Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Clinical Research Quantitative

Canadian Journal of Kidney Health and Disease
Volume 8: 1–9

DOI: 10.1177/20543581211021742
journals.sagepub.com/home/cjk
SAGE

Retrospective Analysis of Tacrolimus Intrapatient Variability as a Measure of Medication Adherence

Jordana Herblum[1], Niki Dacouris[2], Michael Huang[2], Jeffrey Zaltzman[3], G. V. Ramesh Prasad[3], Michelle Nash[4], and Lucy Chen[4]

Abstract

Background: Increased intrapatient variability (IPV) in tacrolimus levels is associated with graft rejection, de novo donor-specific antibodies, and graft loss. Medication nonadherence may be a significant contributor to high IPV.
Objective: The objective of this study is to determine the utility of tacrolimus IPV in detecting nonadherence by examining the relationship between self-reported adherence and tacrolimus coefficient of variability (COV), a measure of IPV.
Design: Retrospective cohort study.
Setting: St. Michael's Hospital, Toronto, Ontario.
Patients: All patients who were at least 1-year post-kidney transplant as of March 31, 2019, prescribed tacrolimus as an immunosuppressant and had a self-reported adherence status. Patients were excluded from the primary analysis of examining the correlation between COV and self-reported adherence if they lacked a calculatable COV.
Measurements: Self-reported adherence, COV, demographic data, transplant, and medication history.
Methods: A modified Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) administered by healthcare professionals to assess self-reported adherence was used. The COV of tacrolimus trough levels was calculated and its correlation to BAASIS response was noted. The median COV was used as a cutoff to examine the characteristics of patients deemed "high COV" and "low COV."
Results: A total of 591 patients fit the initial criteria; however, only 525 had a recent calculatable COV. Overall, 92.38% of the population were adherent by self-report. Primary analysis identified a COV of 25.2% and 29.6% in self-reported adherent and nonadherent patients, respectively, though the result was not significant ($P = .2$). Secondary analyses showed a significant correlation between younger age at transplant and at the time of adherence self-reporting with nonadherence ($P = .01$). In addition, there was a strong correlation between those nonadherent with routine post-transplant blood work and younger age ($P < .01$).
Limitations: The limitations included modified nonvalidated BAASIS questionnaire, social desirability bias, BAASIS only administered in English, and patients with graft failure not active in clinic not being captured.
Conclusions: The COV should not be used as the sole method for determining medication adherence. However, COV may have some utility in capturing individuals who are not adherent to their blood work or patients who are having a poor response to tacrolimus and should be switched to another medication.

Abrégé

Contexte: Une plus grande variabilité intra-individuelle des taux de tacrolimus est associée au rejet de la greffe, aux anticorps spécifiques au donneur de novo et à la perte du greffon. La non-observance du traitement médicamenteux pourrait être un facteur important de cette variabilité élevée.
Objectif: L'objectif de cette étude était d'évaluer la pertinence de la variabilité intra-individuelle des taux de tacrolimus pour la détection de la non-observance en examinant la relation entre l'observance autodéclarée et le coefficient de variabilité (CoV) du tacrolimus, une mesure de la variabilité intra-individuelle.
Type d'étude: Étude de cohorte rétrospective.
Cadre: L'hôpital St Michael's de Toronto (Ontario).
Sujets: Tous les patients qui, au 31 mars 2019, avaient subi une transplantation depuis au moins un an, à qui on avait prescrit du tacrolimus comme immunosuppresseur et qui déclaraient adhérer à leur traitement. Les patients qui ne disposaient

pas d'un CoV calculable ont été exclus de l'analyse principale examinant la corrélation entre le CoV et l'observance autodéclarée.
Mesures: L'observance autodéclarée, le CoV, les données démographiques, ainsi que les antécédents de transplantation et pharmaceutiques des patients.
Méthodologie: Une version modifiée du questionnaire BAASIS (Basel Assessment of Adherence to Immunosuppressive Medications Scale) administrée par les professionnels de la santé a été employée pour évaluer l'observance autodéclarée. Le CoV des concentrations minimales de tacrolimus a été calculé et sa corrélation avec les réponses au questionnaire BAASIS a été notée. Le CoV médian a été employé comme mesure limite pour examiner les caractéristiques des patients réputés avoir un « CoV élevé » ou un « CoV faible ».
Résultats: Au total, 591 patients satisfaisaient aux critères initiaux, mais seulement 525 disposaient d'une mesure récente et calculable du CoV. Dans l'ensemble, 92,38 % de la population étudiée déclarait adhérer au traitement. L'analyse primaire a permis d'établir le CoV à 25,2 % chez les patients adhérents et à 29,6 % chez les patients non-adhérents; bien que les résultats n'aient pas été jugés significatifs ($p = 0,2$). Les analyses secondaires ont montré une corrélation significative entre la non-observance autodéclarée au traitement et le fait d'être plus jeune au moment de la transplantation ($p = 0,01$). On a en outre observé une forte corrélation entre la non-observance des bilans sanguins habituels post-transplantation et un plus jeune âge ($p < 0,01$).
Limites: La version modifiée du questionnaire BAASIS n'a pas été validée, l'étude comporte de possibles biais de désirabilité sociale, le questionnaire BAASIS n'a été passé qu'en anglais et les patients avec échec de la greffe qui étaient inactifs en clinique n'ont pu être saisis.
Conclusion: Le coefficient de variabilité ne devrait pas être le seul élément à considérer pour déterminer l'adhérence au traitement. Ce coefficient peut cependant avoir une certaine utilité pour repérer les patients qui ne font pas leurs bilans sanguins ou les patients qui répondent peu au tacrolimus et qui devraient passer à un autre médicament.

Keywords
adherence, tacrolimus, intrapatient variability, kidney transplant

Received January 9, 2021. Accepted for publication April 26, 2021.

What was known before

Elevated coefficient of variability (COV) in tacrolimus levels is correlated with poorer kidney transplant outcomes, such as rejection or graft loss. Although some authors suggest medication nonadherence as an important mechanism for increased COV, a recent small study refuted this and found a lack of correlation between COV and measures of nonadherence.[1]

What this adds

This study offers the largest retrospective analysis known to date to examine the relationship between self-reported medication adherence and tacrolimus COV.

Introduction

Kidney transplant recipients are expected to adhere to a strict regimen of immunosuppressive medications indefinitely after transplantation. Tacrolimus (tac) is a key immunosuppressant of the calcineurin inhibitor class, which must be maintained within a narrow therapeutic window.[2,3] High blood tac levels are associated with nephrotoxicity and new-onset diabetes,[4,5] whereas low tac levels can lead to rejection and graft loss.[3,5]

Tacrolimus displays both interpatient variability and intrapatient variability (IPV). Interpatient variability occurs between different individuals and may be the result of differences in ethnicity, CYP3A[6] and/or P-glycoprotein genotypes,[7,8] or concomitant medications. Intrapatient variability is the variability in blood drug levels within the same person over time without altering the tac dose. High IPV has been attributed to drug-food interactions, drug-drug interactions,[6] diarrheal illness, and importantly nonadherence.[9] Both nonadherence and high IPV make patients more susceptible to solid organ graft loss,[3,10-12] de novo donor-specific antibodies,[13] renal fibrosis,[5] acute rejection,[10,14] and deterioration of chronic histologic lesions.[15]

[1]Keenan Research Summer Student Program, St. Michael's Hospital, Toronto, ON, Canada
[2]Kidney and Metabolism Program, Unity Health Toronto, ON, Canada
[3]Division of Nephrology, Department of Medicine, St. Michael's Hospital, Toronto, ON, Canada
[4]Kidney Research Program, St. Michael's Hospital, Toronto, ON, Canada

Corresponding Author:
Lucy Chen, Kidney Research Program, St. Michael's Hospital, 61 Queen St E, 9th Floor, Toronto, ON, Canada M5C 2T2.
Email: lucychen.ut@gmail.com

Kidney transplant recipients are the most nonadherent group compared with other transplant recipients.[16] Estimations of nonadherence vary based on the given patient cohort, as well as the method used to capture nonadherers. The percentage of tac nonadherers has been reported to be as high as 67%.[17,18] Given the narrow therapeutic window of tac and that high tac IPV has a stronger correlation with graft loss compared with other immunosuppressants, nonadherence to this medication may have a more deleterious effect than other drugs.[3]

Studies have attempted to find accurate and consistent techniques for measuring nonadherence to identify patients at risk of adverse events. Commonly used techniques include the self-reported Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS),[8,19-24] counting pills,[9] electronic pill bottle monitoring,[9,19,25] and measuring IPV.[8,9] However, there is currently no gold standard for measuring adherence, and the correlation of the tests has been inconsistent.[19,21,25] Although Medication Event Monitoring System was once coined as the gold standard for accurately measuring adherence for research purposes, it is impractical in a clinical setting, and pill bottle opening does not necessarily correlate with medication-taking behavior.[19]

This study primarily aims to determine the utility of measuring IPV by determining whether it correlates with self-reported adherence status. There are a number of variables that may affect a patient's adherence; therefore, this study secondarily examines the correlation between IPV and patients' age, sex, age at transplant, transplant type (living related, living unrelated, or deceased donor kidney), and transplant number. As it has been proposed that adherence decreases over time,[18,22,25-27] this study also aims to describe the longitudinal change in IPV. Measuring IPV may be a potentially objective method to measure adherence in clinic[5,23,28]; determining at-risk populations would allow early intervention by health care professionals and maintain patients on a trajectory of proper post-transplant care.

Methods

Patient Selection

This retrospective cohort study was performed using data from St. Michael's Hospital Transplant Clinic in Toronto, Canada, from patients who received kidney transplants between January 1, 2004, and March 31, 2019. The year 2004 was chosen because that is when the clinic's electronic medical record system (DCCP database) was implemented. Patients included were those who were at least 1-year post-transplant, active in the post-transplant clinic, had a recorded adherence response by self-report to the modified BAASIS,[29] and were prescribed tac as an immunosuppressant (Figure 1).

Adherence Determination

Immunosuppressant adherence was evaluated by an interview-based modified BAASIS questionnaire. The questionnaire consisted of (1) medication review with the patient (nonadherent if not taking the prescribed medicine/dose/time), (2) in the past month, how often did you miss a dose of your medicine? and (3) in the past month, how often did you take a dose of medicine late or early by 2 hours or more? If the patient provided any answer other than "none" to questions 2 and 3, they were scored as nonadherent. The BAASIS questionnaire was administered verbally by a health care professional (transplant nurse or pharmacist) as part of routine assessment during follow-up visits. Clinical protocol dictates that this assessment be completed at 6 months, 12 months, 18 months and 2 years after transplant and then annually thereafter. The result of assessment was documented in the electronic medical record as "adherent" or "nonadherent." The BAASIS questionnaire is a strongly supported self-report scale for transplant patients as it is short, validated, and sensitive to timing.[29] It is intentionally strict with an understanding that self-report scales often underestimate nonadherence.[30]

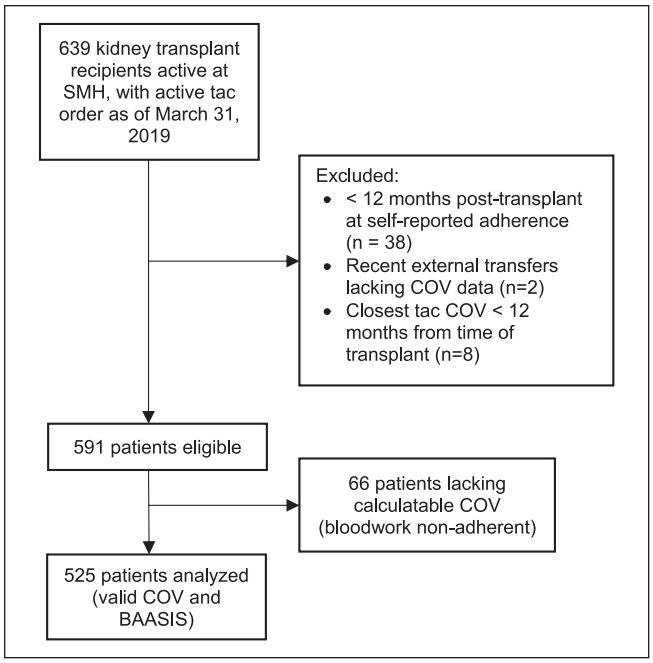

Figure 1. Flowchart of patients included and excluded within the study file.
Note. COV = coefficient of variability; SMH = St. Michael's Hospital Monitoring.

Tac Variability

Tacrolimus trough drug levels are routinely obtained through blood work which is done monthly in the first 2 years after transplant and then every 3 months after the second year of transplant. The tac trough levels are then recorded in the DCCP database.

All tac drug levels were measured at our institution using high-performance liquid chromatography mass spectrometer

(HPLC-MS; Shimadzu Scientific, Tokyo, Japan). Tacrolimus assay performance was characterized by 6 standardization references on a twice-daily basis.

Both inpatient and outpatient tac levels were used. A running coefficient of variability (COV) is calculated from all previous blood work once the patient is 1-year post-transplant, which is when tac concentrations are stable in the blood. COV was calculated as follows:

$$\mathrm{COV}(\%) = \left(\frac{\mathrm{SD}}{\text{mean tacrolimus concentration}} \right) \times 100$$

COV calculation closest in date to the most recent adherence questionnaire was used for the purpose of correlation between COV and self-report. To be included in the primary analysis, patients must have had a minimum of 3 tacrolimus levels over a 12-month period after 1-year post-transplant and a self-reported adherence within 12 months from the most recent COV calculation. To be included in the secondary outcome of COV over time, patients must have had a minimum of 3 tacrolimus levels within two 12-month periods. The COV was chosen as the measurement for IPV as it is the most common method in other studies.[31]

Demographic and Clinical Data

Patient information was obtained from the kidney transplant clinic database and the hospital electronic medical record system. Data collected included sociodemographic factors (age, sex, language, ethnicity, socioeconomic status based on postal code), clinical data (transplant type received, age at transplantation, history of prior transplant, serum creatinine), and pharmacological data (tac dose). Patients without certain demographic, clinical, or pharmacological data were excluded from the secondary outcome analyzing that parameter. There was no analysis performed on language and ethnicity variables as approximately half of the records were missing data for these fields. Socioeconomic status was also not included in the analysis. The partial postal code data gathered provided too broad of a geographical area, such that median income in those areas does not provide an accurate indicator of an individual's income.

COV as an Adherence Measure

In addition to measuring adherence according to BAASIS, adherence was measured by splitting the study population into high COV and low COV cohorts. The cutoff point between the 2 cohorts was set at the median COV value for the population, as previously done in other studies.[14,32] In addition, COV was used as a continuous variable to examine the relationship between COV with age at transplant, estimated glomerular filtration rate (eGFR), and tac dose using a linear regression model.

COV Over Time

For each patient, a regression model was used to calculate the change in COV over time: $b = \; b = \dfrac{(\Sigma(x-\underline{x})\times(y-\underline{y}))}{\Sigma(x-\underline{x})^2}$. These values were then merged together to examine the change in COV over time for the self-reported adherent and nonadherent populations.

Patients Without Measured COV

We also examined the patient characteristics of those 66 individuals who were nonadherent with post-transplant blood work and in whom a COV could not be calculated.

Statistical Analyses

Statistical analyses were performed using SAS software 9.1.3. Comparisons between the self-reported adherent and nonadherent groups examining continuous variables, such as current age, age at transplantation, years after transplant, kidney function measures, tac dose, and COV, were analyzed using the Student's t-test. χ^2 analysis was used to examine the differences in adherent and nonadherent groups for dichotomous variables: sex, transplant type, and previous transplant. The Fisher exact test was used, when appropriate, if a cell in the χ^2 test was less than 5. Similar analyses were performed to measure the differences between the high COV and low COV cohorts, and the COV calculatable and COV missing groups. Significance was determined using a threshold for α of 0.05. All confidence intervals (CIs) reported represent a 95% CI. This retrospective study was approved by the research ethics board at St. Michael's Hospital.

Results

Patient Characteristics

A total of 639 unique patient files were identified, of whom 525 patients were included in the primary analysis after inclusion and exclusion criteria were applied. Figure 1 describes the reasons and numbers for exclusion of specific participants. The overall adherence rate according to BAASIS was 92.4% for patients with a calculatable COV; 485 patients were adherent to their medication regimen, whereas 40 patients were nonadherent.

BAASIS and Baseline Characteristics

Based on BAASIS, there were differences between the adherent and nonadherent groups (Table 1). Overall, there were 194 women included in the study, comprising 36.1% of the adherent subjects and 47.5% of nonadherent subjects ($P = .2$). Nonadherent patients were more likely to be younger with a mean age of 53.4 ± 13.0 (95% CI, 49.2-57.5) years, compared with adherent patients who were

Table 1. Baseline Demographic and Health Characteristics of Patients With Available COV Values, by BAASIS Adherence Status.

	Adherent n = 485	Nonadherent n = 40	*P* value
Age at adherence questionnaire, y	58.3 ± 12.9	53.4 ± 13.0	.02
Age at transplant, y	52.6 ± 12.9	47.1 ± 12.7	.01
Years post-transplant at adherence questionnaire	5.8 ± 3.7	6.3 ± 3.5	.4
Transplant type			
Living donor, No. (%)	183 (37.7)	17 (42.5)	.6
Females, No. (%)	175 (36.1)	19 (47.5)	.2
Previous transplant, No. (%)	37 (6.9)	2 (3.8)	.2
Creatinine, μmol/L	121.1 ± 52.0	130.1 ± 53.1	.3
GFR (CKD-EPI), mL/min	59.2 ± 20.5	54.8 ± 20.6	.2
COV, %	25.2 ± 15.2	29.6 ± 22.9	.2
Tacrolimus dose, mg/d	5.9 ± 4.9	7.7 ± 5.4	.03

Note. Results are mean ± SD unless otherwise indicated. BAASIS = Basel Assessment of Adherence to Immunosuppressive Medications Scale; COV = coefficient of variability; GFR = glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

older with a mean age of 58.3 ± 12.9 (95% CI, 57.2-59.5) years ($P = .02$). Similarly, nonadherent patients were more likely to be younger at the time of transplant, with a mean age of 47.1 ± 12.7 (95% CI, 43.0-51.1) years, compared with adherent patients who had a mean age at transplant of 52.6 ± 12.9 (95% CI, 51.4-53.7) years ($P = .01$).

There was no significant difference in adherence according to BAASIS with respect to length of time since transplant, with means of 5.8 ± 3.7 (95% CI, 5.4-6.1) years and 6.3 ± 3.5 (95% CI, 5.2-7.4) years after transplant in the adherent and nonadherent groups, respectively ($P = .4$). A total of 62.3% of the adherent group received deceased donor kidney transplants, and 57.5% of the nonadherent group received deceased donor transplants; however, there was no significant difference as determined by BAASIS in terms of adherence by type of kidney transplant received ($P = .6$).

Estimated glomerular filtration rate and creatinine were compared between adherent and nonadherent groups. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The adherent group had a mean eGFR CKD-EPI of 59.2 ± 20.5 (95% CI, 57.4-61.0) mL/min. The nonadherent group had a mean eGFR CKD-EPI of 54.8 ± 20.6 (95% CI, 48.2-61.3) mL/min. As assessed by BAASIS, there was no difference in eGFR based on adherence status ($P = .2$).

Self-reported nonadherent patients were prescribed a statistically significant higher mean daily tacrolimus dose of 7.7 ± 5.4 (95% CI, 5.9-9.4) mg/d, compared with adherent patients with a mean dose of 5.9 ± 4.9 (95% CI, 5.5-6.3) mg/d ($P = .03$).

COV and BAASIS Correlation

The primary outcome of the study was to examine the correlation between COV and BAASIS. The mean COV for the adherent and nonadherent populations as assessed by BAASIS was 25.2% ± 15.2% (95% CI, 23.8%-26.6%; interquartile range [IQR] = 16.9) and 29.6% ± 22.9% (95% CI, 22.2%-36.7%; IQR = 21.1), respectively. Through a *t* test, it was determined that there was no difference in adherence as assessed by BAASIS with respect to mean COV ($P = .2$).

COV as an Adherence Measure

The median COV for this study population was 21.5%; this cutoff value was used to distinguish between groups with a high COV (>21.5%) and low COV (<21.5%). As a high COV indicates a greater fluctuation in tac drug levels, the high COV group was examined as a potential group of nonadherers and the low COV group as adherers. The same demographic examination between nonadherent (high COV) and adherent (low COV) groups was performed using the COV cutoff as was done with BAASIS. In total, there were 262 patients classified as having a high COV and 263 patients classified as having a low COV.

Patients with a high COV were significantly more recent transplant patients, being 5.3 ± 3.8 (95% CI, 4.8-5.7) years after transplant on average at the time of their BAASIS adherence assessment, compared with 6.3 ± 3.6 (95% CI, 5.9-6.8) years on average after transplant for the low COV group ($P < .01$). Similarly, patients with a high COV were on average 5.6 ± 3.8 (95% CI, 5.2-6.1) years after transplant as of March 2019, compared with longer length of 6.8 ± 3.6 (95% CI, 6.3-7.2) years on average for the low COV group ($P < .01$).

Age at transplant was not statistically significant between high COV and low COV groups, with means of 51.4 ± 13.8 (95% CI, 49.7-53.1) years and 53.0 ± 11.9 (95% CI, 51.5-54.4) years, respectively ($P = .2$). However, current age was significantly different between high COV and low COV groups, with means of 56.6 ± 13.7 (95% CI, 54.9-58.3)

years and 59.3 ± 12.0 (95% CI 57.8-60.7) years, respectively ($P = .02$).

Kidney function was also examined by COV cohort. Patients in the high COV group had a higher mean creatinine of 129.55 ± 59.1 (95% CI, 122.4-136.7) mmol/L compared with those with low COV with creatinine of 113.9 ± 42.7 (95% CI, 108.7-119.1) mmol/L ($P < .01$). Patients with high COV had a mean eGFR CKD-EPI of 56.6 ± 21.4 (95% CI, 54.0-59.2) mL/min, whereas patients with low COV had a higher eGFR of 61.1 ± 19.3 (95% CI, 58.8-63.4) mL/min ($P = .01$).

The COV was also used as a continuous variable to examine the correlation between COV and age at transplant, eGFR, and tac dose using a linear regression model. Age at transplant ($R < -0.01$, $P = .51$) and eGFR ($R < -0.01$, $P < .01$) were negatively correlated with COV; younger age at transplant and low eGFR were correlated with higher COV. Tac dose was positively correlated with COV ($R < 0.01$), although the result was not statistically significant ($P = .12$).

Patients Without COV Value

A total of 66 patients were excluded from the primary analysis correlating BAASIS with COV because they lacked a calculatable COV. This indicated that these patients did not adhere to the requirement of obtaining blood work every month in the first 2 years after transplant and subsequently every 3 months after 2 years of transplant, from which the tac COV is calculated. The COV requires a minimum of 3 independent values in the data set, as standard deviation is not possible with less than 3 values. Therefore, this group represents an additional group of nonadherent patients who completed blood work less than 3 times per year, classified as being nonadherent to their blood work.

Nonadherence to blood work was directly associated with higher likelihood of nonadherence to medication. Fewer patients without a calculatable COV (80.3%) assessed themselves as adherent via self-report, whereas 92.4% of patients with a calculatable COV assessed themselves as adherent ($P < .01$).

Patients without a COV (nonadherent to blood work) were more likely to be younger, 45.7 ± 14.9 (95% CI, 42.1-49.4) years, at the time of transplant, compared with patients with a calculatable COV (52.2 ± 12.9 years; 95% CI, 51.1-53.3 years) ($P < .01$). Similarly, patients who were younger, 54.0 ± 14.9 (95% CI, 50.4-57.7) years, at the time of self-reported BAASIS questionnaire were more likely to be nonadherent to their blood work, and thus had a missing COV, compared with older patients (57.9 ± 12.9 years; 95% CI, 56.8-59.0 years) ($P = .02$). There was no significant difference in the distribution of men and women among COV calculatable and COV noncalculatable groups; 27.3% of COV missing patients were women, and 37% of calculatable COV patients were women ($P = .1$).

Patients who were adherent to their blood work were more likely to have a longer mean length of time after transplant compared with the blood work of non-adherers. Specifically, the number of years after transplant for the blood work adherers and nonadherers were 8.4 ± 3.7 (95% CI, 7.4-9.3) years and 5.8 ± 3.7 (95% CI, 5.5-6.1) years at the time of BAASIS adherence status, respectively ($P < .01$). Similarly, the blood work adherent and nonadherent groups were 8.8 ± 3.8 (95% CI, 8.0-9.8) years and 6.2 ± 3.8 (95% CI, 5.9-6.5) years after transplant, respectively ($P < .01$) as of March 31, 2019. A higher percentage of patients had received a living donor transplant in the COV missing group than the COV calculatable group. In total, 38.1% of patients within the COV calculatable group had received a living donor transplant, whereas 56.1% of patients within the COV noncalculatable group were living donor transplant recipients ($P < .01$).

There was no difference in kidney function between the COV missing and COV calculatable groups. The mean creatinine for the group with a calculatable COV was 121.7 ± 52.1 (95% CI, 117.3-126.2) μmol/L, which was not significantly different from the mean creatinine of 128.9 ± 62.7 (95% CI, 113.5-144.3) μmol/L in the group without a calculatable COV ($P = .4$). The COV calculatable group had an eGFR CKD-EPI of 59 ± 20.5 (95% CI, 57.1-60.6) mL/min, and the COV noncalculatable group had an eGFR of 60 ± 24.0 (95% CI, 53.7-65.5) mL/min ($P = .8$).

COV Over Time

Using the regression model to calculate the slope in COV over time, it was determined that COV decreases over time for both self-reported adherent and self-reported nonadherent patients. Interestingly, the mean change in COV for the adherent population was −16.8 ± 291.2 (95% CI, −43.3 to 9.6) and for the nonadherent population was −1.0 ± 12.8 (95% CI, −4.6 to 2.6) ($P = .2$). There was a greater change over time in the COV of the adherent group.

Discussion

Results of this study showed that patients who self-reported adherence had lower COV compared with those who self-reported nonadherence. However, this finding was not statistically significant, thus confirming previous investigations that also demonstrated lack of association between patient-reported nonadherence and tac level variability.[8,33] Given the lack of statistical significance, our results do not support authors[34,35] who concluded that elevated COV was associated with medication nonadherence. In one of these positive studies, Hsiau et al[34] assessed nonadherence only as occurrence of rejection. However, biopsy-proven rejections do occur in adherent patients, and nonadherence does not always predict rejection. The other study by Pizzo et al[35] only found a statistically significant relationship between the

combination of tac COV and sirolimus COV and adherence to another immunosuppressant. This study represents the largest retrospective study to date to examine the relationship between patient-reported adherence and tac COV in an adult kidney transplant population.

There may be several reasons to explain the lack of statistically significant correlation between self-reported medication adherence and tac COV. First, the original BAASIS questionnaire consists of 6 questions referring to the taking and timing of medication, as well as self-medication and drug holidays, and requires 5 minutes to complete. To improve the clinical utility of the questionnaire in a busy outpatient setting, the questionnaire was modified to 3 questions. The modification uses open-ended questions to more quickly pose the questions on dosing and drug holidays from the original questionnaire. However, this modified questionnaire has not been formally validated. Second, patients may intentionally underestimate their nonadherence in self-report due to social desirability bias. This phenomenon has been well described as a validity concern with medication adherence self-reporting.[36] The questionnaire is administered face-to-face by a clinic nurse or pharmacist during routine visit. Patients may be unwilling to be candid about medication nonadherence due to fear of reprisal by the medical professional. The population served by this inner-city hospital is diverse, and thus many patients may not understand English as well as they do their native language. This may have altered their full comprehension of the questions being asked and may have therefore provided inaccurate information. Interestingly, our population demonstrated a relatively higher rate of adherence compared with other published findings.[12,13] This confirms the findings of Leino et al who concluded that tac has low IPV in a population of kidney and liver transplant recipients with high adherence determined through objective measurements of pill counts, patient diary, and medication monitoring.[9] Third, another limitation is the inclusion of only patients actively followed by the local institution's post-kidney transplant clinic. This was necessary because routine administration of the modified BAASIS questionnaire was a recent initiative in the clinic. Only patients who have had at least 1 clinic visit between May 2018 and March 2019 had a documented adherence measurement which was required for analyzing the primary outcome. Patients who had suffered graft loss and who were therefore discharged from the post-kidney transplant clinic were excluded from the data set. Such patients represent a distinct population in whom medication nonadherence may be overrepresented. Inclusion of patients whose transplant has failed may result in inclusion of higher COV values as well as higher rates of self-reported nonadherence. This may explain the low rate of nonadherence observed in our study compared with those previously reported. Finally, the modified BAASIS questionnaire evaluates adherence to immunosuppressant drugs in general and does not distinguish among tac, antimetabolite, or steroid therapy. Patients may be nonadherent to other components of the immunosuppression regimen only and therefore still display minimal variability in tac levels.

Our study is unique in its consideration of the population of patients noneligible for COV calculation due to missed blood work. At the local institution, post-kidney transplant patients are instructed to present themselves at a phlebotomy lab for blood work monitoring on a monthly or quarterly basis, depending on the length since transplant. Patients who did not adhere to the recommended monitoring were more likely to also be nonadherent to medication by self-report. These results suggest a direct relationship between medication nonadherence and other forms of treatment nonadherence, such as blood work monitoring.

In secondary analyses, our findings confirm previous studies in that high COV was associated with poorer kidney function as measured by serum creatinine and eGFR as estimated by CKD-EPI. High COV was additionally associated with shorter duration of time since transplant. This is expected because in patients who adhere to their medication, tac levels stabilize and have less variability over time. Initially, during the more acute post-transplant time period, COV is expected to be higher due to changing tac target ranges, changing concomitant medications, and the empirical nature of tac dosing and adjustment. Over time, these additional factors stabilize, and patients maintain the same tac dose and concentration for many years.

Our study observed a higher tac dosage prescribed for patients who self-reported nonadherence, which was statistically significant. This may be mediated by clinicians' response to low tac concentrations by assuming adherence and titrating up the dosage. This phenomenon wastes medication and may cause toxicity if patients begin taking doses as prescribed. Given the results of this study, our program has increased vigilance for medication nonadherence behavior and is seeking to understand reasons for it. We avoid impulsive uptitration of dose, which reduces unnecessary administrative burden of prescription changes and medication wastage.

Conclusion

Intrapatient variability is an objective measurement for determining fluctuations in tac exposure within an individual. However, this study suggests that it cannot be used in isolation to approximate medication adherence nor can it be used as a replacement to self-reported adherence. Although the correlation between COV and self-reported adherence was not statistically significant, COV remains an important clinical indicator. As confirmed by this study, elevated COV is associated with reduced renal function as measured by eGFR and creatinine.

Ethics Approval and Consent to Participate

This study was approved by the institution's REB review board.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Jordana Herblum https://orcid.org/0000-0001-8011-8890
Jeffrey Zaltzman https://orcid.org/0000-0002-0498-9122
G. V. Ramesh Prasad https://orcid.org/0000-0003-1576-7696
Lucy Chen https://orcid.org/0000-0001-7173-8094

References

1. Gokoel SRM, Zwart TC, Moes DJAR, van der Boog PJM, de Fijter JW. No apparent influence of non-adherence on tacrolimus intra-patient variability in stable kidney transplant recipients. *Ther Drug Monit*. 2020; 42:702-709.
2. Rodrigo E, Segundo DS, Fernández-Fresnedo G, et al. Within-patient variability in tacrolimus blood levels predicts kidney graft loss and donor-specific antibody development. *Transplantation*. 2016;100(11):2479-2485.
3. Borra LCP, Roodnat JI, Kal JA, Mathot RAA, Weimar W, van Gelder T. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. *Nephrol Dial Transplant*. 2010;25(8):2757-2763.
4. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant*. 2003;3:178.
5. Vanhove T, Vermeulen T, Annaert P, Lerut E, Kuypers DRJ. High intrapatient variability of tacrolimus concentrations predicts accelerated progression of chronic histologic lesions in renal recipients. *Am J Transplant*. 2016;16(10):2954-2963.
6. Lampen A, Christians U, Guengerich FP, et al. Metabolism of the immunosuppressant tacrolimus in the small intestine: cytochrome P450, drug interactions, and interindividual variability. *Drug Metab Dispos*. 1995;23(12):1315-1324.
7. Srinivas TR, Meier-Kriesche HU, Kaplan B. Pharmacokinetic principles of immunosuppressive drugs. *Am J Transplant*. 2005;5:207-217.
8. Tielen M, van Exel J, Laging M, et al. Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. *J Transplant*. 2014;2014:675301.
9. Leino AD, King EC, Jiang W, et al. Assessment of tacrolimus intrapatient variability in stable adherent transplant recipients: establishing baseline values. *Am J Transplant*. 2019;19(5): 1410-1420.
10. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12(2):388-399.
11. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation*. 2004; 77:769-776. http://www.ncbi.nlm.nih.gov/pubmed/15021846
12. Pollock-Barziv SM, Finkelstein Y, Manlhiot C, et al. Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. *Pediatr Transplant*. 2010;14(8):968-975.
13. Del Bello A, Congy-Jolivet N, Danjoux M, et al. High tacrolimus intra-patient variability is associated with graft rejection, and de novo donor-specific antibodies occurrence after liver transplantation. *World J Gastroenterol*. 2018;24:1795-1802.
14. Ro H, Min S, Yang J, et al. Impact of tacrolimus intraindividual variability and CYP3A5 genetic polymorphism on acute rejection in kidney transplantation. *Ther Drug Monit*. 2012;34(6):680-685.
15. Mo H, Kim SY, Min S, et al. Association of intrapatient variability of tacrolimus concentration with early deterioration of chronic histologic lesions in kidney transplantation. *Transplant Direct*. 2019;5(6):e455.
16. Dew MA, DiMartini AF, De Vito Dabbs A, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation*. 2007;83: 858-873.
17. Denhaerynck K, Dobbels F, Cleemput I, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int*. 2005; 18(10):1121-1133.
18. Abedini S, GÃ¸ransson L, Cockburn E, Kilany S, Holdaas H. Immunosuppression adherence in stable kidney transplant patients converted from immediate- to prolonged-release tacrolimus in clinical practice: a Norwegian study. *Transplant Direct*. 2018;4(2):e338.
19. Low JK, Manias E, Crawford K, et al. Improving medication adherence in adult kidney transplantation (IMAKT): a pilot randomised controlled trial. *Scientific Reports*. 2019;9:7734. http://www.nature.com/articles/s41598-019-44002-y. Accessed May 22, 2020.
20. Denhaerynck K, Schmid-Mohler G, Kiss A, et al. Differences in medication adherence between living and deceased donor kidney transplant patients. *Int J Organ Transplant Med*. 2014;5(1):7-14.
21. Scheel J, Reber S, Stoessel L, et al. Patient-reported nonadherence and immunosuppressant trough levels are associated with rejection after renal transplantation. *BMC Nephrology*. 2017;18:1.
22. Massey EK, Tielen M, Laging M, et al. Discrepancies between beliefs and behavior: a prospective study into immunosuppressive medication adherence after kidney transplantation. *Transplantation*. 2015;99(2):375-380.
23. Fellström B, Holmdahl J, Sundvall N, Cockburn E, Kilany S, Wennberg L. Adherence of renal transplant recipients to once-daily, prolonged-release and twice-daily, immediate-release tacrolimus-based regimens in a real-life setting in Sweden. *Transplant Proc*. 2018; 50:3275. doi:10.1016/j.transproceed.2018.06.027.
24. Lehner LJ, Reinke P, Hörstrup JH, et al. Evaluation of adherence and tolerability of prolonged-release tacrolimus (AdvagrafTM) in kidney transplant patients in Germany: a multicenter, non-interventional study. *Clin Transplant*. 2018;32. doi:10.1111/ctr.13142.

25. Denhaerynck K, Steiger J, Bock A, et al. Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. *Am J Transplant*. 2007;7(1):108-116.
26. Moradi O, Karimzadeh I, Davani-Davari D, Shafiekhani M, Sagheb MM. Pattern and associated factors of adherence to immunosuppressive medications in kidney transplant recipients at a referral center in Iran. *Patient Prefer Adherence*. 2019;13:729. https://www.dovepress.com/pattern-and-associated-factors-of-adherence-to-immunosuppressive-medic-peer-reviewed-article-PPA. Accessed May 22, 2020.
27. Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. *Transplantation*. 2014;98:878-884.
28. Shemesh E, Fine RN. Is Calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating nonadherence to medications in transplant recipients? *Pediatr Transplant*. 2010;14:940-943.
29. Dobbels F, Berben L, De Geest S, et al. The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. *Transplantation*. 2010;90:205.
30. Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients. *Pharmacoeconomics*. 2007;25(4):269-286.
31. Shuker N, Van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. *Transplant Rev*. 2015;29:78. doi:10.1016/j.trre.2015.01.002.
32. 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.
33. Parrish N, Kaiser T, McCann A, et al. Evaluation of patient-reported nonadherence with tacrolimus level variability in renal transplant recipients. *Am J Transplant*. 2016;16:789.
34. Hsiau M, Fernandez HE, Gjertson D, Ettenger RB, Tsai EW. Monitoring nonadherence and acute rejection with variation in blood immunosuppressant levels in pediatric renal transplantation. *Transplantation*. 2011;92:918-922.
35. Pizzo HP, Ettenger RB, Gjertson DW, et al. Sirolimus and tacrolimus coefficient of variation is associated with rejection, donor-specific antibodies, and nonadherence. *Pediatr Nephrol*. 2016;31(12):2345-2352.
36. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med*. 2015;5(4):470-482.