Tacrolimus Intrapatient Variability on Graft Outcomes in Adherent Renal Transplantation Patients: A Cross-Sectional Study

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Introduction. Tacrolimus is the mainstem of immunosuppressive therapy in kidney transplant patients. It has high intrapatient variability (Tac-IPV), which has been reported to affect graft function by predisposing patients to rejection or nephrotoxicity. We conducted this study with the aim of assessing the influence of Tac-IPV on 2-year graft function, biopsy-proven rejection, and infections in compliant renal recipients.

Methods. In this single-center retrospective analytic cross-sectional study, 250 patients who underwent transplantation from March 21, 2018, to March 20, 2020 and had at least three outpatient tacrolimus trough levels on the same daily dose 6 to 12 months after transplantation were recruited. Tac-IPV was defined as a coefficient variation of > 15%. Graft function, biopsy-proven rejection, cytomegalovirus (CMV) and BK virus viremia, and calcineurin inhibitor (CNI) toxicity were evaluated.

Results. Of 202 transplant recipients, 128 were included with a mean age of 45.48 ± 13.14 years. The median Tac-IPV was 13.28% with 43.75% of patients with Tac-IPV > 15%. There were no significant differences in graft function, rejection, CNI toxicity, and CMV viremia among the groups during the 24-month study ($P > .05$). However, BK viremia was significantly higher among patients with Tac-IPV > 15% (13 vs. 2.9%, $P = .042$). The risk of antibody-mediated rejection alone (22.7 vs. 2.9%) or any kind of rejection (22.7 vs. 11.8%) was significantly higher in patients with higher Tac-IPV, and in those who had mean trough levels below 7 ng/mL ($P = .015, .032$; respectively).

Conclusion. Tac-IPV is low in adherent patients (with the median of 13.28%) and maintaining tacrolimus trough level above 7 ng/mL can overcome the adverse graft outcome of Tac-IPV in compliant kidney transplant recipients.

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Original Paper

INTRODUCTION

Kidney transplantation is the ideal treatment option for end-stage kidney disease (ESKD). Even though short-term graft survival with the advent of new immunosuppressive treatments has been improved over the years, long term-graft survival is still unsatisfactory.[1] Several reasons, both modifiable and unmodifiable, had been outlined for this,

including graft-related factors, immunologic factors, noncompliance, over- or underimmunosuppression, episodes of rejection, de novo donor-specific antibody (de novo DSA) formation, and drug toxicity. [1,2] Tacrolimus is the cornerstone of most of the current immunosuppressive protocols, however, the correlation between its trough concentration (C0) as a sole way to evaluate therapeutic drug monitoring with clinical outcomes has not been reported.[3] Tacrolimus intrapatient variability (Tac-IPV) is used as a new marker of drug exposure over the time. Tac-IPV can result from noncompliance, drug- drug or drug-food interaction, and polymorphisms in cytochrome enzyme.[2] Various reports on the effect of Tac-IPV on graft survival have been published. High Tac-IPV might lead to higher incidence of acute rejection, chronic histologic changes and graft loss.[4] There are various definitions and cutoffs for Tac-IPV, yet, among which the coefficient variation (CV) is the most commonly used method of measurement.[2] Most studies have calculated CV in a period between 6 to 12 months after transplantation, in an outpatient setting, with at least three trough concentrations.[2] CV cutoff varied in studies on graft outcome from 12.5 to more than 30% based on the median value, tertiles, and quartiles of IPV.[2] As noncompliance is correlated with higher Tac-IPV, studies have used a cutoff of 15% in compliant patients to address the effects of Tac-IPV on graft survival.[4]

The frequency and the extent to which Tac-IPV contributes to graft outcomes in Iranian kidney recipients remain unclear due to a lack of evidence. This study was set out to assess the influence of Tac-IPV in compliant transplant recipients' 2-year graft function, biopsy-proven rejection, and infections.

MATERIALS AND METHODS

In this single-center retrospective analytic cross-sectional study, kidney transplant patients 6-12 months after transplantation were recruited. Two hundred and two patients who underwent transplantation from March 21, 2018, to March 20, 2020, at Labbafinejad Medical Center, Tehran, Iran, were recruited and followed for two years. The sample size was based on the available cases. This study was approved by the Ethical Committee of Shahid Beheshti Medical University (IR.SBMU.UNRC.REC.1400.020). Data were anonymized, and we had the participants' consent for utilizing their data for this study at the time of transplantation. The study was designed to evaluate the frequency and effects of Tac-IPV on graft function, rejection, infection and diabetes post-transplantation.

Inclusion criteria were as follows: triple maintenance immunosuppressants (tacrolimus twice daily, mycophenolic acid (MMF 1g/d or Myfortic 360 mg/twice per day) and prednisolone 5 mg/d), no history of acute rejection in the first 6 months after transplantation, stable graft function, and availability of at least three tacrolimus outpatient trough levels within 6 to12 months post-transplantation on the similar daily dose of tacrolimus. As induction therapy, all recipients received Thymoglobulin Ò in Labbafinejad Medical Center, except low immunologic risk patients (first transplant, calculated panel reactive antibody (cPRA = 0); less than 3/6 HLA mismatch). Patients with a history of multiorgan transplantation, incomplete baseline or outcome data, pre-formed donor-specific antibody (DSA), noncompliance (evaluated by self-reported compliance and Immunosuppressant therapy adherence scale (ITAS) at enrollment), and those with the administration of any medications known to have interactions with tacrolimus during the study period were excluded. ITAS is based on a 4-question scale, asking about forgetting immunosuppressant medication during the last 3 months before recruitment. Scores ranged between 0 to 12, with twelve being defined as adherent[5] (Supplementary-1). Patients with confounding factors of non-adherence, and high immunologic risk were excluded from the study. The baseline demographic and laboratory characteristics and transplant biopsy pathology reports (if available) of participants were recorded from patients' files. All trough levels were measured by high-performance liquid chromatography-mass spectroscopy (HPLC) at a referral laboratory. Tac-IPV was calculated by CV based on at least three consecutive outpatient levels within 6 months on the similar daily dose, using the formula, where SD is the standard deviation and mean C0 is the mean Tacrolimus trough level during the observation time:

$$\text{coefficient variation} = \text{SD} / \text{mean C0} \times 100 \quad (2)$$

In addition, we measured dose-adjusted trough concentration (C0/D) and mean trough level. The median Tac-IPV in our study population was 13.28%, and our patients were considered adherent based on self-reported compliance and ITAS. Thus, we used

a CV cut-off point of ≥ 15%, based on the results of various studies demonstrating the difference in allograft outcome can be significant even at this level of Tac-IPV in compliant patients.[6] Accordingly, participants were divided into two groups, high Tac-IPV (CV ≥ 15%) and low Tac-IPV (CV < 15%).

Graft function was measured by estimated glomerular filtration rate (eGFR (creatinine-based CKD-EPI equation 2021)) at 6, 12, 18, and 24 months after transplantation. Graft function, biopsy-proven rejection (T cell-mediated (TCR) and antibody-mediated rejection (AMR)) were extracted from the medical records and analyzed as the primary outcome of the study. Secondary outcomes of cytomegalovirus (CMV) (considered relevant ≥ 1.000 copies/mL)[22] and BK virus viremia (Any positive BKV viral load)[8], CNI toxicity in pathology, and New-onset Diabetes After Transplant (NODAT, according to the American Diabetes Association (ADA))[24] were also evaluated.

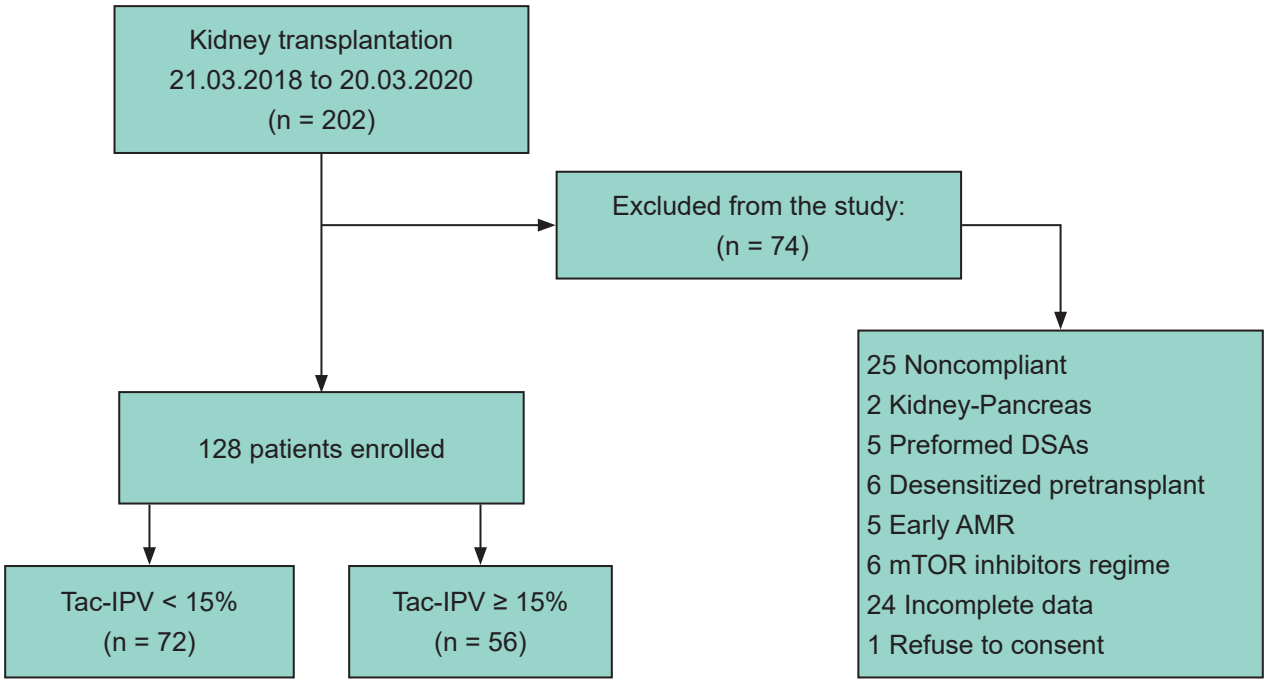
Statistical Analysis

Patients missing with data, and confounding factors of non-adherence, and high immunologic risk were excluded from the study. Data were described as mean ± standard deviation and range, and frequency (percentage) for quantitative and qualitative variables, respectively. Chi-square or Fischer's exact tests were used to evaluate the association between qualitative factors. Quantitative variables were compared by using an independent sample T-test or Mann-Whitney U-test; based on results from the Kolmogorov-Smirnov normality tests and the number of variables. Freidman test was applied to explore the eGFR trends during the time in each study group. In all statistical analyses, a *P* value < .05 was considered statistically significant. Statistical analyses of all data were performed by using SPSS software version 23 (IBM, Armonk, NY, United States).

RESULTS

Of 202 transplant recipients who were transplanted during the recruitment period, 128 were included, 91 (71.1%) male and 37 (28.9%) female, with a mean age of 45.48 ± 13.14 years. The causes of exclusion from study were as the following: Noncompliance (25); Kidney-Pancreas Transplantation (2); Preformed DSAs (5); Desensitization before transplantation (6); Early AMR (5); mTOR inhibitors regime (6); Incomplete data (24) and Refusal to consent (1).

Ten patients (8.1%) were second and third-transplant cases. The baseline clinical and laboratory characteristics of the participant are demonstrated in Figure and Table 1.



Patients' Flowchart

Table 1. Baseline Clinical and Laboratory Characteristics

Characteristic	Value (n = 128)
Sex (male), n (%)	91 (71.1%)
Age, y (mean ± SD)	45.48 ± 13.14
Donor type (Deceased), n (%)	75 (58.6%)
Number of kidney transplant, n (%)	
1st	118 (92.2%)
2nd	8 (6.3%)
3rd	2 (1.6%)
Cause of ESKD, n (%)	
Diabetes mellitus	18 (14.1%)
Hypertension	36 (28.1%)
ADPKD	20 (15.6%)
Glomerulopathy	16 (12.5%)
Others	21 (16.4%)
Unknown	17 (13.3%)
BMI, Kg/m^2 (mean ± SD)	26.7 ± 14.91
eGFR at discharge, cc/min (mean ± SD)	52.16 ± 20.04
eGFR at 6th month, cc/min (mean ± SD)	64.96 ± 21
eGFR at 12th month, cc/min, (mean ± SD)	66.4 ± 21.78
eGFR at 18th month, cc/min (mean ± SD)	71.72 ± 23.2
eGFR at 24th month, cc/min (mean ± SD)	73.83 ± 21.62
Tac level (C0) during 6 months ng/mL (mean ± SD)	7.7 ± 1.94
C0/ D during 6 months, ng/mL/mg (mean ± SD)	2.6 ± 1.2
Tac-IPV median	13.28 (Q1:8.15 to Q3:20.56)

Abbreviations: *ADPKD,* autosomal dominant polycystic kidney disease; *BMI,* body mass index; *C0/ D,* dose-adjusted trough concentration; *eGFR,* estimated glomerular filtration rate; *ESKD,* end-stage kidney disease; *Tac-IPV,* intrapatient variability

The median Tac-IPV was 13.28 and 43.75% of patients had high Tac-IPV. The effects of Tac-IPV on graft function, and biopsy-proven acute rejection were assessed in the study groups. Table-2 displays serum creatinine and eGFR during 24 months of follow-up. No significant difference in graft function, evaluated by eGFR, were found among the groups during the 24-month study ($P > .05$). There was a significant improvement in eGFR during the follow-up period in Tac-IPV < 15% group ($P < .01$). The two groups had no significant difference with respect to hematocrit (35.2 ± 3.1 vs. 34.9 ± 2.9%, $P > .05$) and serum alanine aminotransferase (19.5 ± 9.1 vs. 21 ± 11.1 IU/L) at 6 months. Mean Tacrolimus level at 12 months post-transplantation was 7.6 ± 2.9 ng/mL.

Furthermore, we analyzed the impact of high Tac-IPV on the incidence of biopsy-proven rejection, both TCR and AMR, among the patients. As can be seen in Table 3, there is no significant difference between the groups in the incidence of biopsy-proven rejection, both TCR and AMR (P value > .05). Other outcomes of our study were biopsy-proven CNI toxicity and CMV viremia as markers of over-immunosuppression, which were not significantly different between groups. However, BK viremia was significantly higher among patients with Tac-IPV > 15% (13% vs. 2.9%, $P = .042$). Surprisingly, the incidence of NODAT was higher in patients with Tac-IPV < 15% ($P = .013$).

Since there was no significant difference in rejection between groups, further analysis was done. A number of studies reported that the mean trough levels above 7 ng/mL or slow metabolizer patients are protected from under-exposure and rejection even though they have high Tac-IPV.[7] Since the genetic evaluation of drug metabolism rate is cumbersome, C0/D can be used as a surrogate marker of the metabolism rate, the higher the ratio the slower the metabolism rate, and patients with a C0/D > 1.55 ng/mL/mg were defined as slow metabolizers.[8,9] Hence, we assessed drug exposure and metabolism rate among the cohort, and found that 34 (60.7%) of patients had mean trough level > 7 ng/mL, and 46 (82.1%) patients had C0/D > 1.55 ng/mL/mg. To assess the role of the above-mentioned

Table 2. eGFR at Different Time-point Among Tac-IPV ≥ 15 and < 15% Patients

Tac-IPV %	Tac-IPV < 15% (n = 72)	Tac-IPV ≥ 15% (n = 56)	*P*
eGFR, cc/min (at discharge)	50.65 ± 17.61	54.14 ± 22.86	> .05
eGFR, cc/min, (at 6 months)	64.96 ± 21.68	64.96 ± 20.26	> .05
eGFR, cc/min (at 12 months)	66.54 ± 11.7	66.24 ± 21.96	> .05
eGFR, cc/min (at 18 months)	70.61 ± 23.82	73.24.47 ± 24.47	> .05
eGFR, cc/min (at 24 months)	74.69 ± 21.24	72.98 ± 22.25	> .05

Abbreviations: *eGFR,* estimated glomerular filtration rate; *Tac-IPV,* intrapatient variability.

Table 3. Variables Under the Influence of Immunosuppression

Variables	Tac-IPV < 15% (n = 72)	Tac-IPV ≥ 15% (n = 56)	*P*
AMR, n (%)	6 (8.3)	6 (10.7)	> .05
TCR, n (%)	5 (6.9)	4 (7.1)	> .05
AMR or TCR, n (%)	10 (13.9)	9 (16.1)	> .05
BK viremia, n (%)	2 (2.9)	7 (13)	< .05
CMV viremia, n (%)	3 (4.3)	2 (3.8)	> .05
CNI toxicity, n (%)	2 (2.8)	2 (3.65)	> .05
NODAT, n (%)	21 (29.2)	6 (10.9)	< .05

Abbreviations: *AMR,* antibody-mediated rejection; *BKV,* BK virus; *CMV,* cytomegalovirus; *CNI,* calcineurin inhibitor; *NODAT,* new-onset diabetes after transplant; *Tac-IPV,* intrapatient variability; *TCR,* T cell-mediated rejection.

variables, we performed two various subgroup analyses in patients with Tac-IPV > 15%. The risk of AMR alone (22.7 vs 2.9%) or having any kind of rejection (22.7 vs 11.8%) were significantly higher in patients with higher Tac-IPV, who had mean trough levels below 7 ng/mL (P = .015, .032; respectively). To assess the effects of differences in Tacrolimus metabolism rate, we measured C0/D at various time points. There was no significant difference in the rate of AMR between groups (10.9 vs 10%, P = 1).

DISCUSSION

The objectives of this project were to determine the frequency of Tac-IPV among kidney transplant recipients throughout 6 to 12 months after transplantation and study its effects on 2-year graft function, biopsy-proven acute rejection, and infections. Using CV, the mean Tac-IPV was 16.39 ± 11.6%, with a median of 13.28%. Several reports have shown a wide range of Tac-IPV between 12.5 to > 30% among transplant patients.[2] This low level of Tac-IPV in our patients could be attributed to medication adherence. Apart from adherence, concurrent medications (e.g., anticonvulsants and diltiazem) or medical conditions (e.g., diarrhea) might affect Tac-IPV, so we excluded patients with these confounding factors from our study in order to solely analyze the effect of Tac-IPV on graft. As stated by a number of studies, higher Tac-IPV is correlated with worse graft survival [10-13], higher risk of de novo DSA formation[14,15], increased incidence of acute rejections[2,16], and chronic pathologic changes[17,18]. Non-adherence has been reported as a contributing factor for Tac-IPV in previous studies[2]. Among adherent patients, low thresholds of Tac-IPV, even less than 15%, have been reported. However, no data was found on the association between Tac-IPV and allograft outcome at that level.[6] As our cohort had medication compliance and the median Tac-IPV was close to 15%, we analyzed the outcome by comparing groups based on the 15% threshold, previously described by Leino *et al*.[6] Accordingly, there was no significant difference in terms of biopsy-proven acute rejection and 2-year graft function between the groups. Patients with Tac-IPV < 15% had a better eGFR trajectory over the years (64.96 ± 21.68 at 6 months vs 74.69 ± 21.24 at 24 months, P < .001). This lack of difference might be in part due to the mean trough level over the study period, as stated by Opelz in Collaborative Transplant Study (CTS); lower trough level at 12 months after transplantation associated with inferior 5-year graft survival.[19] Thus, we analyzed patients with high Tac-IPV based on the mean trough level. Patients with high Tac-IPV and the mean Tac-trough level below 7 ng/ml had a significantly higher risk of AMR alone (22.7 vs. 2.9%, P = .015) or had other kinds of rejection (22.7 vs. 11.8%, P = .032). In accordance with our results, previous studies have demonstrated that non-dose-corrected Tac levels are more correlated with immunologic and pathologic outcomes than Tac-IPV itself.[15, 18, 20, 21] Genetic factors including CYP3A5 polymorphism and expression have been proposed as a determinant of Tac-IPV.[2] Due to difficulties in genetic studies, C0/D can be considered a surrogate marker of enzyme activity. Based on previous studies, C0/D > 1.55 ng/mL/mg was defined as slow metabolizer.[9] Almost 82% of patients with high Tac-IPV in our study were slow metabolizers. There was no significant difference among high Tac-IPV when comparing slow metabolizers with moderate or

fast metabolizers in terms of renal outcomes. Consistent with the literature, slow metabolism and a higher trough-to-dose ratio protects against rejection and progression of fibrosis.[9, 15] To our knowledge, there are no reports on CYP3A5 polymorphism in Iranian population, and only one study evaluated dose concentration among Iranian patients and demonstrated lower daily dose requirements in our population.[22] From this study and ours, we may conclude that most Iranian patients are slow metabolizers, and this might be protective against rejection in patients with high Tac-IPV, as stated by Thölking *et al.*[23]

CMV viremia, BK viremia, CNI toxicity, and NODAT were also evaluated as markers of overimmunosuppression among patients with high Tac-IPV. The current study found a higher rate of BK viremia among patients with high Tac-IPV, while there was no significant difference in CMV viremia and CNI toxicity. These results are in agreement with those obtained by Turgut *et al.* and Thölking *et al.* which demonstrated an association between high IPV and fast metabolizers with BK virus nephropathy.[9, 24] However, we did not find any difference in CNI toxicity and CMV viremia. Lack of difference in CMV viremia might be due to the fact that all patients received universal prophylaxis with valganciclovir. Another variable was NODAT, which was higher in the low Tac-IPV group. This finding was contrary to the study of Carrera *et al.*, suggesting high Tac-IPV as a risk factor for NODAT,[25] while Whalen *et al.* found no difference in NODAT between the groups.[4] A possible explanation for our finding might be higher BMI (although not statistically significant) in the group with lower Tac-IPV (25.14 ± 4.66 vs. 28.77 ± 21.51 kg/m2, P = .189).

To our knowledge, this was the first study in Iranian kidney transplant recipients that evaluated the effects of Tac-IPV on graft outcome. These findings have some limitations including the small number of participants, retrospective design and lack of genetic evaluation of CYP3A5 polymorphism.

According to our data, we can infer that Tac-IPV is low in adherent patients (with the median of 13.28%), and its effects on graft outcomes including eGFR and biopsy-proven acute rejection are attenuated by maintaining mean trough level above 7 ng/ml. Apart from that, almost 82% of our cohort has C0/D > 1.55 ng/mL/mg, which might suggest high prevalence of slow metabolizer among Iranian population.

According to our finding, maintaining tacrolimus trough level above 7 ng/mL can overcome the adverse graft outcome of Tac-IPV in compliant outpatient kidney transplant recipients.

ABBREVIATIONS

AMR: Antibody-mediated Rejection
BKV: BK virus
C0: Trough Level
C0/ D: Dose-adjusted Trough Concentration
CMV: Cytomegalovirus
CNI: Calcineurin Inhibitor
CV: Coefficient Variation
de novo DSA: de novo Donor-specific Antibody
eGFR: Estimated Glomerular Filtration Rate
ESKD: End-stage kidney disease
NODAT: New-Onset Diabetes After Transplantation
Tac-IPV: Intrapatient Variability
TCR: T cell-mediated Rejection

Supplementary File 1

Immunosupprresant thherapy adherence scale (ITAS)

Questions:

1. In the last 3 months, how often did you forget to take your immunosupprresant medication(s)?
2. In the last 3 months, how often were you careless about taking your immunosupprresant medication(s)?
3. In the last 3 months, how often did you stop taking your immunosupprresant medication(s) because you felt worse?
4. In the last 3 months, how often did you miss taking your immunosupprresant medication(s) for any reason?

Coded: 3 for "0% (none) of the time; 2 for "1-20% of the time"; 1 for "21-50% of the time"; 0 for "greater than 50% of the time"

Scoring: low 0 to a high 12

12 is defined as compliant. (5)

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