Transplant Research and Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Tacrolimus Trough Level Variation and Its Correlation to Clinical Outcomes and Consequences in Solid Organ Transplantation

Sarah Albilal[1,*], Mohammad S Shawaqfeh[2–4,*], Salwa Albusaysi[5], Lolwa Fetyani[2,3], Fai Alnashmi[2,3], Shaden D Alshehri[2,3], Nataleen A Albekairy[6], Amal Akhulaif[2], Lamees Alzahrani[2], Mariah Alwuhayde[2], Aiman A Obaidat[2,3,7], Abdulkareem M Al Bekairy[1–3,*]

[1]Department of Pharmaceutical Care, King Abdulaziz Medical City-Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; [2]College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [3]King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia; [4]Department of Pharmacy Practice, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [5]Department of Pharmaceutics, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; [6]College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [7]Department of Pharmaceutical Sciences, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabi

*These authors contributed equally to this work

Correspondence: Abdulkareem M Al Bekairy, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, Tel +966505550055, Email bekairya@ngha.med.sa; bekairy@gmail.com; Mohammad S Shawaqfeh, College of Pharmacy, Department of Pharmacy Practice, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, Tel +966502590643, Email shawaqfehm@ksau-hs.edu.sa; Shawaqfehms@gmail.com

Purpose: Tacrolimus is a calcineurin inhibitor that suppresses immunity by inhibiting T-lymphocyte activation. It has a high intra- and inter-patient variability in its pharmacokinetics. Therefore, therapeutic drug monitoring is required to individualize the dose. High tacrolimus trough level variability is associated with a higher risk of adverse effects. In practice, the initial dosing and sampling time of tacrolimus levels is not standardized, which may result in resource wastage, frequent blood sampling, and a longer time to achieve therapeutic levels. The aim of this study was to evaluate tacrolimus trough level variation and its correlation to clinical outcomes and consequences.

Patients and Methods: A retrospective cohort study At King Abdulaziz Medical City in Riyadh, Saudi Arabia, 01/01/2018 to 31/12/2021. Inclusion Criteria: >18 years old solid organ transplant patients who received tacrolimus as part of their initial immunosuppression regimen. Tacrolimus initial dosing, trough levels, and dose adjustments were recorded during the early post-transplantation period (first 10 days). The coefficients of variation (CV%) in tacrolimus doses and trough concentrations were calculated and compared for different demographics and clinical characteristics.

Results: The higher coefficient of variation in dose and trough level is associated with different demographic and clinical factors that will predict the incidence of adverse events. In our study, there was a significant increase in adverse effect reporting in the high variability group but was not clear for the risk of graft function, acute rejection, or infections.

Conclusion: The variation in trough levels is associated with clinical consequences. Therefore, better dosing strategies can be modified to reduce the variation (fluctuation) which is associated with poor outcomes.

Keywords: concentration, variability, monitoring, clinical, therapeutic

Summary Statement

Tacrolimus is used as the main immunosuppressant and requires dosage adjustment and monitoring. This can be done by measuring the trough level following the recommended dose administration. The variability in dosing resulted in variable measured concentrations. This was evaluated by calculating the coefficient of variation. The clinical outcomes like adverse effects, infections, as well as graft function, and acute rejection were evaluated among two distinct groups (high

Received: 21 April 2023
Accepted: 26 July 2023
Published: 8 August 2023

variation group and low variation group). This study may be utilized to avoid fluctuations in tacrolimus levels and may lead to better optimization of doses at the initiation of the immunosuppressant. High tacrolimus trough level variability is associated with a higher risk of adverse events. In practice, initial dosing and sampling time of tacrolimus levels are not standardized, which may result in resource wastage, frequent blood sampling, and a longer time to achieve therapeutic levels. The variation in trough levels is associated with clinical consequences. Therefore, better dosing strategies can be modified to reduce the variation (fluctuation) which is associated with poor outcomes.

Introduction

Tacrolimus (TAC) has been the primary agent as immunosuppressive agent in solid organ transplants since the 1990s. It is a potent calcineurin inhibitor that suppresses cellular immunity by inhibiting T-lymphocyte activation where it has a significant contribution to considerable five-year survival rates after a solid organ transplant.[1,2] Compared to the other calcineurin inhibitor, cyclosporine, TAC is known to provide higher organ and patient survival rates. Therefore, it leads to lower rejection rates and higher span and freedom from incidents of rejection.[3–5]

TAC is rapidly absorbed after oral administration reaching a maximum concentration (Cmax) in the blood within a mean time (Tmax) of one to two hours. However, its absorption is highly affected by the composition of food where its Cmax may significantly decrease along with prolongation of Tmax in the presence of fat-rich meals as well as high carbohydrates and this could be attributed to its highly lipophilic character.[6,7] Its pharmacokinetics is best described by a two-compartment model and first-order pharmacokinetics.[8] Its mean elimination half-life is about 12 hours which indicates that it reaches the steady-state level within two to three days after multiple dosing.[9] TAC therapeutic level of whole blood trough concentrations ranges from 5 to 20 ng/mL, while the usual range is reduced to 5–12 ng/mL to prevent toxicity.[10] Its bioavailability may vary widely in healthy subjects; however, it is approximately 15%. This drug is highly bound to plasma proteins and other blood components with only 0.3–2% unbound or free in the plasma.[11,12] The volume of distribution (Vd) of TAC based on plasma concentration is about 30 L/kg, while based on whole blood it is much lower where it is in the range of 1–1.5 L/kg and this is due to its extensive distribution into the erythrocytes.[13] It is well known that partitioning of TAC between plasma and red blood cells is rapid and due to this, it is preferable to use the whole blood tacrolimus concentration rather than plasma concentration for therapeutic drug monitoring (TDM) assuming normal levels of erythrocytes and proteins.[14]

TAC has a narrow therapeutic index with high intra- and inter-patient variability in its pharmacokinetics; therefore, TDM is required to individualize the dose to minimize toxicity and rejection rates.[15] Tacrolimus clearance and its trough level variabilities are affected by multiple factors including liver function, age, body weight, hematocrit, ethnic origin, drug–drug interactions, gastrointestinal conditions, adherence, genotype, and genetic polymorphism in CYP enzymes.[16–23] Routinely, its dose is only given based on body weight even though there is not much-supporting evidence for this practice based on pharmacokinetic modeling.[24] Further or subsequent dosing is based on TDM which minimizes the patient's exposure to fluctuations outside the target range. However, to reach the target exposure, it may take up to 14 days.[25] Therefore, during the first weeks after transplantation, patients are at increased risk of sub- or supra-therapeutic levels of TAC resulting in an increased level of adverse effects and/or rejection. TAC trough level inter-patient and intra-patient variabilities (IPV) have been linked to graft and patient survival, as high IPV could lead to worst graft outcomes and biopsy-proven rejection.[26–30]

In routine clinical practice, initial dosing and sampling time of TAC levels are not standardized which may result in a waste of resources, frequent blood sampling, and a longer time to achieve therapeutic exposure. TAC trough level concentration monitoring is a common practice necessary for dose adjustment. The variability of dosage adjustment and consequently the trough level concentration will be evaluated during the transplantation surgery admission. This coefficient of variation is a calculated parameter from the standard deviation divided by the average of all measurements. This parameter indicates the level of variability towards having a stable initiation dose of TAC at the shortest time possible and to avoid the production of sub- or supra-therapeutic levels during early time post-transplantation. We proposed this study to investigate whether TAC-level variation upon the initiation period (the surgery admission) may impose any effect on clinical outcomes. The retrospective study generated information that may help to establish

guidelines that could assist healthcare providers in the monitoring of TAC trough levels in the blood and subsequent dose adjustment.

Materials and Methods

Study Design, Setting, and Participants

This study is a retrospective cohort study conducted using data from electronic healthcare records (BEST Care) of solid organ transplant patients at the Solid Organ Transplant Unit in King Abdulaziz Medical City, Saudi Arabia, from January 1, 2018, to December 31, 2021. We included solid organ transplant patients who are ≥18 years old and received TAC as a part of their initial immunosuppression regimen. The study included 384 patients, 292 of whom were kidney recipients, and 91 patients were liver recipients. These patients were followed-up for 10 consecutive days to assess the correlation between tacrolimus trough level variability and clinical outcomes. The study was approved by the Institutional Review Board at King Abdullah International Medical Research Center (KAIMRC) in May 2022 (reference number SP22R/027/03). Informed consent was waived due to the retrospective nature of the study, and the patient data confidentiality was assured in compliance with the declaration of Helsinki. All organs were donated voluntarily with written informed consent and that was conducted in accordance with the declaration of Istanbul.

Data Collection and Outcomes

The data collected for the study included patients' demographic data, comorbidities (eg, hypertension, diabetes, dyslipidemia, cardiac diseases, liver diseases, renal diseases, and history of latent tuberculosis), infections present during the time of admission (ie, cytomegalovirus and Epstein Barr virus), and transplant-related factors (ie, type of organ transplanted, human leukocyte antigen (HLA) matching, and transplant medications, which included both induction and maintenance regimens). The appropriateness of the induction regimen was assessed for each patient. Appropriate pre-operative induction regimen was defined as low-risk patients (ie, HLA A:B:DR mismatch of ≤2) receiving any acceptable induction option, whereas moderate and high-risk patients (ie, HLA A:B:DR mismatch of ≥3) receiving anti-thymocyte globulin (ATG) and steroids. For maintenance, all transplant recipients received TAC as per hospital protocol. TAC initial dosing, trough levels, and dose adjustments were recorded and assessed for appropriateness during the first ten days after transplantation. Appropriate initial dosing was defined as 0.1–0.15 mg/kg/day, and lower doses were considered appropriate in the event of one or more of the following upon admission: history of uncontrolled diabetes (random blood glucose of ≥12 mmol/L), neurological symptoms, or elevated serum creatinine. TAC dose adjustments were appropriate if a change in dosing was performed once TAC levels were expected to be in a steady state (at least two days since any dose increase, decrease, or hold). Screening of medications known to affect TAC levels was performed, primarily interactions mediated by the cytochrome P450 3A5 enzyme and P-glycoprotein. The CV was calculated in dose as well as concentrations in the first 10 days post-transplantation. This was utilized to stratify the patients into two groups: high variability and low variability groups. This stratification relied on the median value of the coefficient of variation that will split our cohort into two distinct groups. For clinical outcomes, the patients were monitored throughout the entire transplant admission period. Clinical outcomes included incidence and type of acute cellular rejection, delayed graft function (ie, kidney transplant recipients in need of dialysis within seven days of transplantation), and any infection causing prolonged hospitalization (≥ ten days). Incidence of TAC-induced side effects presenting within the ten-day timeframe was documented (eg, hyperglycemia, headache, tremor, hypertension, nephrotoxicity) along with any necessary dose adjustments. All demographics and baseline characteristics as well as clinical outcomes were compared among the two distinct groups (high variability group > median coefficient of variation median and low variability group < median coefficient of variation median).

Statistical Analysis

Statistical analyses were performed using IBM SPSS statistical software version 25.0 (SPSS Inc., Chicago, IL, USA), and results are reported as mean ± standard deviation. We assessed the normality of our potential predictor variables using Kolmogorov–Smirnov tests with a p-value <0.05 indicating a non-normal distribution. The association between

two categorical variables was assessed using the chi-square test or Fisher's exact test if any group showed a frequency of five or less. A comparison between two groups was performed using the Student's *t*-test and a comparison between more than two groups was performed using ANOVA with Bonferroni post hoc test. The association between two continuous variables was evaluated using the Pearson correlation coefficient. In addition, logistic regression was used to explore the relationship between predictor variables and categorical outcomes by the stepwise backward method after adjustment for all possible confounding factors. Variables with $p < 0.1$ in the univariate analysis were included in the logistic regression analysis. Two-tailed p-values below 0.05 were regarded as statistically significant in all analyses.

Results

Demographic and Clinical Characteristics in TAC Trough Level Variability Groups

The high TAC trough level variability group was characterized by lower body weight (69.9 ± 17.4 kg vs 73.5 ± 18.0, P = 0.047), lower BMI (27.4 ± 6.3 vs 26.2 ± 5.6 kg/m^2, P = 0.049), lower rate of hypertension (57.2% vs 69.4%, P = 0.014), higher rate of renal disease (67.3% vs 45.8%, P = 0.005), higher rate of liver disease (93.7% vs 79.4%, P < 0.001), a higher percentage of kidney transplant patients (66.7% vs 33.3%, P < 0.001), quadrable vs triple maintenance therapy (73.4% vs 26.6%, P = 0.047), higher incidence of side effect (32.4% vs 14.3%, P = 0.017). Patients' characteristics according to the TAC trough level variability group are presented in Table 1.

Table 1 Patients Characteristics According to Tacrolimus Trough Level Variability Group

Variable	Low TAC Trough Level Variability Group (n=198)	High TAC Trough Level Variability Group (n=186)	P value
Age (years)	46.4 ± 14.7	46.5 ± 15.8	0.944
Weight (kg)	73.5 ± 18.0	69.9 ± 17.4	0.047*
BMI (kg/m^2)	27.4 ± 6.3	26.2 ± 5.6	0.049*
Gender %(n)			
Male	61.6 (122)	62.4 (116)	0.880
Female	38.4 (76)	37.6 (70)	
Hypertension %(n)			
No	30.6 (60)	42.8 (77)	0.014*
Yes	69.4 (136)	57.2 (103)	
DM %(n)			
No	62.3 (119)	61.4 (108)	0.853
Yes	37.7 (72)	38.6 (68)	
Dyslipidemia %(n)			
No	93.0 (172)	93.0 (160)	0.985
Yes	7 (13)	7 (12)	
Liver Disease %(n)			
No	54.2 (39)	32.6 (32)	0.005*
Yes	45.8 (33)	67.3 (66)	

(*Continued*)

Table 1 (Continued).

Variable	Low TAC Trough Level Variability Group (n=198)	High TAC Trough Level Variability Group (n=186)	P value
Renal disease %(n)			
No	6.3 (11)	20.6 (28)	<0.001*
Yes	93.7 (164)	79.4 (108)	
Cardiac disease %(n)			
No	83.9 (156)	88.4 (153)	0.212
Yes	16.1 (30)	11.6 (20)	
Hypothyroidism %(n)			
No	93.5 (172)	93.0 (160)	0.864
Yes	6.5 (12)	6.9 (12)	
CVA %(n)			
No	99.5 (183)	99.4 (171)	1.000
Yes	0.54 (1)	0.58 (1)	
Organ transplanted %(n)			
Kidney	85.3 (168)	66.7 (124)	<0.001*
Liver	14.7 (29)	33.3 (62)	
Induction therapy %(n)			
No	1.0 (2)	3.3 (6)	0.161
Yes	98.9 (194)	96.7 (176)	
Appropriate induction %(n)			
No	2.1 (4)	4.8 (8)	0.158
Yes	97.9 (188)	95.2 (160)	
Maintenance therapy %(n)			
Triple	18.2 (36)	26.6 (49)	0.047*
Quadrable	81.8 (162)	73.4 (135)	
Appropriate starting dose %(n)			
No	11.2 (22)	17.9 (33)	0.063
Yes	88.8 (174)	82.1 (151)	
Incidence of side effects %(n)			
No	85.7 (48)	67.6 (50)	0.017*
Yes	14.3 (8)	32.4 (24)	

(*Continued*)

Table 1 (Continued).

Variable	Low TAC Trough Level Variability Group (n=198)	High TAC Trough Level Variability Group (n=186)	P value
Infection %(n)			
No	90.9 (180)	86.8 (158)	0.203
Yes	9.1 (18)	13.2 (24)	
Rejection %(n)			
No	94.6 (174)	94.2 (163)	0.887
Yes	5.4 (10)	5.8 (10)	
AKI %(n)			
No	97.5 (193)	94.6 (175)	0.737
Yes	2.5 (5)	5.4 (10)	

Note: *Indicates significant difference.

TAC Trough Levels and Coefficient of Variation (CV)

There was no significant difference in the mean TAC levels between the low and high TAC variability group (7.54± 2.33 vs 7.12 ± 2.54, P = 0.089). Similarly, there was no significant difference in the mean TAC dose between the low and high TAC variability group (6.57 ± 2.31 vs 6.62 ± 2.80, P = 0.835). Patients in the high TAC trough level variability group had lower mean dose-adjusted concentration compared with the low TAC trough level variability group (2.09 ± 0.38 vs 4.22 ± 1.94, P < 0.001). Patients in the high TAC trough level variability group had higher mean dose CV compared with the low TAC trough level variability group (44.19 ± 13.06 vs 32.04 ± 13.62, P < 0.001). Patients in the high TAC trough level variability group had higher mean trough CV compared with the low TAC trough level variability group (49.57 ± 10.31 vs 26.28 ± 6.72, P < 0.001). The percentage of patients in the high TAC trough level variability group who were within, below, and above the therapeutic range (5–10 ng/mL) was 72.5%, 19.7%, and 7.9%, respectively (Table 2 and Figure 1).

Organ Transplant and TAC Trough Levels

Upon stratification of a dataset based on organ transplant (liver vs kidney), we found that in the kidney transplant patients, there was a negative low correlation between weight, BMI, and mean trough TAC levels (r = −0.222, P < 0.001

Table 2 TAC Parameters According to Trough Level Variability Groups

Variable	Low TAC Trough Level Variability Group (n=198)	High TAC Trough Level Variability Group (n=186)	P value
Mean tacrolimus level, ng/mL	7.54± 2.33	7.12 ± 2.54	0.089
Mean tacrolimus dose, mg	6.57 ± 2.31	6.62 ± 2.80	0.835
Mean dose-adjusted conc.	4.22 ± 1.94	2.09 ± 0.38	<0.001*
Mean dose CV	32.04 ± 13.62	44.19 ± 13.06	<0.001*
Trough CV	26.28 ± 6.72	49.57 ± 10.31	<0.001*
No. of patients within therapeutic range 5–10 ng/mL (%)	143/186 (76.9)	129/178 (72.5)	0.425
No. of patients below therapeutic range <5 ng/mL (%)	27/186 (14.5)	35/178 (19.7)	
No. of patients above therapeutic range >10 ng/mL (%)	16/186 (8.6)	14/178 (7.9)	

Note: *Indicates significant difference.

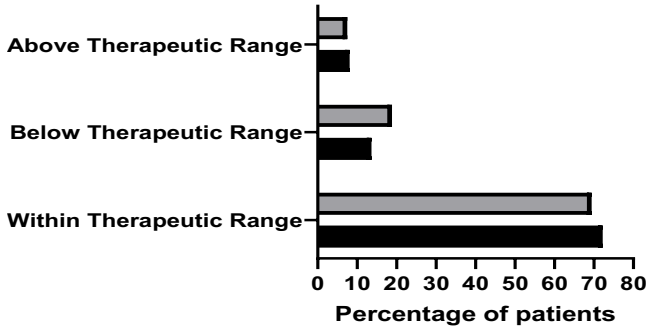

Figure 1 The percentage of patients within above and below therapeutic range according to trough level variability groups. Low Tac Variability group. High Tac Variability group.

and r = −0.208, P = 0.001), respectively (Table 3). This association was not seen in liver transplant patients (Table 4). Also, in kidney transplant patients, higher mean TAC trough levels were associated with a higher incidence of side effects (47.60 ± 18.71 vs 34.22 ± 12.09, P = 0.006) (Table 5). This association was not seen in liver disease patients

Table 3 The Association Between Demographic and TAC Trough Level CV in Kidney Disease

Variables	Kidney Disease		
	N	Correlation (r)	P value
Age	272	−0.104	0.087
Weight	272	−0.222	<0.001*
BMI	272	−0.208	0.001*

Note: *Indicates significant difference.

Table 4 The Association Between Demographic and TAC Trough Level CV in Liver Disease Patients

Variables	Liver Disease		
	N	Correlation (r)	P value
Age	99	0.014	0.894
Weight	99	0.007	0.943
BMI	98	0.046	0.651

Note: *Indicates significant difference.

Table 5 The Association Between Clinical Outcomes and TAC Trough Level CV in Kidney Disease

Variables	Group	Kidney Disease	
		Mean ± SD (n)	P value
Hypertension	**No**	35.05 ± 13.58 (72)	0.984
	Yes	35.01 ± 14.23 (196)	
Incidence of side effects	**No**	34.22 ± 12.09 (47)	0.006*
	Yes	47.60 ± 18.71 (21)	

Note: *Indicates significant difference.

Table 6 The Association Between Clinical Outcomes and TAC Trough Level CV in Liver Disease Patients

Variables	Group	Liver Disease	
		Mean ± SD (n)	P value
Hypertension	**No**	45.55 ± 13.98 (62)	0.006*
	Yes	37.42 ± 12.57 (33)	
Incidence of side effects	**No**	43.73 ± 13. 94 (28)	0.569
	Yes	46.35± 11.27 (12)	

Note: *Indicates significant difference.

Table 7 Logistic Regression for Associated Risk Factors

Outcome	Risk Factor	Odds Ratio	95% Confidence Interval	P value
Trough TAC variability	**Acute kidney injury (AKI)**	8.850	0.820–95.467	0.072
	Hypertension	3.033	1.125–8.174	0.028*
	Renal disease	3.525	1.322–9.397	0.012*

Note: *Indicates significant difference.

(Table 6). In addition, in liver transplant patients, lower mean TAC trough levels were associated with hypertension (37.42 ± 12.57 vs 45.55 ± 13.98, P = 0.006) (Table 6). This association was not seen in kidney transplant patients (Table 5).

Multivariate logistic analysis showed that trough TAC-level variability (as previously defined) was significantly associated with hypertension (odds ratio 3.033, 95% confidence interval 1.125-8.174, P = 0.028) and renal disease (odds ratio 3.525, 95% confidence interval 1.322-9.397, P = 0.012; Table 7).

Discussion

The literature suggested an association between TAC trough concentration coefficient of variation and variable clinical outcomes in the transplant population. However, the results were variable depending on the cohort of investigation, type of transplant organ, age, comorbidities, and the variable dosing strategies.

In our retrospective evaluation, we evaluated the variation in TAC trough concentrations at the initiation of the immunosuppression. The trough concentrations of TAC in the first several days following transplantation will define the optimal dose. The literature cited an acceptable coefficient of variation of less than 15–30%; however, higher variations were anticipated due to additional clinical and non-clinical factors.[31]

Measuring the coefficient of variation had been applied during different times following transplantation. The highest predictive potential was applied at least 3 to 6 months post-transplant, and the longer the time post-transplant the less the prediction power will be. In our study, we targeted the first admission post-transplantation, as this period will result in a baseline-adjusted dosage regimen that will stay with the patient. This approach provides an excellent real-life insight into trough level concentration that was measured, while the patient is still admitted and most of the external and other confounding variables are controlled. The main critique cited by literature for concentration variation in transplant cohorts was the patient non-adherence during the time following transplantation.[31] In our study, this factor did not exist as we followed all transplant patients from day 0 until discharge on a stable TAC dose. The main concern regarding our approach is that many patients might need a longer time to achieve target TAC trough levels.[32]

Most of the TAC dose monitoring studies associated the trough level variations with variable risks that included risk of acute rejection, graft failure, infections, and adverse events. However, these studies did not suggest a cut-off level of variation. Some studies associated higher variability of TAC trough level with increased risk of acute rejection in kidney

transplant recipients.[33] In our study, there was a significant increase in adverse effect reporting in the high variability group but was not clear for the risk of graft function, acute rejection, or infections. This may be explained by the short duration of the evaluation period as these events usually evolved at longer, later times post-transplantation.

Our study evaluated the risk of variation in the trough concentration in terms of clinical outcomes relevant to transplantation. However, the subgroup analysis distinguishes the variation between kidney and liver transplant recipients. TAC is a known immunosuppressant that will need renal dose adjustment which adds a layer of conservative dosing and thus less variation when compared with liver transplant patients. The different protocols adopted by different services made the comparison rather less valuable. In our study, we looked at each cohort independently from others which revealed a more significant effect of dose variation on kidney transplant recipients. This can be explained by baseline variation of TAC dosing, target trough level, concurrent medications, and other comorbidities.[34]

The study provides insight into clinical pharmacy service intensive therapeutic drug monitoring upon the initiation of the immunosuppressant agent. However, this can be modified and added to the protocol to avoid several rather too frequent trough level measurements. The trough level should be measured at steady state concentration which approximately takes about 3–5 half-lives to achieve. Based on these preliminary findings, more investigations looking for the magnitude of the effect of variability for longer time beyond the first admission will shed light on the importance of appropriate early monitoring to avoid variability upon tacrolimus initiation. Moreover, the proactive pharmacist led therapeutic drug monitoring should be further evaluated for clinical benefits.

This study is limited by its design as retrospective data collection may miss some important information. There might be some confounders that were not addressed in the notes. Furthermore, we included patients who had multiple-tacrolimus trough level records. The study was a single center which included only liver and kidney transplant patients that limited our data sample size. The study period time is limited to the first admission period which is variable among patients.

Conclusion

High TAC trough concentration coefficient of variation is associated with clinical outcomes in various organ transplant recipients. The different practices can utilize the clinical pharmacist therapeutic drug monitoring service to control the variability in dosing and thus the trough concentration measurements. This coefficient of variation can be utilized to better predict clinical outcomes, and further measurements of trough level concentration should be appropriately ordered and utilized.

Acknowledgment

The authors would like to acknowledge the contributions of KAIMRC for helping in reviewing and approving the proposal and granting the IRB approval and ultimately for the preliminary research data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding information to disclose.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Kaczmarek I, Zaruba -M-M, Beiras-Fernandez A, et al. Tacrolimus with mycophenolate mofetil or sirolimus compared with calcineurin inhibitor-free immunosuppression (sirolimus/mycophenolate mofetil) after heart transplantation: 5-year results. *J Heart Lung Transplant*. 2013;32:277–284. doi:10.1016/j.healun.2012.11.028
2. Neurohr C, Huppmann P, Zimmermann G, et al. Tacrolimus and mycophenolate mofetil as first-line immunosuppression after lung transplantation. *Transpl Int*. 2009;22:635–643. doi:10.1111/j.1432-2277.2009.00843.x
3. Griffith BP, Bando K, Hardesty RL, Armitage JM. A prospective randomized trial of FK506 versus cyclosporine after human pulmonary transplantation. *Transplantation*. 1994;57:848–851. doi:10.1097/00007890-199403270-00013
4. Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. *J Heart Lung Transplant*. 2012;31:797–804. doi:10.1016/j.healun.2012.03.008
5. Guethoff S, Meiser BM, Groetzner J, et al. Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine in combination with mycophenolate mofetil after heart transplantation. *Transplantation*. 2013;95:629–634. doi:10.1097/TP.0b013e318277e378
6. Maes BD, Lemahieu W, Kuypers D, et al. Differential effect of diarrhea on FK506 versus cyclosporine trough levels and resultant prevention of allograft rejection in renal transplant recipients. *Am J Transplant*. 2002;2:989–992. doi:10.1034/j.1600-6143.2002.21018.x
7. Bekersky I, Dressler D, Mekki QA. Effect of low- and high-fat meals on tacrolimus absorption following 5mg single oral doses to healthy human subjects. *J Clin Pharmacol*. 2001;41:176–182. doi:10.1177/00912700122009999
8. Monchaud C, de Winter BC, Knoop C, et al. Population pharmacokinetic modeling and design of a Bayesian estimator for therapeutic drug monitoring of tacrolimus in lung transplantation. *Clin Pharmacokinet*. 2012;51:175–186. doi:10.2165/11594760-000000000-00000
9. Phapale PB, Kim S-D, Lee HW, et al. An integrative approach for identifying a metabolic phenotype predictive of individualized pharmacokinetics of tacrolimus. *Clin Pharmacol Ther*. 2010;87:426–436. doi:10.1038/clpt.2009.296
10. Undre NA, Meiser BM, Uberfuhr P, et al. Pharmacokinetics of tacrolimus (FK506) in primary orthotopic heart transplant patients. *Transplant Proc*. 1998;30:1112–1115. doi:10.1016/S0041-1345(98)00173-0
11. Jusko WJ, Piekoszewski W, Klintmalm GB. Pharmacokinetics of tacrolimus in liver transplant patients. *Clin Pharmacol Ther*. 1995;57:281–290. doi:10.1016/0009-9236(95)90153-1
12. Zahir H, Nand RA, Brown KF, Tattam BN, McLachlan AJ. Validation of methods to study the distribution and protein binding of tacrolimus in human blood. *J Pharmacol Toxicol Methods*. 2001;46:27–35. doi:10.1016/S1056-8719(02)00158-2
13. Wallemacq DPE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in pediatric and adult patients. *Clin Pharmacokinet*. 2001;40:283–295. doi:10.2165/00003088-200140040-00004
14. Chow F-S, Piekoszewski W, Jusko WJ. Effect of hematocrit and albumin concentration on hepatic clearance of tacrolimus (FK506) during rabbit liver perfusion. *Drug Metab Dispos*. 1997;25:610–616.
15. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet*. 2004;43:623–653. doi:10.2165/00003088-200443100-00001
16. Tang JT, Andrews LM, van Gelder T, et al. Pharmacogenetic aspects of the use of tacrolimus in renal transplantation: recent developments and ethnic considerations. *Expert Opin Drug Metab Toxicol*. 2016;12:555–565. doi:10.1517/17425255.2016.1170808
17. Oetting WS, Schladt DP, Guan W, et al. Genomewide association study of tacrolimus concentrations in African American kidney transplant recipients identify multiple CYP3A5 alleles. *Am J Transplant*. 2016;16:574–582. doi:10.1111/ajt.13495
18. van Gelder T. Drug interactions with tacrolimus. *Drug Saf*. 2002;25:707–712. doi:10.2165/00002018-200225100-00003
19. Antignac M, Barrou B, Farinotti R, Lechat P, Urien S. Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients. *Br J Clin Pharmacol*. 2007;64(6):750–757. doi:10.1111/j.1365-2125.2007.02895.x
20. de Jonge H, Naesens M, Kuypers DR. New insights into the pharmacokinetics and pharmacodynamics of the calcineurin inhibitors and mycophenolic acid: possible consequences for therapeutic drug monitoring in solid organ transplantation. *Ther Drug Monit*. 2009;31(4):416–435. doi:10.1097/FTD.0b013e3181aa36cd
21. Scholten EM, Cremers SC, Schoemaker RC, et al. AUC-guided dosing of tacrolimus prevents progressive systemic overexposure in renal transplant recipients. *Kidney Int*. 2005;67(6):2440–2447. doi:10.1111/j.1523-1755.2005.00352.x
22. Staatz CE, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: part I. *Clin Pharmacokinet*. 2010;49(3):141–175. doi:10.2165/11317350-000000000-00000
23. Shuker N, van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. *Transplant Rev*. 2015;29(2):78–84. doi:10.1016/j.trre.2015.01.002
24. Andrews LM, de Winter BC, Tang JT, et al. Overweight kidney transplant recipients are at risk of being overdosed following standard body weight-based tacrolimus starting dose. *Transplant Direct*. 2017;3:e129. doi:10.1097/TXD.0000000000000644
25. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther*. 2010;87:721–726. doi:10.1038/clpt.2010.17
26. Waiser J, Slowinski T, Brinker-Paschke A, et al. Impact of the variability of cyclosporin A trough levels on long-term renal allograft function. *Nephrol Dial Transplant*. 2002;17(7):1310–1317. doi:10.1093/ndt/17.7.1310
27. 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
28. 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(8):918–922. doi:10.1097/TP.0b013e31822dc34f
29. 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
30. Borra LC, Roodnat JI, Kal JA, Mathot RA, 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. doi:10.1093/ndt/gfq096
31. Schumacher L, Leino AD, Park JM. Tacrolimus intrapatient variability in solid organ transplantation: a multiorgan perspective. *Pharmacotherapy*. 2021;41(1):103–118. doi:10.1002/phar.2480

32. Alghanem Sarah S, Soliman Moetaza M, Alibrahim Ali A, Osama G, Kenawy Ahmed S, Abdelmoneim A. Monitoring tacrolimus trough concentrations during the first year after kidney transplantation: a national retrospective cohort study. *Front Pharmacol*. 2020;2020:11.
33. 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;48:1978–1980. doi:10.1016/j.transproceed.2016.02.081
34. Giza P, Ficek R, Dwulit T, et al. Number of regularly prescribed drugs and intrapatient tacrolimus trough levels variability in stable kidney transplant recipients. *J Clin Med*. 2020;9(6):1926. doi:10.3390/jcm9061926