dose adjustments were associated with the CYP3A5 metabolism phenotype in adult kidney transplant recipients. There were significantly more dose adjustments in the EM/IM phenotype group compared to the PM group in the first 6 months post transplant (8.1 vs 6.1 respectively, p=0.015). This is consistent with expectations since most transplant protocols use a standardized tacrolimus dose which has been designed and refined for the PM phenotype (i.e. CYP3A5 non-expressers) [20], and several studies have previously reported an association between the inclusion of CYP3A5 phenotype information and improved clinical outcomes and management of kidney transplant recipients [21,22]. A randomized controlled trial of 280 kidney transplant recipients found that participants who received a tacrolimus dose based

on their CYP3A5 phenotype required fewer dose adjustments[23]. Another randomized controlled trial of 63 kidney transplant recipients found that the genotype-guided group had an increased proportion of participant reaching therapeutic tacrolimus concentrations within the first few days post transplant[21]. In a retrospective cohort study of 125 adult kidney transplant recipients, those who had a CYP3A5 EM/IM phenotype had higher total hospitalization costs compared to PM[22]. A recent study in 85 pediatric kidney and heart transplant recipients also found that CYP3A5 phenotype was associated with greater healthcare resources utilization (such as number of dose adjustment and tacrolimus troughs) among heart transplant recipient, but not kidney transplant recipients[24]. However, other studies reported that genotype based tacrolimus dosage did not decrease the incidence of long term clinical outcomes such as the incidence of biopsy-proven acute rejection and graft survival in kidney transplant recipients[21,23,25].

While it may seem that increased number of dose adjustments is a minor issue, each dose adjustment represents an opportunity for a medication error. Dose adjustments are generally communicated electronically or by phone which may be forgotten, missed, or misunderstood by patients. Frequent medication changes after transplant have been shown to affect medication adherence[26,27]. A review of lung transplant recipients found that 74% of medication errors stemmed from improperly updated pill containers or medication lists[28]. As the number of troughs measured and dose changes made increases, resource utilization from laboratory, phlebotomy, pharmacy, and nursing may be increased in an already resource limited setting. We did not evaluate the cost of these resources, but in a recent study, total first year Medicare reimbursement differed by CYP3A5 phenotype where EM had greater spending ($p = 0.02$)[29]. A recent study showed that *de novo* DSA development was more likely to occur in CYP3A5 expressors (EM or IMs) than nonexpressors (PM) (19% vs 10%, p=0.02) and that expressors experienced more antibody mediated rejection and lower survival rates than non-expressors[30]. Management of antibody mediated rejection may be associated with greater costs.

In our study, there was no difference in the number of trough measurements by CYP3A5 phenotype. This is not surprising since most transplant centers have set therapeutic drug monitoring protocols in the early posttransplant period and additional measurements in between protocol directed troughs may not be necessary after a dose change given the regularity of protocol troughs. Time in therapeutic range in the first 6 months post-transplant was similar between the CYP3A5 phenotype groups (49.7%–51.0%) and was lower than optimal TTR. Time in therapeutic range has been shown to be important towards clinical outcomes in numerous studies[31–33].

We observed a low frequency of biopsy-proven acute rejection ($n = 2$) in our study population. A larger number of immunologic events will be needed to determine the role of CYP3A5 phenotype in the risk of rejection, as 46 DSA events were needed to detect an association between *de novo* DSA development and CYP3A5 expression status [30,34]. A previous meta-analysis comparing CYP3A5*3 and CYP3A5*1 alleles showed an increased risk of acute rejection for patients that carry a CYP3A5*1 allele[35].

The differences in tacrolimus dose requirements and dose-normalized troughs among the CYP3A5 metabolism phenotypes are well known[20]. We also found significantly higher tacrolimus dose requirements in EM (~4-fold) and IM (~1.6-fold) relative to patients with a PM phenotype (p=<0.001). Dose-normalized troughs were 2-fold higher in the PM phenotype group compared to the EM/IM group (p=0.02).

We were not able to exclude the role of race as a confounder in our study, as the CYP3A5*1 genotype is highly correlated with African ancestry. Further, we did not evaluate patient non-adherence or dietary information which may impact tacrolimus absorption. The presence of CYP3A4*22 and drug-drug interactions which may have resulted in a small subset of patients (3–5%) with a misclassified metabolism phenotype. These factors may influence the number of trough measurements and dose adjustments and an understanding all the factors which increase resource utilization may provide an opportunity to provide genotype directed therapeutic drug monitoring, early intervention in at risk individuals thereby improving tacrolimus post-transplant management. Future studies should evaluate additional endpoints such as length of stay, time to stable dose and cost expenditures in a larger population.

Pharmacogenomic testing is becoming more common in clinical practice, and patients are now presenting for transplantation with testing already conducted. Patients without testing could be genotyped while on the waitlist and available at time of transplant for guiding the starting dose or decisions about the regularity of trough monitoring. CYP3A5 genotypes can be measured alongside additional genetic variants as part of a multigene panel which would also provide information relevant for drugs that patients may receive over the lifetime of transplant care. Higher tacrolimus doses are often used in African American patients due to lower HLA matching, and pharmacogenomic testing provides a method to move away from race-based medication decisions and instead use pharmacogenomic testing to select treatments, doses and direct post-transplant monitoring.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements and Funding

The authors would like to thank the investigators, and clinical research staff who participated in the creation of the DeKAF and GEN03 GWAS cohorts. These cohorts were supported by NIH/NIAID grants 5U19-AI070119 and 5U01-AI058013. Additional support was provided by the Hennepin Healthcare Research Institute and R01-AI140303.

## Data Availability Statement

Aggregated data that support the findings of this study are available from the corresponding author upon reasonable request.

## Abbreviations Page

| | |
|---|---|
| **BMI** | body mass index |
| **CI** | confidence interval |

| | |
|---|---|
| **CPIC** | Clinical Pharmacogenomics Implementation Consortium |
| **CYP3A4** | Cytochrome P450 (CYP) 3A4 enzyme |
| **CYP3A5** | Cytochrome P450 (CYP) 3A5 enzyme |
| **DeKAF** | the Deterioration of Kidney Allograft Function study |
| **dnDSA** | *de novo* Donor Specific Antibody |
| **DSA** | Donor Specific Antibody |
| **eGFR** | estimated glomerular filtration rate |
| **EM** | extensive metabolizer |
| **EMR** | electronic medical record |
| **GEN03** | Genomics of Kidney Transplantation study |
| **GWAS** | genome-wide association study |
| **HR** | hazard ratio |
| **IM** | intermediate metabolizer |
| **IPV** | intra-patient variability |
| **kg** | kilogram |
| **LoF** | loss of function |
| **MDRD** | Modification of Diet in Renal Disease |
| **mg** | milligram |
| **mL** | milliliter |
| **ng** | nanograms |
| **NIAID** | National Institute of Allergy |
| **NIH** | National Institutes of Health |
| **PM** | poor metabolizer |
| **TTR** | time in therapeutic range |

## Works Cited

1. Whalen HR, Glen JA, Harkins V, et al. High Intrapatient Tacrolimus Variability Is Associated with Worse Outcomes in Renal Transplantation Using a Low-Dose Tacrolimus Immunosuppressive Regime. Transplantation. 2017;101(2):430–436. doi:10.1097/TP.0000000000001129 [PubMed: 26950724]
2. Sablik KA, Clahsen-Van Groningen MC, Hesselink DA, Van Gelder T, Betjes MGH. Tacrolimus intra-patient variability is not associated with chronic active antibody mediated rejection. PLoS One. 2018;13(5):1–13. doi:10.1371/journal.pone.0196552

3. Shuker N, Shuker L, van Rosmalen J, et al. A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. Transpl Int. 2016;29(11):1158–1167. doi:10.1111/tri.12798 [PubMed: 27188932]
4. Huang CT, Shu KH, Ho HC, Wu MJ. Higher Variability of Tacrolimus Trough Level Increases Risk of Acute Rejection in Kidney Transplant Recipients. Transplant Proc. 2016;48(6):1978–1980. doi:10.1016/j.transproceed.2016.02.081 [PubMed: 27569931]
5. Sapir-Pichhadze R, Wang Y, Famure O, Li Y, Kim SJ. Time-dependent variability in tacrolimus trough blood levels is a risk factor for late kidney transplant failure. Kidney Int. 2014;85(6):1404–1411. doi:10.1038/KI.2013.465 [PubMed: 24336032]
6. Gonzales HM, McGillicuddy JW, Rohan V, et al. A comprehensive review of the impact of tacrolimus intrapatient variability on clinical outcomes in kidney transplantation. Am J Transplant. 2020;20(8):1969–1983. doi:10.1111/ajt.16002 [PubMed: 32406604]
7. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. Clin Pharmacol Ther. 2015;98(1):19–24. doi:10.1002/cpt.113 [PubMed: 25801146]
8. Oetting WS, Schladt DP, Guan W, et al. Genomewide Association Study of Tacrolimus Concentrations in African American Kidney Transplant Recipients Identifies Multiple CYP3A5 Alleles. Am J Transplant. 2016;16(2):574–582. doi:10.1111/ajt.13495 [PubMed: 26485092]
9. Trofe-Clark J, Brennan DC, West-Thielke P, et al. Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients. Am J Kidney Dis. 2018;71(3):315–326. doi:10.1053/j.ajkd.2017.07.018 [PubMed: 29162334]
10. Tsuchiya N, Satoh S, Tada H, et al. Influence of CYP3A5 and MDR1 (ABCB1) polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplantation. 2004;78(8):1182–1187. doi:10.1097/01.TP.0000137789.58694.B4 [PubMed: 15502717]
11. Hesselink DA, Van Schaik RHN, Van Agteren M, et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients. Pharmacogenet Genomics. 2008;18(4):339–348. doi:10.1097/FPC.0b013e3282f75f88 [PubMed: 18334918]
12. Asempa TE, Rebellato LM, Hudson S, Briley K, Maldonado AQ. Impact of CYP3A5 genomic variances on clinical outcomes among African American kidney transplant recipients. Clin Transplant. 2018;32(1):2–3. doi:10.1111/ctr.13162
13. Yaowakulpatana K, Vadcharavivad S, Ingsathit A, et al. Impact of CYP3A5 Polymorphism on Trough Concentrations and Outcomes of Tacrolimus Minimization during the Early Period after Kidney Transplantation. Vol 72.; 2016:277–283. doi:10.1007/s00228-015-1990-0
14. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;1(98):19–24. doi:10.1002/cpt.113
15. Li YR, van Setten J, Verma SS, et al. Concept and design of a genome-wide association genotyping array tailored for transplantation-specific studies. Genome Med. 2015;7(1):1–13. doi:10.1186/s13073-015-0211-x [PubMed: 25606059]
16. Oetting WS, Wu B, Schladt DP, et al. Genome-wide association study identifies the common variants in CYP3A4 and CYP3A5 responsible for variation in tacrolimus trough concentration in Caucasian kidney transplant recipients. Pharmacogenomics J. 2018;18(3):501–505. doi:10.1038/tpj.2017.49 [PubMed: 29160300]
17. Keating BJ, Van Setten J, Jacobson PA, et al. Design and Implementation of the International Genetics and Translational Research in Transplantation Network. Transplantation. 2015;99(11):2401–2412. doi:10.1097/TP.0000000000000913 [PubMed: 26479416]
18. Torn M, Bollen WLEM, Van Der Meer FJM, Van Der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med. 2005;165(13):1527–1532. doi:10.1001/archinte.165.13.1527 [PubMed: 16009869]
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med. 1999;130(6):461–470. doi:10.7326/0003-4819-130-6-199903160-00002 [PubMed: 10075613]

20. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. doi:10.1002/cpt.113
21. Anutrakulchai S, Pongskul C, Kritmetapak K, Limwattananon C, Vannaprasaht S. Therapeutic concentration achievement and allograft survival comparing usage of conventional tacrolimus doses and CYP3A5 genotype-guided doses in renal transplantation patients. Br J Clin Pharmacol. 2019;85(9):1964–1973. doi:10.1111/BCP.13980 [PubMed: 31077425]
22. Vannaprasaht S, Limwattananon C, Anutrakulchai S, Chan-on C. Effect of CYP3A5 genotype on hospitalization cost for kidney transplantation. Int J Clin Pharm. 2019;41(1):88–95. doi:10.1007/S11096-018-0750-5 [PubMed: 30446894]
23. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721–726. doi:10.1038/CLPT.2010.17 [PubMed: 20393454]
24. Pasternak AL, Marshall VD, Gersch CL, Rae JM, Englesbe M, Park JM. Evaluating the Impact of CYP3A5 Genotype on Post-Transplant Healthcare Resource Utilization in Pediatric Renal and Heart Transplant Recipients Receiving Tacrolimus. Pharmgenomics Pers Med. 2021;14:319. doi:10.2147/PGPM.S285444 [PubMed: 33746516]
25. Pallet N, Etienne I, Buchler M, et al. Long-Term Clinical Impact of Adaptation of Initial Tacrolimus Dosing to CYP3A5 Genotype. Am J Transplant. 2016;16(9):2670–2675. doi:10.1111/AJT.13788 [PubMed: 26990694]
26. Patzer RE, Serper M, Reese PP, et al. Medication understanding, non-adherence, and clinical outcomes among adult kidney transplant recipients. Clin Transplant. 2016;30(10):1294–1305. doi:10.1111/ctr.12821 [PubMed: 27447351]
27. Gordon EJ, Gallant M, Sehgal AR, Conti D, Siminoff LA. Medication-taking among adult renal transplant recipients: Barriers and strategies. Transpl Int. 2009;22(5):534–545. doi:10.1111/j.1432-2277.2008.00827.x [PubMed: 19175560]
28. Irani S, Seba P, Speich R, Boehler A. Medication Errors: An Important Component of Nonadherence to Medication in an Outpatient Population of Lung Transplant Recipients. Vol 7.; 2007:2561–2566. doi:10.1111/j.1600-6143.2007.01962.x
29. Obayemi JE;Keating BJ; Lentine K; Schnitzler M; Xiao H; Dharnidharka V; Axelrod DA. Impact of Cypa5 Status on the Clinical and Financial Outcomes of Kidney Transplant. Scientific Registry of Transplant Recipients. https://www.srtr.org/media/1505/obayemi-cyp.pdf. Published 2021.
30. Friebus-Kardash J, Nela E, Möhlendick B, et al. Development Of De Novo Donor-Specific HLA Antibodies and ABMR in Renal Transplant Patients Depends on CYP3A5 Genotype. Transplantation. 2021;(Jul 1):Epub ahead of print. doi:10.1097/tp.0000000000003871
31. Song T, Yin S, Jiang Y, et al. Increasing Time in Therapeutic Range of Tacrolimus in the First Year Predicts Better Outcomes in Living-Donor Kidney Transplantation. Front Immunol. 2019;10. doi:10.3389/FIMMU.2019.02912 [PubMed: 30723470]
32. Davis S, Gralla J, Klem P, et al. Lower tacrolimus exposure and time in therapeutic range increase the risk of de novo donor-specific antibodies in the first year of kidney transplantation. Am J Transplant. 2018;18(4):907–915. doi:10.1111/ajt.14504 [PubMed: 28925597]
33. Pierce DR, West-Thielke P, Hajjiri Z, et al. Clinical Implications of Tacrolimus Time in Therapeutic Range and Intrapatient Variability in Urban Renal Transplant Recipients Undergoing Early Corticosteroid Withdrawal. Transplant direct. 2021;7(6). doi:10.1097/TXD.0000000000001155
34. Wiebe C, Rush DN, Nevins TE, et al. Class II eplet mismatch modulates tacrolimus trough levels required to prevent donor-specific antibody development. J Am Soc Nephrol. 2017;28(11):3353–3362. doi:10.1681/ASN.2017030287 [PubMed: 28729289]
35. . Rojas L, Neumann I, Herrero MJ, et al. Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J. 2015;15:38–48. doi:10.1038/tpj.2014.38 [PubMed: 25201288]

**Table 1.**

Baseline Recipient Characteristics by CYP3A5 Metabolism Phenotype

| | Poor Metabolizer (n = 55) | Intermediate Metabolizer (n = 17) | Extensive Metabolizer (n = 6) |
|---|---|---|---|
| N (%) Male | 30 (54.5) | 11 (64.7) | 5 (83.3) |
| Age at Transplant, y (mean + SD) | 50.9 (14.2) | 46 (14.5) | 44.5 (10.7) |
| BMI at Transplant (mean + SD) | 28 (5.9) | 28.8 (5.5) | 31.1 (6.2) |
| N (%) Caucasian | 44 (80) | 6 (35.3) | 0 (0) |
| N (%) African American | 4 (7.2) | 6 (35.3) | 3 (50) |
| N (%) Asian | 2 (3.6) | 4 (23.6) | 2 (33.3) |
| N (%) American Indian or Alaska Native | 2 (3.6) | 1 (5.8) | 0 (0) |
| N (%) race not reported | 3 (5.4) | 0 (0) | 1 (16.7) |
| Cause of Kidney Disease, n (%) | | | |
| Congenital | 11 (20) | 1 (5.9) | 0 |
| Diabetes | 12 (21.8) | 2 (11.8) | 1 (16.7) |
| Glomerular Disease | 13 (23.6) | 9 (52.9) | 3 (50) |
| Hypertension | 4 (7.3) | 2 (11.8) | 1 (16.7) |
| Polycystic Kidneys | 8 (14.5) | 1 (5.9) | 0 |
| Other/Unknown | 7 (12.3) | 2 (11.8) | 1 (16.7) |
| Deceased Donor, n (%) | 24 (43.6) | 6 (35.3) | 5 (83.3) |
| Re-Transplant, n (%) | 9 (16.4) | 1 (5.9) | 1 (16.7) |
| Biopsy-proven Acute Rejection at 12 Months, n (%) | 2 (3.6) | 0 | 0 |
| Graft Failure at 12 months, n (%) | 2 (3.6) | 0 | 0 |

**Table 2.**

Outcomes by CYP3A5 Metabolism Phenotype

| Outcomes | Mean (95% CI) | Relative Risk (95% CI) | P-value ‡ |
|---|---|---|---|
| **Number of tacrolimus trough measurements †** | | | |
| Poor Metabolizers | 19.5 (18.3 – 20.7) | Reference | Reference |
| Intermediate & Extensive Metabolizers | 20.2 (17.7 – 22.7) | 0.97 (0.86 – 1.09) | 0.66 |
| **Number of tacrolimus dose adjustments †** | | | |
| Poor Metabolizers | 6.1 (5.4 – 6.8) | Reference | Reference |
| Intermediate & Extensive Metabolizers | 8.1 (6.8 – 9.1) | 1.28 (1.05 – 1.56) | 0.015 |
| **Time to first therapeutic trough in days †** | | | |
| | **Median (Range)** | **Hazard Ratio (95% CI)** | **P-value** |
| Poor Metabolizers | 6 (2–61) | Reference | Reference |
| Extensive & Intermediate metabolizers | 5 (2–31) | 0.86 (0.49 – 1.49) | 0.59 |
| **Time in Therapeutic Range, % †** | | | |
| | **Mean (95% CI)** | **Percent Difference (95% CI)** | **P-value** |
| Poor Metabolizers | 49.7 (12.4 – 94) | Reference | Reference |
| Extensive & Intermediate metabolizers | 51.02 (44.8 – 57.2) | 0.02 (−0.08 – 0.11) | 0.72 |
| **eGFR at 6 months, mL/min/1.73m $^2$** | | | |
| | **Mean (SD)** | **Difference in eGFR level (95% CI)** | **P-value** |
| Poor Metabolizers | 60 (20.3) | Reference | Reference |
| Extensive & Intermediate metabolizers | 58.8 (18.1) | 1.18 (−8.71 – 11.06) | 0.81 |
| **Dose-normalized tacrolimus troughs [ng/ml per mg tacrolimus daily dose]** | | | |
| | **Mean (SD)** | **Change in dose-normalized tacrolimus trough (95% CI)** | **P-value** |
| Poor Metabolizers | 2.05 (1.67) | Reference | Reference |
| Extensive & Intermediate metabolizers | 0.84 (0.53) | −0.57 (−1.01 ; −0.13) | 0.012 |

† adjusted for age, gender, BMI, diabetes at time of transplant, and initial tacrolimus dose,

‡ p-values are a comparison to the reference group (poor metabolizers)