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THERAPEUTIC DOSAGE RANGES AND CHRONIC ADVERSE EFFECTS OF TACROLIMUS IN THAI KIDNEY TRANSPLANT PATIENTS

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ABSTRACT

Objective: This study proposed to study the therapeutic dosage ranges and to determine the prevalence of and the risk factors for the adverse effects of Thai tacrolimus-based therapy kidney transplant patients.

Methods: The fifty-nine kidney transplant patients who had kidney transplantation between January 2016 and May 2018 and were non-diabetic, non-hypertension, and normal kidney parameters before kidney transplantation were enrolled and followed up for 6 months. Data on graft rejection episodes and three significant adverse effects of tacrolimus, nephrotoxicity, hypertension (HTN), and post-transplant diabetes mellitus (PTDM) at each time point were recorded and analyzed.

Results: The range and mean (±standard deviation) of tacrolimus troughs level for the 204 points were 3.9–10.2 ng/ml and 6.4±1.8 ng/ml, respectively. About 73% of patients had HTN, 61% were on antihypertensive drugs, and 32% had PTDM. Seven patients (12%) proved to have allograft rejection by kidney biopsy. Only four patients did not have any three adverse effects. Similarly, laboratory parameters (SCr, BUN, and blood pressure) were identical during each period. All patients received prednisolone and mycophenolate mofetil as part of the comedication immunosuppressive regimen.

Conclusion: There was no significant difference between tacrolimus chronic adverse effects and therapeutic tacrolimus trough concentrations in Thai kidney transplant patients. Further investigations concerning pharmacokinetics and pharmacodynamics will be needed to improve the efficacy and safety of tacrolimus.

Keywords: Therapeutic dosage ranges, Chronic adverse effects, Tacrolimus, Kidney transplant patients.

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INTRODUCTION

Kidney transplantation is the most frequently performed solid transplantation in the world. It is the best treatment of end-stage renal disease because it enhances survival rate, decreases complications, and improves the quality of life of transplant recipients. After transplantation, the best goal of the immunosuppressive treatment is to prevent graft rejection with minimal adverse effects [1].

Tacrolimus is an essential immunosuppressive agent in the calcineurin inhibitors, which inhibits T cells activation and reduces immune response to prevent graft rejection in kidney transplant patients [2]. It is widely used in kidney transplantation in many countries because the current 1-year survival rate reaches more than 95% [3]. Tacrolimus has a narrow therapeutic window; therefore, therapeutic drug monitoring is required. Tacrolimus trough concentration is the standard marker of drug exposure and is ideal for monitoring post-transplantation clinical outcomes, especially allograft rejection. It is recommended at 10–15 ng/ml during the first 3 months (induction phase), followed by 5–10 ng/ml in the maintenance phase. Significant toxicity is seen with trough levels of 15 ng/ml [4]. At Srinagarind Hospital, Thailand, the dose ranges with trough levels tacrolimus is 5–8 ng/ml (induction phase) and 3–5 ng/ml (maintenance phase), which are lower than the general information [5].

Other immunosuppressive agents that most prescribed in the kidney transplantation regimen are mycophenolate mofetil (MMF) and steroids. The frequency and type of immunosuppressive adverse effects are dependent on the drug regimen. Common significant adverse effects of tacrolimus include nephrotoxicity, hyperglycemia, and hypertension (HTN), which are dose-related [2,6].

Data on tacrolimus induced adverse effects are available in the United States and Europe. In Thailand, kidney transplant patients mostly receive grafts from cadaveric donors and did not have more data to correlate the adverse effects of tacrolimus with their dosages. The objectives of this study were to propose the therapeutic dosage ranges of tacrolimus and to estimate the prevalence of three adverse effects (nephrotoxicity, HTN, and post-transplant diabetes mellitus [PTDM]) in Thai kidney transplant patients who receive tacrolimus-based therapy and to assess the correlation of adverse effects with the trough tacrolimus blood levels, as well as with the other clinical data.

METHODS

Study design and populations

The study group consisted of 59 adult Thai kidney transplant recipients who had a kidney transplantation between January 2016 and June 2018. Only cadaveric (deceased) donor kidney transplant patients were enrolled. Kidney transplant patients who older than 18 years of age and were outpatients currently on tacrolimus-based therapy were included in the study. Exclusion criteria were pediatric patients, patients with pre-transplant comorbid illness with chronic kidney disease, HTN, and diabetes mellitus. Endpoints of the study were at the time tacrolimus was discontinued or the death of patients. Patient history, clinical examination, and laboratory examinations were recorded on inclusion and after 2 weeks, 1, 3, and 6 months after kidney transplantation. This study was approved by the Khon Kaen University Ethics Committee in Human Research, which Institutional Review Board Number was IRB00001189 (Reference No. HE581019). Written informed consent was obtained from all participants.

Immunosuppressive drugs

The immunosuppressive protocol followed in this study is a triple-drug regimen consisting of tacrolimus, MMF, and steroids. Tacrolimus was started within 12 h after kidney transplantation with an initial dose of 0.05 mg/kg twice daily. Tacrolimus trough concentrations were measured every visit, and the dosage of tacrolimus was adjusted to achieve the range 5–8 ng/ml (induction phase) and 3–5 ng/ml (maintenance phase). This assay was done when there was evidence of graft rejection. Tacrolimus trough level was detected by chemiluminescent microparticle immunoassay (Architect tacrolimus reagent kit, Abbott ARCHITECT System [i1000SR] and Abbott Laboratories Ltd [IL, USA]) [7].

Data collection

Data were collected between January 2016 and November 2017 and followed up for 6 months. Fifty-nine patients were followed up until May 2018. The data included daily dose of tacrolimus, tacrolimus trough concentrations, details of biopsy-proven graft rejection, and three significant adverse effects: Nephrotoxicity, HTN, and PTDM. Follow-up for tacrolimus-associated adverse effects after discharge was done at the following intervals: Twice a week for the 1st month and then at 3-month intervals for 6 months.

Evaluation

Tacrolimus adverse effects were recorded and analyzed at routine visits at 2 weeks–6 months. Clinical laboratory data were recorded and analyzed.

Adverse effects criteria

Patients who had serum creatinine (SCr) >1.5 mg/dl (normal range, 0.6–1.2 mg/dl) were considered as nephrotoxicity. Persistence of elevated creatinine levels for more than three visits was taken as progression to chronic kidney disease. Biopsy-proven acute rejection was diagnosed if the patient increased SCr and had confirmation by kidney biopsy.

If a patient was on antihypertensive medications or had either sitting systolic blood pressure (BP) ≥130 mmHg, a diastolic BP ≥80 mmHg, or both was considered hypertensive.

PTDM was defined as when the fasting blood glucose concentration (FBS) was higher than 126 mg/dl or if insulin, hypoglycemic agents, or both were required. Steroid-induced glucose intolerance was not considered as PTDM. All patients were tested for fasting plasma glucose, HbA1C, or the presence of diabetes mellitus history for excluding diabetes mellitus before transplantation.

Statistical analysis

The abnormal clinical parameters and mean biochemical values were presented as percent means with standard deviations. All the adverse effects were compared between periods of follow-up. All statistical analyses were carried out by STATA statistical software package version 14.1 (StataCorp LP, College Station, Texas).

RESULTS

This study was carried out to determine the prevalence of adverse effects of tacrolimus in Thai kidney transplant patients. Over 17 months (January 2016 to May 2018), a total of 59 consecutive kidney transplant patients visited nephrology clinics at Srinagarind Hospital for 6 months were included in this study. Demographic and clinical data are shown in Table 1. Men were recruited more than women (men 63%). All patients were Thais and were relatively middle age (45.6±9.6 years).

All patients received a graft from deceased donors. It should be noted that in one-third of patients, the primary diagnosis was unknown.

Mean tacrolimus trough blood levels during 6 months were 6.4±1.8 ng/ml (Fig. 1). Only 65% of patients had tacrolimus concentrations within the target range of 5–8 ng/ml, and 35% had a level above 8 ng/ml. All patients were treated with tacrolimus, prednisolone, and MMF.

Table 1: Demographic and clinical characteristics of the patients at 6 months (n=59)

Characteristic	Mean±SD/ n (%)
Age in years	45.6±9.6
Gender (F/M)	22/37 (37.29/62.71)
Tacrolimus trough blood concentration (ng/ml)	6.4±1.8
Kidney function	
Serum creatinine (SCr), mg/dl	1.6±0.5
• Number of patients with SCr >1.5 mg/dl	20 (33.90)
• Number of patients with SCr >2.0 mg/dl	9 (15.25)
Patients with acute graft rejection	7 (11.86)
Blood pressure	
Systolic, mmHg	121.8±12.5
Diastolic, mmHg	77.6±9.4
Hypertensive patients with BP 130/80 mmHg	43 (72.88)
Hypertensive patients on antihypertensive drugs	36 (61.02)
Glycemic status	
Fasting blood sugar (FBS) (mg/dl)	113.8±19.5
Patients with PTDM (FBS >126 mg/dl)	19 (32.20)

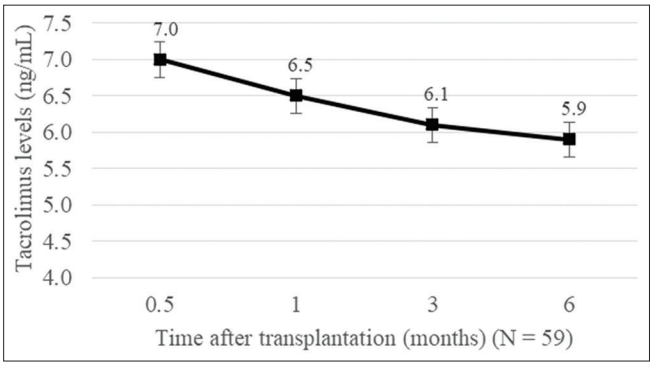

Fig. 1: Tacrolimus trough blood levels during the 6 months

Concomitant medications included mostly antihypertensive, lipid-lowering, hypoglycemic, antiplatelet, and anti-ulcer drugs.

Table 1 shows that seven patients had episodes of biopsy-proven acute rejection (12%). The rejection treatment regimens depended on individual patients. About 73% of renal transplantation patients had HTN, but only 61% had controlled BP by hypertensive agents. No patient had diabetes mellitus before transplantation, but PTDM developed in 32% of cases. One-third of patients had their FBS uncontrolled (>126 mg/dl).

When categorized patients into three trough levels (levels under range, levels in therapeutic range, and levels over range), the three significant chronic adverse effects (nephropathy, HTN, and PTDM) were not related. There was no significant difference between tacrolimus trough levels and chronic adverse effects, except patients with levels in the therapeutic range and levels over range had lower FBS <126 mg/dl, $p<0.05$ (Fig. 2).

The significant association between PTDM and the patient's age was found by complementary log-log link models ($p<0.001$) (Table 2).

DISCUSSION

There have been few reports of long-term (6 months and longer) adverse effects of tacrolimus-based immunosuppression therapy in kidney transplant patients [8,9]. Ethnic disparity has been shown for clinical outcomes after organ transplantation [10]. Furthermore, few

Table 2: Factors associated with three significant adverse effects in patients

Variables	HTN[a]		PTDM[a]		Nephrotoxicity[a]	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value
Age (Years)	0.95 (0.89, 1.00)	0.066	1.24 (1.11, 1.38)	<0.001	1.08 (0.98, 1.18)	0.102
Sex (Male)	0.64 (0.25, 1.65)	0.354	1.21 (0.23, 6.48)	0.823	0.13 (0.02, 0.78)	0.026
SBP (mmHg)	-	-	1.08 (0.97, 1.21)	0.163	1.09 (0.97, 1.22)	0.147
DBP (mmHg)	-	-	1.09 (0.97, 1.23)	0.139	0.93 (0.82, 1.06)	0.276
SCr (mg/dl)	0.58 (0.13, 2.50)	0.464	1.30 (0.24, 7.10)	0.759	-	-
FBS (mg/dl)	1.02 (0.99, 1.05)	0.229	-	-	0.99 (0.94, 1.04)	0.609

[a]HTN: SBP ≥130 mmHg and/or DBP ≥80 mmHg, PTDM: FBS ≥126 mg/dl, Nephrotoxicity: SCr >1.5 mg/dl

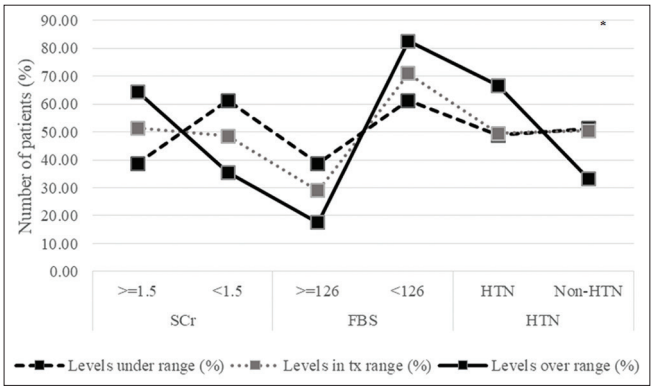

Fig. 2: Percent of patients categorized by three tacrolimus trough blood levels (levels under range, levels in therapeutic range, and levels over range), and three significant chronic adverse effects (nephropathy, PTDM, and hypertension)

studies were conducted to evaluate risk factors for only some, for example, PTDM, alopecia, malignancies, hearing impairment, and gum hypertrophy [11-15], but not the three significant adverse effects of tacrolimus-based immunosuppressant. This study is the first report that evaluates the prevalence of adverse effects of tacrolimus in Thai tacrolimus-based therapy kidney transplant patients, in which tacrolimus trough levels were lower than in other western countries.

In this study, the average tacrolimus dose was 0.05 mg/kg, which is lower than that in the earlier studies among kidney transplant recipients (0.1–0.15 mg/kg) [16]. The average tacrolimus trough concentration was 6.4±1.8 ng/ml, very similar to that in other studies. Despite using lower than usual tacrolimus doses, only 65% of patients were maintained in the target tacrolimus range of 5–8 ng/ml compared to 80% in a multicenter study [17], and 35% of patients had a tacrolimus level exceeding 8 ng/ml, which may cause tacrolimus adverse effects. Such an aggressive immunosuppressive regimen may have accounted for the low frequency of acute rejection episodes being very similar to that published for living related HLA identical donors. Unfortunately, it could have resulted in a higher incidence of adverse effects.

The mean SCr level was 1.6±0.5 mg/dl, similar to a 3-year study in kidney transplant patients [17]. Tacrolimus trough concentrations in this study were between 3.9 and 10.2 ng/ml and were associated with the least overall toxicity and graft rejection. Seven patients (12%) proved to have graft rejection by kidney biopsy, which was lower than other studies around the world (15–30%) [8]. Some studies showed that tacrolimus trough levels were directly related to acute graft rejection events [18-20]. On the other hand, this study demonstrated no association between tacrolimus levels and acute graft rejection.

Cardiovascular morbidity and mortality among kidney transplant patients are substantially higher than in the general population, and cardiovascular disorders are responsible for about one-third of all deaths with a functioning graft [21]. Hyperlipidemic, diabetogenic, and hypertensive effects of calcineurin inhibitors such as cyclosporine and tacrolimus increase the risk of significant atherosclerotic cardiovascular disease outcomes and are believed to be risk factors for chronic graft nephropathy in kidney transplant patients [22].

In this study, the majority of Thai kidney transplant patients (73%) had HTN, which was much more prevalent than in other studies in organ transplantation patients (10–68%) [4,9,23,24]. It should be noted that the incidence of HTN per 100,000 population was 1,146.70 in 2015. It was lower than the United States population (30% in males and 27% in females) [25]. Despite a high prevalence of HTN among kidney transplantation patients in Thai, the mean number of antihypertensive medications was lower than in a study where patients were converted from cyclosporine to tacrolimus [22].

PTDM is a common complication of kidney transplant patients. It is associated with an increased incidence of infectious and cardiovascular complications, impaired long-term graft function, and reduced survival rate [26]. Although most of the patients develop PTDM in the first 3 months after transplantation, its incidence increases with follow-up [27]. PTDM was identified in 32% of our patients, close to results obtained in cadaveric kidney transplant patients in Japan (29%) [11].

The estimated national prevalence of diabetes in Thai adults was less than in our study in kidney transplant patients (7.5% vs. 33%, $p<0.05$) [28]. PTDM patients in our study were 32%, which is close to results in the 3-year study in cardiac transplantation patients in Germany (29%) [29]. Mean fasting blood sugar in this study was lower than in cardiac transplantation patients (108 mg/dl vs. 114 mg/dl) [29]. However, only about half of diabetic patients in our study achieved glycemic control.

CONCLUSION

This study demonstrated a significant prevalence of cardiovascular and metabolic adverse effects in long-term kidney transplant recipients from cadaveric donors. These adverse effects may be explained in part by elevating tacrolimus blood concentrations despite low tacrolimus doses. It would be useful to assess more carefully the tacrolimus dose-concentration relationship among Thai kidney transplant patients. Further investigations concerning pharmacokinetics and pharmacodynamics will be needed to evaluate the efficacy and safety of tacrolimus. In addition, identifying patients at high risk for the development of tacrolimus induced three significant adverse effects will help clinicians to select the proper immunosuppressant dose to avoid these three adverse effects.

CONFLICTS OF INTEREST

The authors have indicated that they have no other conflicts of interest concerning the content of this article.

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