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Tacrolimus Variability In Transplantation

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Abstract

Introduction. Current immunosuppressive drug treatment in renal transplantation includes tacrolimus (TAC). Individual variability of TAC blood level burdens the efforts of clinicians to achieve its optimal dose and to reduce the chance of either rejection or toxicity. The purpose of our study was to determine the intra-patient variability and metabolism type of tacrolimus.
Methods. Weekly tacrolimus trough levels were obtained in 40 stable kidney transplant recipients 6 months after transplantation, receiving TAC twice daily. As inclusion criteria, at least three consecutive TAC values were needed. Demographic (age, gender, body weight), laboratory (albumin, creatinine, TAC) and TAC prescription data was obtained from medical charts. Renal function was estimated by Cockroft-Gault Equation. TAC variability was quantified as the coefficient of variation (CV). TAC metabolism rate was estimated as TAC blood trough concentration (C) divided by the daily dose (D). Fast TAC metabolism was defined by C/D rate below 1.05 Predictors of intra-patient TAC variability were estimated with regression analysis on the demographic, laboratory data and renal function.
Results. The mean age of study participants was 43± 13.37 years, 29(72%) were men. TAC values ranged from 2.46-12.48, with mean value of 6.42±1.86 ng/ml. The median CV for the entire population was 22.49% (range 7.95%-48.12%). The regression analysis did not identify any demographic, laboratory characteristics, or graft function associated with CV. Twenty percentage of patients had CV > 30% and 12.5% were identified as fast metabolizers.
Conclusions. In our study tacrolimus did display a moderate intra-patient variability. High tacrolimus variability may identify a subset of patients who warrant increased surveillance and patient education regarding dietary and medication compliance.

Keywords: tacrolimus, intra-patient variability, fast metabolizers, predictors, transplantation

Introduction

Current immunosuppressive drug treatment in renal transplantation includes tacrolimus (TAC). Individual variability of TAC blood level burdens the efforts of clinicians to achieve its optimal dose and to reduce the chance of either rejection or toxicity [1,2]. The importance of trough level as a practical indicator is widely used from introducing the drug [3] and still being investigated [4,5]. After rapid absorption and peak achieved within the first 3 hrs following the dose TAC shows marked intra-and inter-patient variability in its absorption [6]. It depends on gastrointestinal transit time and may be affected by interaction with food, especially lipids [7]. The daily dosage requirements also depend on age, gender, body mass index, serum albumin, hematocrit, and liver disease [8,9]. The industry is still seeking for different and new formulations with better pharmacokinetic and tolerability profiles [10], even including genotype investigations [11,12]. The purpose of our study was to determine the intra-patient variability and metabolism type of tacrolimus in stable kidney transplant patients.

Material and methods

A retrospective analysis on a cohort of kidney transplant patients at our Department in the period between 2014 until 2018 was conducted. As inclusion criteria, at least three consecutive TAC values were required during the outpatient follow up. Weekly tacrolimus trough levels were obtained in 40 stable kidney transplant recipients 6 months after transplantation, receiving TAC twice daily. All patients were blood sampled in the morning at 9 o'clock, 12 hours after the last tacrolimus dose was taken. Demographic (age, gender, body weight), laboratory (albumin, creatinine, TAC) and TAC prescription data was obtained from medical charts. Renal function was estimated by Cockroft-Gault Equation calculation. TAC variability was quantified as the coefficient of variation (CV), when the standard deviation was divided with the mean and multiplied by 100. Patients with CV >30% were considered with high va-

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riability. TAC metabolism rate was estimated as the TAC blood trough concentration (C) divided by the daily dose (D). Fast TAC metabolism was defined by C/D rate below 1.05 Predictors of intra-patient TAC variability were estimated with regression analysis on the demographic, laboratory data and graft function.

Results

Out of 40 transplanted patients, in 33 of them first living kidney transplantation was performed. The remaining 7 were transplanted from cadavers, and in one patient this was second transplantation. Clinical, demographic and laboratory parameters of study group are shown in Table 1. The mean age of study participants was 43±13.37 years, 29 (72%) were men. TAC values ranged from 2.46-12.48, with mean value of 6.42±1.86 ng/ml. The median CV for the entire population was 22.49% (range 7.95% - 48.12%). The mean daily dose of TAC ranged from 1-7.2 mg. Twenty percentage of patients had CV > 30% and 12.5% were identified as fast metabolizers.

Table 1. Clinical, demographic and laboratory parameters of the study cohort

N=40	Mean SD	min-max
Men (%)	29(72%)	
Age (years)	43.0± 13.37	19-75
Body weight (Kg)	69.47±12.88	35-96
Albumin (g/l)	41.82±3.39	32-49
Creatinine (mol/l)	148.45±80.42	61.67-431.51
eGFR (ml/min)	65.28±24.99	22-128
$C_{(Mean\ TAC\ in\ blood)}$ (ng/ml)	6.43±1.86	2.46-12.48
$D_{(Mean\ TAC\ daily\ dose\ )}$(mg)	2.96±1.31	1-7.2
$SD_{(Mean\ TAC\ in\ blood)}$	1.43±0.71	0.45-3.26
Mean CV_{TAC} (%)	22.41± 9.10	7.95-48.12
Mean C/D	2.69±1,57	0.34-8.90
CV > 30%	(20%)	
C/D <1.05	(30%)	

Out of 238 TAC measurements, 169 (71%) were within the target range of 5-10 ng/ml, 57(24%) were below and 12 (5%) were above it. The bell-shaped curves of both parameters for TAC blood level and CV showed the normal distribution (Figure 1 and 2). In only one patient the mean level of TAC was above 10 and in three it was below 5 ng/ml.The regression analysis did not identify any demographic, laboratory characteristics, or graft function associated with CV (Table 2). There was no significant correlation between CV and C/D ratio (r=0.073, p=0.654).

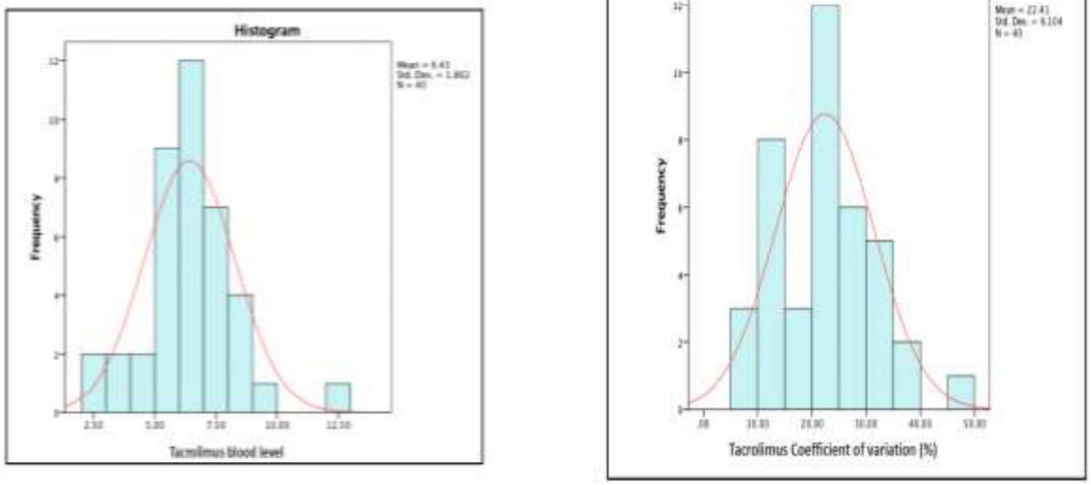

Fig. 1 and 2. Bell shape curves of Tacrolimus blood level and Coefficient of variation

Table 2. Regression analysis on tacrolimus variability

Factor		p
Gender	- 0.121	0.897
Age (years)	- 0.115	0.485
Body weight (Kg)	- 0.120	0.467
Albumin (g/l)	0.047	0.366
eGFR (ml/min)	0.115	0.487

Discussion

Our results on TAC blood though levels suggest appropriate drug management in the vast majority of patients. Even though, 20% of patients had tacrolimus variability over 30%, the value that was found in other study was as significant predictor of worsened graft survival [2]. Also the standard deviation of tacrolimus level in our patients was rather low, when compared to other studies where the values above were found as significant predictor of worse graft outcomes. In the Sapir-Pichhadzes study, among 356 patients, there was a significant 27% increase in the adjusted hazard of the composite end point for every 1-unit increase in TAC

SD [1]. Considering suboptimal dosing of tacrolimus as risk for graft loss [13], we found 24% of all 238 tacrolimus measurements to be under 5mg/ml. No significant factor of tacrolimus variability emerged from the regression analysis. As a limitation of our study, we did not have any data on food patterns or gene expressions, which are currently being explored [7,11]. Also, the number of patients was only forty, with potential influence on statistical significance considering gender. Partly, the variability could be explained by fast metabolism, and 30% of our patients were identified in this group. In this retrospective analysis based on patients' charts, we did not found prescribed medications that could interact with tacrolimus, apart from diltiazem in few of them. The medication compliance is also potent factor on tacrolimus variability that we did not take into consideration [14]. Since no other influencing factor on variability of tacrolimus levels we found modifiable, we considered exploring it and providing education for patients at risk for the graft lost.

Conclusion

In our study tacrolimus did display a moderate intra-patient variability. High tacrolimus variability may identify a subset of patients who warrant increased surveillance and patient education regarding dietary and medication compliance.

Conflict of interest statement. None declared.

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