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Original Article

Studying the Blood Trough Level of Tacrolimus on Patients after Kidney Transplant at the Uronephreulogical Department, Bach Mai Hospital, Vietnam

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Abstract: Tacrolimus, a calcineurin inhibitor, is a first-choice drug for the anti-rejection treatment regimen after kidney transplantation. The daily adjusted Tacrolimus dose by therapeutic drug monitoring is essential for patients to achieve optimal effects and minimize complications. We conducted a retrospective analysis of 70 kidney transplant patients at Bach Mai Hospital from January 2019 to the end of June 2020 to monitor changes in the blood trough level of Tacrolimus over time and analyze some risk factors affecting the blood trough level of Tacrolimus after a kidney transplant. Total whole-blood samples were collected at 6 time points: pre-transplant, on transplant day, and the 1st, 2nd, 4th, and 8th day after surgery. During the study, we recorded 4 cases with accelerated acute rejection with the blood trough level of Tacrolimus on the first day after transplantation of 5.325 ± 1.531 ng/mL and lower than the medium level in the remaining group of patients 10.371 ± 4.550 ng/mL at the same time ($p = 0.031$). There was no significant difference between the two groups of patients in age, gender, BMI, chronic disease status (hypertension, hepatitis C, type 2 diabetes), pre-transplant blood urea, and serum creatinine concentrations. These characteristics were included in the linear regression models which affected the blood trough level of Tacrolimus. This showed that none of the above risk factors had a significant effect on the blood trough level of Tacrolimus on the first day after transplantation ($p > 0.05$).

Keywords: Kidney transplantation, rejection, blood trough level of Tacrolimus, therapeutic drug monitoring.

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1. Introduction

Kidney transplantation is an optimal treatment therapy for patients with end-stage renal failure [1]. Worldwide, the number of kidney transplant patients has been in-creasing due to the treatment demand [2, 3]. Although renal transplantation is an essential treatment for patients with end-stage renal failure, transplant rejection is still a challenge for clinical physicians [4]. An annual data report in 2015 showed that the incidence of acute rejection within the first year is around 7.9% [5]. In order to stabilize the function of the transplanted kidney, prevent complications and prolong the time of the transplanted kidney, patients are screened and selected appropriate kidney and maintained lifelong immunosuppressive therapy [6].

Among the antirejection drugs group, Tacrolimus, the calcineurin inhibitor, is the first choice for the anti-rejection regimen after kidney transplantation. Tacrolimus is evaluated as a drug with high efficacy, low rate of acute rejection and minor ne-phrotoxicity [7, 8]. However, it has complex pharmacokinetic variability and a nar-row therapeutic range [9, 10]. Therefore, monitoring and adjusting the dosage of tacrolimus in the patients is indispensable. This process is accomplished by adjusting the daily dosage to maintain optimal drug concentrations; however, the therapeutic range of Tacrolimus has not been defined clearly yet. Many factors affect drug's pharmacokinetics and the relationships between drug concentrations and parameters are not fully confirmed [11, 12]. In Vietnam, along with the increasing demand for kidney transplant, studies on the use of antirejection drugs are essential but at present, there are not many studies on this issue.

To provide more scientific evidence on the monitoring of Tacrolimus after kidney transplantation at the Uronephreulogical Department, Bach Mai Hospital, we carried out this research to determine the trough concentration of Tacrolimus in patients within first eight days after renal transplantation and explore some risk factors toward Tacrolimus trough level in patients after kidney transplantation.

2. Research Subjects and Methods

2.1. Research Subjects

The patient underwent a kidney transplant hospitalized at the Department of Neph-rology and Urology, Bach Mai Hospital from January 1, 2019 to June 30, 2020.

2.2. Selection Criteria

All kidney transplant patients hospitalized at Bach Mai hospital between 1 January 2019 and 30 June 2020 were included in the study at the age upper 18 years and maintained on daily tacrolimus therapy.

2.3. Exclusion Criteria

Patients had multiple organ transplants besides kidney transplantation.

2.4. Research Methods

In this retrospective study and convenience sampling method from the medical records, we selected 70 eligible patients over 18 months to be included in the study.

2.5. Data Collection

The data collected from patient medical records included:

- General patient information: age, sex, height, weight, cause of kidney failure, history of diseases, kidney transplantation day and length of hospital stay, serum urea and creatinine before transplantation.
- Data on Tacrolimus therapy: the trough tacrolimus level was measured at 6 time points: pre-transplant N; on the day of transplant and after transplant N0; day 1 post-transplant N1; day 2 post-transplant N2; day 4 post-transplant N4 and day 8 post-transplant N8. Cases of graft rejection and tacrolimus dose change were also investigated. Diagnosis of chronic renal failure

was according to National Kidney Foundation (2012) [13] and BMI classification was according to the World Health Organization WHO specifically for Asians over 20 years old (IDI & WPRO) [14].

2.6. Statistical Analysis

Data were collected and cleaned before statistical analysis using IBM SPSS 26 software. Categorical variables were expressed as numbers (%), and continuous variables were expressed as mean ± standard deviation or as the median and interquartile range (IQR). The comparison of difference between quantitative variables was analyzed by the t-student test if the samples had normal distribution and Mann-Whitney U Test if the samples had non-normal distribution. The difference between qualitative variables was analyzed by the Chi-square $\chi 2$ test or Fisher Exact test. Univariable linear regression analysis identified the risk factors influencing the trough tacrolimus level. P-value less than 0.05 was considered to be a statistically significant difference.

2.7. Ethical Statement

The study was approved by Department of Biochemistry, Bach Mai Hospital. The patient's information was guaranteed to be safe, confidential and used only for research purposes.

3. Results

3.1. General Characteristics of Study Population

The general characteristics of study patients are shown in Table 1. The average age of patients in our study was 34 years old, of which most patients were less than 40 years old, accounting for 74.3%. The proportion of male patients was higher than female patients, accounting for 70% and 30%, respectively. More than half of the patients had a normal BMI (54.8%). The proportions of patients having chronic disease including hypertension, hepatitis C virus and type 2 diabetes accounting for 60%, 10% and 2.9%, respectively.

Table 1. General characteristics of study population

Characteristics (n)		n (%)	Mean ± SD
Age (years)	< 40 40 - 59 ≥60	52 (74.3) 16 (22.9) 2 (2.9)	34.70 ± 10.88
Sex	male Female	49 (70) 21 (30)	
BMI (kg/m2)	< 18.5 18.5 – 22.99 23 – 24.99 ≥ 25	16 (25.8) 34 (54.8) 6 (9.7) 6 (9.7)	20.51 ± 2.89
Chronic diseases	Hypertension Hepatitis C virus Type 2 diabetes	42 (60) 7 (10) 2 (2.9)	
Days of hospital stay			16.04 ± 3.14

3.2. The trough level C_0 and doses of Tacrolimus in study patients

In this study, we analyzed the trough concentration and dose of Tacrolimus at 6 time points: pre-transplant (N); on transplant day, post-transplant (N0), day 1 post-transplant (N1), day 2 post-transplant (N2), day 4 post-transplant (N4) and day 8 post-transplant (N8). Tacrolimus dose was expressed as the total dose over 24 hours (mg/kg/day). The results are presented in Table 2 and Figure 1. The trough tacrolimus level C_0 before renal transplantation has an average value of 5.094 ± 3.16 ng/mL. On the first

day after transplantation, the trough tacrolimus level was the highest (10.083 ng/mL) and fluctuated (ranging from 2.8 to 23.1 ng/mL). At the end of the following period, the Tacrolimus trough level was 5,394 ± 1.518 ng/mL. Correspondingly, the starting dose of Tacrolimus was around 0.1 mg/kg/day twice per day (0.097 ± 0.012 mg/kg/day), the doses were adjusted based on the patient's response through the trough level C_0. Generally, the doses of tacrolimus tended to increase gradually over time. At the end of the follow-up period, the maximum dose of Tacrolimus was 0.154 ± 0.046 mg/kg/day.

Table 2. The trough tacrolimus level C_0 and tacrolimus dose on patients

Time	Trough level C_0 (ng/mL)		Tacrolimus dose (mg/kg)	
	$\bar{x}$± SD	Min-Max	$\bar{x}$± SD	Min-Max
N	5.094 ± 3.160	1.2 – 15.7	0.097 ± 0.012	0.060 – 0.146
N0			0.104 ± 0.017	0.057 – 0.149
N1	10.083 ± 4.582	2.8 – 23.1	0.095 ± 0.028	0.040 – 0.173
N2	7.875 ± 3.697	2.3 – 20.1	0.098 ± 0.033	0.031 – 0.191
N4	4.805 ± 1.656	1.8 – 9.1	0.117 ± 0.036	0.040 – 0.243
N8	5.394 ± 1.518	2.6 – 9.2	0.154 ± 0.046	0.051 – 0.301

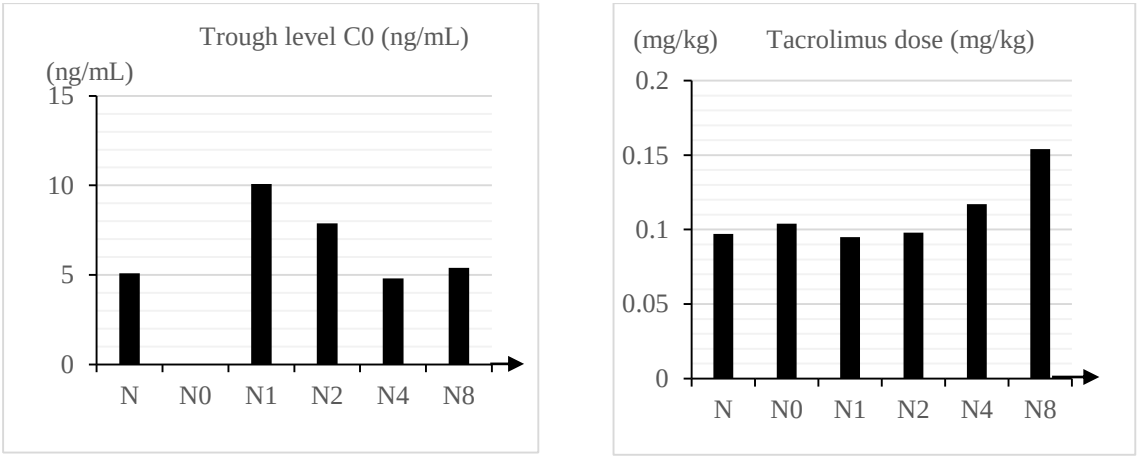

Figure 1. The trough tacrolimus levels and tacrolimus doses.

(At 6 time points: pre-transplant N; on the day of transplant and after transplant N0; day 1 post-transplant N1; day 2 post-transplant N2; day 4 post-transplant N4 and day 8 post-transplant N8) During the follow-up period, we noted any clinical abnormalities, laboratory tests, and adverse events in the patients, especially graft rejection complications. The results recorded 4 cases with acute rejection complications. To investigate the correlation between the trough tacrolimus level and the acute rejection event, we analysed the serum trough tacrolimus level. The results showed that the patients with acute rejection had a significant difference in the trough tacrolimus level C0 compared to the non-acute rejection group on day 1 and day 4 post-transplant (Table 3). The trough tacrolimus level on the first day after transplantation in the group with acute rejection was lower ($p = 0.031$) and on the 4th day was higher than that of the group without acute rejection ($p = 0.018$). By the end of the follow-up time, the trough tacrolimus concentrations C0 in both groups were similar.

Table 3. The trough tacrolimus level in two patient groups with and without acute graft rejection

Time	Acute graft rejection group (n=4)	Non- acute graft rejection group (n=66)	p
N	3.200 ± 1.985	5.211 ± 3.191	0.219
N1	5.325 ± 1.531	10.371 ± 4.549	0.031
N2	5.700 ± 2.712	8.011 ± 3.723	0.228
N4	7.450 ± 2.334	4.666 ± 1.531	0.018
N8	4.725 ± 1.340	5.438 ± 1.529	0.367

3.3. Some Factors Affecting the Trough Tacrolimus Level in Patients on the First Day after Kidney Transplantation

We compared some characteristics between the two groups with acute rejection and non-acute rejection including age, gender, BMI, chronic diseases (hypertension, hepatitis C virus, type 2 diabetes), serum urea and serum creatinine before transplantation (Table 4). At the same time, we used the univariate linear regression model to explore the correlation between these factors and the trough tacrolimus level C_0 on the first day after kidney transplantation (Table 5).

Table 4. General characteristics of patients in two groups with and without acute rejection

Characteristics (n = 70)		Acute rejection group (n = 4)	Non-acute rejection group (n = 66)	p
Tacrolimus trough level on the 1st day post-transplant (ng/mL) $\bar{x}$± SD		5.325 ± 1.531	10.371 ± 4.550	0.031
Tacrolimus starting dose (mg/kg) $\bar{x}$± SD		0.098 ± 0.012	0.097 ± 0.012	0.852
Age (years) $\bar{x}$± SD		29.25 ± 5.32	35.03 ± 11.07	0.306
Gender, n (%) Male Female		 3 (75.0) 1 (25.0)	 46 (69.7) 20 (30.3)	0.822
BMI (kg/m^2) $\bar{x}$± SD		19.94 ± 1.13	20.55 ± 2.98	0.684
Pre-transplant serum urea (mmol/L) $\bar{x}$± SD		12.60 ± 4.01	16.52 ± 4.23	0.078
Pre-transplant serum creatinine (µmol/L) $\bar{x}$± SD		705.50 ± 154.57	804.57 ± 211.20	0.363
Chronic diseases n (%)	Hypertension	3 (75.0)	39 (59.1)	0.528
	Hepatitis C	0 (0.0)	7 (10.6)	0.492
	Type 2 diabetes	0 (0.0)	2 (3.0)	0.724

Table 5. Univariate analysis of some factors affecting the trough tacrolimus level on the first day after kidney transplantation

Risk factor		Effect coefficient Beta	p
Age (years)		-0.083	0.492
Gender (Female/ Male)		-0.005	0.967
BMI (kg/m^2)		-0.178	0.166
Chronic diseases	Hypertension	-0.008	0.95
	Hepatitis C	0.020	0.869
	Type 2 diabetes	-0.062	0.613
Pre-transplant serum urea (mmol/L)		-0.094	0.483
Pre-transplant serum creatinine (µmol/L)		-0.075	0.568

4. Discussion

4.1. General Characteristics of the Study Population

The mean age of the patients in this study was 34.70 ± 10.88 years old, lower than that of other studies conducted on kidney transplant patients. In the research of C. Staatz in a hospital, Australia (2001) [15] and Kinga Krzyhowska at Silesia Medical University (2018) [16], the average age of patients was 47 years old, or around 50 years old in the study of P. Stratta in 2012 [17]. Moreover, in our study, the number of patients over 60 years old was only recorded 2 cases.

In our study, the mean BMI was 20,512 ± 2,898 kg/m^2, 54.8% of patients had normal BMI and the proportion of overweight and obese patients was only 19.4%. This rate was lower than in the Kinga Krzyhowska's study (the proportion of overweight and obese patients were 43.2%) [16].

Regarding the history of chronic diseases, the rate of patients with hypertension was the highest, followed by hepatitis C virus and type 2 diabetes, accounting for 60%, 10% and 2.9%, respectively. In the study of K. Krzyhowska, these diseases accounted for 91%, 7.2% and 9.2%, respectively [16]. The rate of patients with hepatitis C virus in P. Stratta's study was also 10%, similar to this of our study [17].

4.2. Tacrolimus Trough Level and Tacrolimus Doses on Patients

The study results showed that the trough concentration of Tacrolimus C_0 in 70 patients fluctuated most on the first day after kidney transplantation, even though all patients had the same Tacrolimus treatment regimen with a starting dose of 0.1 mg/kg/day. Acute kidney rejection usually occurs within a first few days post-transplant [4]. We recorded 4 cases of acute graft rejection during the follow-up time after kidney transplantation. The acute rejection group had a mean trough level of Tacrolimus on the first day post-transplant of 5.325 ± 1.531 ng/ml, which was significantly lower than the non-acute rejection group of 10.371 ± 4.550 ng/ml (p = 0.031). The study by C. Staatz showed that the mean the trough tacrolimus level in the first month after transplantation was 5.09 ± 1.16 ng/mL and 9.20 ± 3.52 ng/mL in the non-acute rejection group [11]. Patients were assigned a triple regimen of Tacrolimus + Azathioprine + corticosteroids with an initial Tacrolimus dose of 0.075 mg/kg/day divided 2 times to reach a target trough tacrolimus level of 10 - 20 ng/mL. This study also showed a strong correlation between the low trough concentration of Tacrolimus and the high rejection rate, with 5/29 cases of rejection [11]. Our study used a 3-drugs regimen of Tacrolimus + Mycophenolate + corticosteroids with a higher starting dose of Tacrolimus (0.1 mg/kg/day) and a lower target concentration of 5-15 ng/mL. The use of mycophenolate mofetil instead of azathioprine helped the higher graft survival rate and lower rejection rate in our study (4/70 patients) compared with C. Staatz's study [11].

4.3. Some Factors Affecting the Trough Tacrolimus Level on the First Day after Kidney Transplantation

In clinical practice, the dose of Tacrolimus is adjusted daily on each patient's response to maintain the trough concentration of Tacrolimus in the range of 5-15 ng/mL [6, 18]. Many studies confirmed that trough levels post-transplant below 5 ng/mL increased the risk of transplant rejection [7, 8, 19, 20].

In this study, we found that at the same dose of Tacrolimus, the trough concentration on the first day post-transplant of 4 patients with acute rejection was significantly lower than that of non-acute rejection patients ($p<0.05$). Several risk factors have been concluded in the previous research affecting the rejection of tacrolimus such as age, gender, BMI and hepatitis C virus [16, 21, 22]. In this study, we analyzed the correlation between factors (including age, sex, BMI, chronic diseases, pretransplant blood urea concentration and serum creatinine level) and the trough tacrolimus level using a univariate

linear regression analysis model. The results showed no significant differences in these characteristics between the two groups of patients with and without acute transplant rejection. Our study also showed that none of the above factors significantly affected the trough concentration of tacrolimus on the first day after transplantation. This result was similar to the previous study by P. Stratta (2012) [17], which indicated that the factors including age, sex, BMI and hepatitis C virus did not affect the trough tacrolimus level.

Many published researches suggested that there were many other risk factors affecting tacrolimus metabolisms such as genetic polymorphisms (CYP3A5*1, CYP3A5*3, CYP3A4*1B, CYP3A4*1G) [22-27] or drug-drug interactions with some antihypertensive drugs (nifedipine) [25], proton pump inhibitors (PPIs), antibiotics (trimethoprim/ sulfamethoxazole) [16], drug-food interactions [7]. However, due to limited resources, we have not been able to analyze these factors in this study. In addition, the sample size of this study was small and many parameters had not been evaluated, so it was impossible to determine the overall impact on Tacrolimus concentration.

However, our study initially showed a correlation between the acute rejection rate and the low trough level on the first day after kidney transplantation. This result suggests the high risk of rejection in patients with a low trough tacrolimus level on the first day post-transplant during the postoperative care of kidney transplant patients.

5. Conclusion

This study was conducted on 70 kidney transplant patients, with 4 cases of acute rejection. Within 8 days after kidney transplantation, the trough concentration of Tacrolimus on the first day after transplantation had the highest mean value and the largest fluctuation. Four patients with acute rejection had lower mean trough tacrolimus level and a higher tacrolimus dose than the group without acute rejection. On the first day post-transplant, the trough concentration of the patients with acute rejection was 5.325 ± 1.531 ng/ml, which was significantly lower than that of the other group of 10.371 ± 4.550 ng/ml ($p = 0.031$). Univariate linear regression analysis did not find any factors among age, sex, BMI, chronic diseases (hypertension, hepatitis C virus, type 2 diabetes), pre-transplant serum urea concentration and serum creatinine affecting the trough tacrolimus concentration in patients on the first day after kidney transplantation in our study ($p > 0.05$).

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