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 (creatinine, 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.

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 patients with chronic kidney disease, HTN, and diabetes mellitus. Endpoints of the study were 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. H5801019). 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 [11000SR] 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 biopsied-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, CoBege 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±10.6 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          |
| 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 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
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.

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%) [19,23,24]. 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.

REFERENCES

1. Omotoso BA, Turgut F, Abdel-Rahman EM, Xin W, Ma JZ, Scully KW, et al. Dialysis requirement and long-term major adverse cardiovascular
events in patients with chronic kidney disease and superimposed acute kidney injury. Nephron 2017;136:95-102.
2. Katzung B, Knudering-Hall M, Trevor A. Katzung and Trevor’s Pharmacology Examination and Board Review. 11th ed. New York: McGraw-Hill Education; 2015.
3. Klaassen RA, Bergan S, Bremer S, Daleg L, Andersen AM, Midtvedt K, et al. Longitudinal study of tacrolimus in lymphocytes during the first year after kidney transplantation. Ther Drug Monit 2018;40:556-66.
4. Fukuhara N, Ono Y, Hattori R, Nishiyama N, Yamada S, Kamihigashi O, et al. The long-term outcome of tacrolimus in cadaveric kidney transplantation from non-heart beating donors. Clin Transplant 2005;19:153-7.
5. Anutrakulchai S, Pongskul C, Kritmetapak K, Linwattananon C, Vannaprasath S. Therapeutic concentration achievement and allograft survival comparing usage of conventional tacrolimus doses and CYP3A5 genotype-guided doses in renal transplantation patients. Br J Clin Pharmacol 2019;85:1964-73.
6. Filler G. Finding the optimal therapeutic window for tacrolimus. Pediatr Transplant 2014;18:783-5.
7. Boonsom S, Vannaprasat S, Tassaneeyakul W, Wongratanacheewin S, Kaewraemruen C. Long term stability of immunophenotypic T cell subsets from whole blood of tacrolimus-based therapy kidney transplantation patients and healthy volunteers by flow cytometric analysis. Asia Pac J Sci Technol 2019;24:14456.
8. Hamida FB, Barbouch S, Bardi R, Helal I, Kaaroud H, Fatma LB, et al. Acute rejection episodes after kidney transplantation. Saudi J Kidney Dis Transpl 2009;20:370-4.
9. Pascual J, Ortuno J, Spanish, Italian Tacrolimus Study G. Simple tacrolimus-based immunosuppressive regimens following renal transplantation: A large multicenter comparison between double and triple therapy. Transpl Proc 2002;34:89-91.
10. Marcon R, Morales JM, del Castillo D, Canpistol JM, Seron D, Valdes F, et al. Posttransplant diabetes mellitus in renal allograft recipients: A prospective multicenter study at 2 years. Transpl Proc 2006;38:3530-2.
11. Numakura K, Satoh S, Tsuchiya N, Horikawa Y, Inoue T, Kakinuma H, et al. Clinical and genetic risk factors for posttransplant diabetes mellitus in adult renal transplant recipients treated with tacrolimus. Transplantation 2005;80:1429-34.
12. Tricot L, Lebbe C, Pillebout E, Martinez F, Legendre C, Thervet E. Tacrolimus-induced alopecia in female kidney-pancreas transplant recipients. Transplantation 2006;80:1546-9.
13. Caillard S, Agodoa LY, Bohan EM, Abbott KC. Myeloma, hodgkin disease, and lymphoid leukemia after renal transplantation: Characteristics, risk factors and prognosis. Transplantation 2006;81:888-95.
14. Rifaï K, Kirchner GI, Bahr MJ, Canti T, Restani P, Boni A, et al. A new side effect of immunosuppression: High incidence of hearing impairment after liver transplantation. Liver Transpl 2006;12:411-5.
15. Sekiguchi RT, Paixao CG, Saravia L, Romito GA, Pannuti CM, Lotufo RF. Incidence of tacrolimus-induced gingival overgrowth in the absence of calcium channel blockers: A short-term study. J Clin Periodontol 2007;34:545-50.
16. Sperschneider H, European Renal Transplantation Study G. A large, multicentre trial to compare the efficacy and safety of tacrolimus with cyclosporine microemulsion following renal transplantation. Transpl Proc 2001;33:1279-81.
17. Jensik SC. Tacrolimus (FK 506) in kidney transplantation: Three-year survival results of the US multicenter, randomized, comparative trial. FK 506 kidney transplant study group. Transpl Proc 1998;30:1216-8.
18. Arecoela-Guerra JM, Serrano M, Morales-Buenrostro LE, Vilatoba M, Alberu J. Tacrolimus trough levels as a risk factor for acute rejection in renal transplant patients. Ann Transplant 2016;21:105-14.
19. Huang CT, Shu KH, Ho HC, Wu MJ. Higher variability of tacrolimus trough level increases risk of acute rejection in kidney transplant recipients. Transpl Proc 2016;48:1978-80.
20. Leblanc J, Subrt P, Mare M, Hartnell D, Senecal L, Blydht-Hansen T, et al. Practice patterns in the treatment and monitoring of acute t cell-mediated kidney graft rejection in Canada. Can J Kidney Health Dis 2018;5:1-12.
21. Howard RJ, Patton PR, Reed AI, Hemming AW, Van der Werf WJ, Pfaff WW, et al. The changing causes of graft loss and death after kidney transplantation. Transplantation 2002;73:1923-8.
22. Margreiter R, Pohanka E, Sparacino V, Sperschneider H, Kunzendorf U, Huber W, et al. Open prospective multicenter study of conversion to tacrolimus therapy in renal transplant patients experiencing ciclosporin-related side-effects. Transpl Int 2005;18:816-23.
23. Margreiter R, European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study G. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: A randomised multicentre study. Lancet 2002;359:741-6.
24. Loinaz C, Marin LM, Gonzalez-Pinto I, Gomez R, Jimenez C, Moreno E: A single-centre experience with ciclosporin microemulsion versus tacrolimus in 100 randomized liver transplant recipients: Midterm efficacy and safety. Transpl Proc 2001;33:3439-41.
25. Zhang Y, Moran AE. Trends in the prevalence, awareness, treatment, and control of hypertension among young adults in the United States, 1999 to 2014. Hypertension 2017;70:736-42.
26. Kangar L, Mar et C, Delahousse M, Lefrancois N, Dantal J, Benhamou P. New onset diabetes mellitus incidence and risk factors in kidney transplantation: Results of the observational cross-sectional study diapason. Transpl Proc 2006;38:2295-9.
27. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation. Am J Transpl 2003;3:178-85.
28. Aekplakorn W, Chariyalertsak S, Kesompoon P, Sangthong R, Inthawong R, Putwatana P, et al. Prevalence and management of diabetes and metabolic risk factors in Thai adults: The Thai national health examination survey IV, 2009. Diabetes Care 2011;34:1980-5.
29. Groetzner J, Meiser BM, Schirmer J, Koglin J, Vseheid W, Klauss V, et al. Tacrolimus or cyclosporine for immunosuppression after cardiac transplantation: Which treatment reveals more side effects during long-term follow-up? Transpl Proc 2001;33:1461-4.