Tacrolimus Therapeutic Drug Monitoring in Vietnamese Renal Transplant Recipients

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ABSTRACT

Background: Use of tacrolimus (Tac) is pivotal to renal transplant (RT) immunosuppressive maintenance regiments. The most frequently used means of Tac monitoring is the measurement of the trough concentration (C0) in whole blood to maintain drug efficacy and minimize the consequences of overexposure. Most previous studies focused on therapeutic drug monitoring of Tac in renal transplant recipients and assessed the clinical response of patients. Our study aimed to describe a real Tacrolimus therapeutic drug monitoring transplantation and determine the clinical outcomes in Vietnamese adult renal transplant recipients. **Methods**: This retrospective study including 114 adult renal transplant patients (89 men and 25 women) with a mean age of 35.4 ± 8.98 years has been performed from August 2012 to March 2018 at Military Hospital 103 (Vietnam). Tac trough concentrations were adjusted according to the target range proposed by the European consensus conference on tacrolimus optimization. Samples for determination of tacrolimus blood levels were subdivided according to the post-transplantation period into three groups (0- 3 months (G1), 3-12 months (G2) and over 1 year (G3). Median Years of follow-up was 15.4 months [range 0.233 to 68.4 months]. **Results**: A total of 3037 blood samples for the determination of tacrolimus trough concentration were obtained. Median concentrations were 6.7 (4.5 – 10.2) ng/ml, 6.4 (5.1 – 8.3) and 5.6 (4.5 to 7.1) ng/ml for G1, G2, G3, respectively. After transplantation, three acute rejection (AR) events were documented (Cellular AR: 2, Humoral AR: 1). Cytomegalovirus, BK polyomavirus, Hepatitis B virus and Hepatitis C virus were detected in 7, 4, 7 and 3 renal post- transplant recipients, respectively. There were 5 patients with post-transplant diabetes (NODAT) and all of them had to convert to cyclosporine. 6 patients developed chronic kidney disease (CKD) after transplantation and 2 case with Tac-associated nephrotoxicity with proven biopsy. This observational study provided a real Tacrolimus therapeutic drug monitoring transplantation in Vietnamese renal transplant recipients. Main outcomes were acute rejection, post-transplant viral infections, neurotoxicity, NODAT, CKD, and Tac-associated nephrotoxicity.

Key words: Tacrolimus, Therapeutic drug monitoring, Renal transplantation, Vietnam.

INTRODUCTION

Tacrolimus (Tac) is a potent immunosuppressant drug that is well established for primary immunosuppression in kidney transplantation. It was introduced in the late 1980s as an alternative to cyclosporine-A for the prevention of graft rejection following solid organ transplantation.[1] Due to a narrow therapeutic index and its large interpatient and intra-patient pharmacokinetic variability, therapeutic drug monitoring (TDM) is routinely performed for individualization of the Tac dose to maintain drug efficacy and minimize the consequences of overexposure.[2] Nowadays, the most frequently used method of Tac monitoring is the measurement of the trough concentration (C0) in whole blood.

Therapeutic ranges of Tacrolimus have been changed remarkably. In 1995, Lake Louise Consensus Conference recommend preliminary target range of 5 to 20 ng/mL.[3] Tacrolimus trough concentrations were targeted at 3-7 ng/mL with Symphony- Elite.[4] Recently, the European experts on tacrolimus (2009) have proposed new target ranges of trough concentration based on both drug combination and post-transplantation delay. In regiment with mycophenolate mofetil (MMF) and steroid minimization, tacrolimus whole blood concentrations should range from10 to 15 ng/ml during the first 3 months after transplantation, 8 - 12 ng/ml in the next period (3 months–12 months), and from 5 ng/ml to 10 ng/ml thereafter.[5]

There were studies have evaluated the trough level tacrolimus according to time post-transplantation as well as efficacy and safety within those targets.[4,6] To now, there have been no reports of such studies performed on Vietnamese kidney transplant recipients. Our study aimed to simple description real Tacrolimus therapeutic drug monitoring and determine the outcomes in Vietnamese adult de novo renal transplant recipients.

MATERIALS AND METHODS

A retrospective study was carried out at Department of Renal and Haemodialysis, Military Hospital 103, including one hundred and fourteen Vietnamese

patients undergoing renal transplantation. Data of patients were obtained between August 2012 and March 2018. Patients between the ages of 18 and 75 years who received the first single-organ renal transplant from either a living donor or a deceased donor were eligible. Exclusion criteria were paediatric kidney transplant recipients, re-transplant or multi-organ transplant patients.

Immunosuppressant protocol used

The immunosuppressive protocol followed in our institution consisted of a triple drug regimen consisting of tacrolimus, mycophenolate mofetil (MMF) and steroids. Induction therapy included basiliximab (Simulect®, Novartis) pre- and 4 days post-operatively and 500 mg intravenous (IV) methyl prednisolone (Solu Medrol®: Pfizer) pre and 12 h postoperatively. Oral tacrolimus (Prograf®, Astellas Pharma) was started preoperatively with a dose of 0.1 mg/kg/day administered in two divided doses. The doses were adjusted in the range therapy followed European consensus conference (2009) or occurrence of the event of adverse effects, rejection. Mycophenolate mofetil (Cellcept®, Roche) was started with tacrolimus at a dose of 1g twice a day and adjusted to lower doses in presence of diarrhea or infection. The next IV dose of steroid decreased by a half in consecutive days to 40 mg/day within one to two weeks' post-transplant. Oral prednisolone (15 mg/day) was initiated right after and was tapered every week to maintaining period of 5 mg/day.

Tacrolimus measurements

Tac whole blood concentrations were determined using chemiluminscent microparticle immunoassay (CMIA, analysed on the Architect system, Abbott Diagnostics, IL, USA). The assay's detection limit was 0.8 ng/ml.

Tac trough concentrations were collected prior to the morning dose. Frequency tacrolimus assays were three times weekly the first two weeks, once every week in the third week and fourth week and then at each patient visit during following months. Samples for determination of tacrolimus blood levels were subdivided according to the post-transplantation period into three groups: 0- 3 months (G1), 3-12 months (G2) and over 1 year (G3).

Clinical outcomes

Efficacy end points included renal function as indicated by the calculated eGFR during the study, acute rejection (AR), overall patient survival. The eGFR were calculated from serum creatinine measures with the use of the Modification of Diet in Renal Disease formula.[7]

Safety was evaluated by clinical assessment including vital signs and laboratory analyses designed to determine the incidence of adverse events. The common adverse events were neurotoxicity, new-onset diabetes (NODAT), post-transplant viral infections, and gastrointestinal disorders, chronic kidney disease and Tac-inducted nephrotoxicity.

NODAT was defined by the American Diabetes Association (ADA) diagnostic criteria [8]. Patients were diagnosed NODAT based plasma glucose criteria, either fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test or A1C ≥ 6.5% or in a patient with classic symptoms of hyperglycemia crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

The blood sample were obtained from recipients who were suspected to have CMV, BK infection upon clinical presentation, physical examination and laboratory results. The disease was diagnosed according to the clinical features and quantitative polymerase chain reaction (qPCR) (and/or CMV antigenemia tests). Viral loads over 10 000 copies/mL for BKV and over 1000 copies/mL for CMV were considered clinically relevant.

The diagnosis of chronic HBV infection was based upon the persistence of hepatitis B surface antigen (HBsAg) for more than 6 months after transplantation. The diagnosis of chronic HBV infection was made in a patient with a positive anti hepatitis C virus test (anti HCV) and positive molecular test that detects the presence of HCV RNA after transplantation.

Chronic kidney disease (CKD) was defined as being present if the glomerular filtration rate (GFR) was < 60 mL/min/1.73 m^2 or evidence of kidney damage such as albuminuria or abnormal findings on renal imaging have been present for 3 months or more.

Research ethics

This study was approved by the Ethical Committee of Vietnam Military Medical University (No.169/2012/CN-HĐĐĐ issued on 20th Jul 2012). The study was in line with the 1964 Declaration of Helsinki. The informed consent forms were signed by all participants after full explanation.

Statistical analyses

Data management and statistical analyses were carried out using RStudio sofware. Variable distribution was determined with the Shapiro-Wilk test. The Anova test was used to compare normally distributed variables, and the Mann-Whitney U test was used to compare non-normally distributed variables. Variables with a normal distribution were expressed as the mean ± standard deviation (SD) and those with an abnormal distribution were expressed as the median and their interquartile range (IQR). Differences in proportions were analyzed using Fisher's exact test. Time to all events, acute rejection (AR), cytomegalovirus (CMV) and chronic kidney disease (CKD) were analysed by the Kaplan–Meier method.

RESULTS

Baseline characterstics of patients

One hundred and fourteen patients (89 men and 25 women) undergoing renal transplantation were included from August 2012 to March 2018. The mean (± SD) age was 35.4 ± 8.98 years. Median time of follow-up was 15.4 months [range 0.233 to 68.4 months]. Donors were mainly living people (97.4%). The patients' general characteristics are presented in Table 1.

The dosage of immunosuppressive drugs and Tac trough concentrations

Dosage of immunosuppressive drugs

Tacrolimus doses in three groups are presented in Table 2. In our population, median tacrolimus doses were reduced after transplantation (0.1 tapered to 0.07 mg/kg/day). Daily dose of mycophenolate mofetil were 1.87 ± 0.3 g.

Tacrolimus concentrations

A total of 3037 blood samples for the determination of Tac concentrations were recorded. The mean number of samples per patient was 26.6 (range 4 to 60). Using a therapeutic range of European consensus conference (2009), 33.3% tacrolimus concentrations were within target ranges in total and this proportion increased over time with the highest proportion in G3 (57%) compared with those in G1 (22.3) and G2 (24.3%). 2113 (48%) trough concentrations were under-threshold with 886 (73.5%), 570 (71.4%) and 377 (36.5%) in G1, G2 and G3, respectively (Figure 1).

Table 1: Demographic and clinical characteristics of patients.

Variable	Value
Age (years), mean (SD)	35.4 (8.98)
Male sex, n (%)	89 (78)
BMI (kg/m²), mean (SD)	20.0 (3.26)
Time follow-up (median month), range	15.4 (0.2 to 68.4)
Hypertension, n (%)	106 (93)
Virus, n (%)	
HBV	11 (9.6)
HCV	21 (18.4)
HBV & HCV	3 (2.6)
Induction therapy, n (%)	80 (70.2)
Type of donor, n (%)	
Deceased	3 (2.6)
Living related	42 (36.8)
Living unrelated	69 (60.5)
PRA, n (%)	
Negative	86 (75.4)
Positive PRA Class I	14 (12.3)
Positive PRA Class II	8 (7.0)
Positive HLA Class I & II	6 (5.3)
HLA mismatches, n (%)	
0	1 (0.7)
1-3	50 (43.9)
4-6	63 (55.4)
Groups divided according post-transplant time	
Group 1 (G1)	0-3 months
Group 2 (G2)	3-12 months
Group 3 (G3)	>12 months

Note: BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PRA: panel-reactive antibodies; HLA: human leucocyte antigen;

Table 2: Concentrations and doses of three groups.

	G1 (n = 114)	G2 (n = 99)	G3 (n = 67)	P value
Dose (mg/kg/day)[a]	0.1 (0.09 – 0.12)	0.1 (0.08 – 0.12)	0.07 (0.05 – 0.09)	<0.001
C0 (ng/ml) [a]	6.7 (4.5 – 10.2)	6.4 (5.1 – 8.3)	5.6 (4.5 – 7.1)	<0.001

[a]Results are expressed as median (IQR)

Clinical outcomes

Efficacy measurements

Renal function: Overall, renal function was remained relatively stable from about 4 weeks postoperatively. The eGFR was the most highest in the second group (G2) [64.9 *v.s* 61.0 (G1) and 62.7 (G3); P< 0,001] and then decreased following a year.

Acute rejection: Three biopsy-proven acute rejections (2.6%) were reported during the study and all of them were in the first three months after transplantation (2 patients were cellular rejection and one case was humoral rejection). Base on Improving Global Outcomes (KDIGO) clinical practice guidelines, three AR patients were high-risk for rejection because of having one or more risk factors for acute rejection include more human leukocyte antigen (HLA) mismatches (2 patients with 6/6 mismatches), positive panel reactive antibody (PRA) Class II and delayed onset of graft function (1 patient).

Patient survival: Overall survival rates for patients were 98.2%. Of the 2 deaths reported, 1 was caused by AR coexisting CMV pneumonia and the other was due to multi-organ CMV infection coexisting cerebral stroke and HCV.

Safety: Serious adverse events were neurotoxicity, new-onset diabetes (NODAT), post-transplant viral infections, chronic kidney disease (CKD), Tac-associated nephrotoxicity and gastrointestinal disorders Table 3. While neurotoxicity and NODAT only occurred early in the study (G1), the others were found in later periods. Cumulative hazard of all events and some separated outcomes were estimated by Kaplan-Meier analysis (Figure 2).

Neurotoxicity were headache (2 case), insomnia (07 cases), nausea or vomit (1 case), tired and anorexia (2 case).

The incidence of post-transplant diabetes mellitus was 4.4 % (5 patients) and all of them had to convert to cyclosporine.

Overall, incidence of post-transplant viral infections including CMV, BKV, HBV and HCV were 6.1 %, 3.5 %, 6.1 % and 2.6%, respectively. In CMV patients, an organ disease was observed primarily (lungs =5; kidney =1) and 1 case of multi-organ infection. All four patients with BKV developed chronic kidney disease and two of these cases had to switch to cyclosporine. In addition to 4 patients with BKV, chronic kidney disease has been detected in two other cases.

Tac-associated nephrotoxicity was observed with proven biopsy in two patients. One patient with prolonged gastrointestinal disorders changed medication from Tac to cyclosporine.
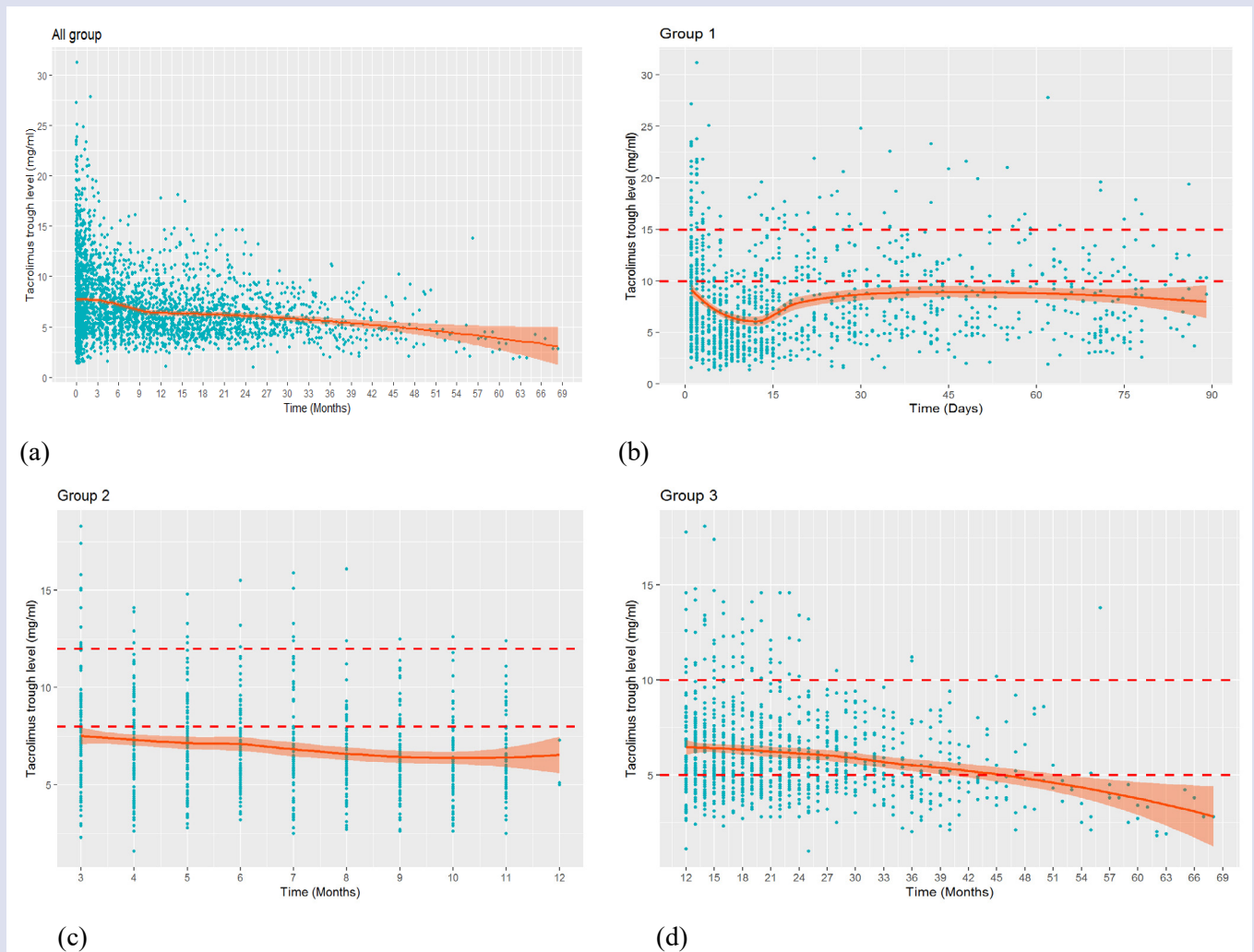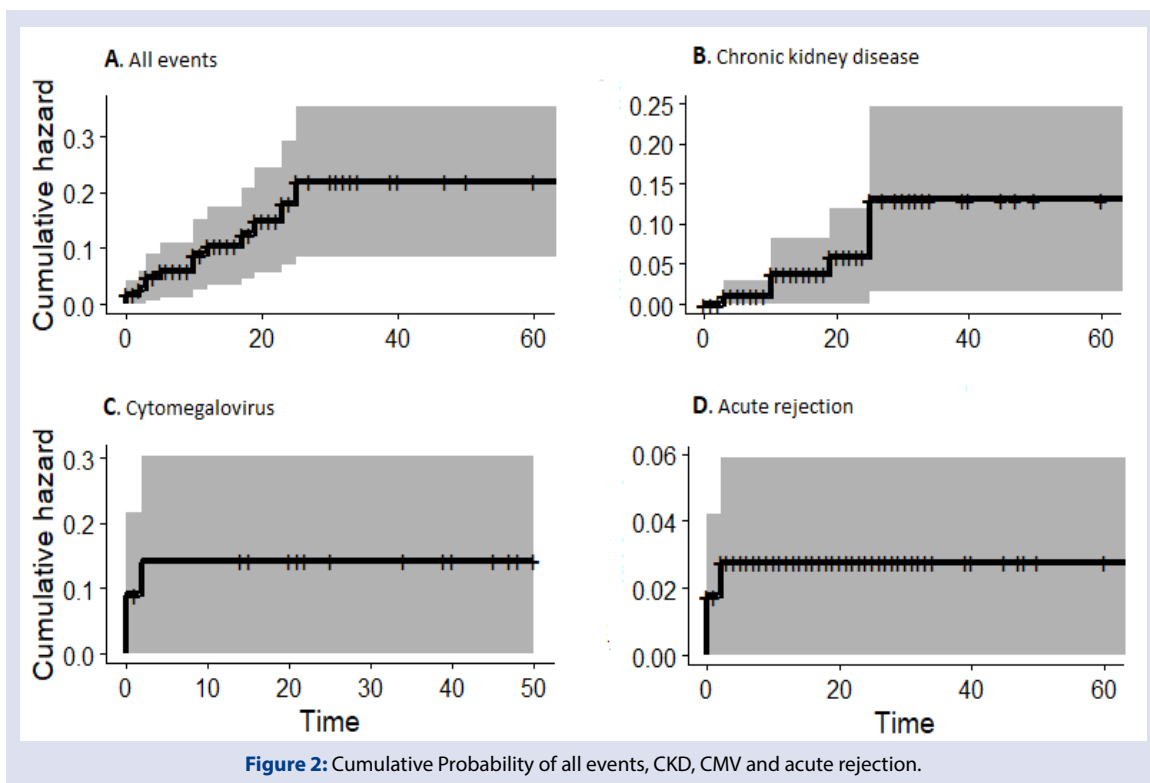
Figure 1: Tacrolimus concentrations after transplantation. (a), (b), (c), (d): Tac concentration in the study, group 1, group 2 and group 3, respectively. Dashed red lines represent the target range limit; solid red lines represent mean concentrations.

Table 3: Common clinical outcomes.

Outcomes	G1	G2	G3	P value
Acute rejection	3	0	0	0.18
CMV	0	4	4	0.02
BKV	0	1	3	0.04
HBV	0	4	3	0.046
HCV	0	2	1	0.34
CKD	0	3	3	0.04
NODAT	5	0	0	0.03

Note: New-onset diabetes (NODAT), chronic kidney disease (CKD).

Figure 2: Cumulative Probability of all events, CKD, CMV and acute rejection.

DISCUSSION

Monitoring blood tacrolimus concentrations is considered necessary in maintaining drug efficacy and minimize the consequences of overexposure.[5] Most previous studies focused on therapeutic drug monitoring of tacrolimus in renal transplant recipients and assessed the clinical response of patients.[9,10] However, only few studies have evaluated the trough tacrolimus according to time post-transplantation as well as efficacy and safety within those targets.[4,6] The primary objective of our study was to summary simply the trough of tacrolimus according to post-transplantation period, as defined by the last European consensus conference (2009) and determine the outcomes in Vietnamese adult renal transplant recipients.

Our results showed that only 33.3% tacrolimus concentrations were within target ranges and 48% of trough blood levels were under-threshold. These results are agreeable with previous observation in Tunisian kidney transplant recipients had similar result.[11] More than 50% of patients were outside the target range. The major reason is presumably the great inter-individual and intra-individual variation of drug levels.[12] However, in some cases it could be attributed directed to an adverse event or to lack of efficacy once a patient has experienced acute rejection. These findings re-emphasized necessity of therapeutic drug monitoring (TDM) in renal transplant recipients.

In our population, the median daily dose was 0.1 (0.09 – 0.12) mg/kg in first 3 months after transplantation and this dose reduced by time after transplantation. Some previous had also similar results. In a study performed on a American population, Narayanan *et al.*[10] showed that the dose in the first month, month 6 and 12 after transplantation were 0.13, 0.1 and 0.09 mg/kg/day, respectively. Takeuchi et al [13] in study on a Japanese population had dose at 41.4 ± 21.4 day after transplantation 0.09 ± 0.05 mg/kg/day. However, in Sugioka' study, the tacrolimus doses were higher during the first 3 months after transplantation (between 0.15 and 0.30 mg/kg/day). These differences in dosing requirement may be due to an interethnic polymorphism in the expression of tacrolimus metabolizing enzymes, i.e. cytochrome CYP3A5 and CYP3A4. It has

been consistently demonstrated that CYP3A5 expressers (CYP3A5*1 carriers) had a lower dose-adjusted C0 and higher clearance, thus requiring higher tacrolimus doses in order to reach the same steady-state C0 when compared with CYP3A5 non-expressers (CYP3A5*3/*3 carriers). Some studies found that expressers require approximately double the starting dose of tacrolimus.[14,15] Moreover, De Jonge *et al.* point out P450 oxydo-reductase (POR)*28 SNP was associated with additional increases in early tacrolimus dose-requirements in patients carrying a CYP3A5*1 allele.[16] Besides, Elens *et al.* found that CYP3A4*22 was associated with a risk of supra-therapeutic Tac concentrations (>15 µg/l) during the first 3 days after transplantation.[17]

The incidence of acute rejection was 2.6 %. Our proportion are low and similar or lower than those in other reports with a similar follow-up.[18,19] Over the last two decades, there have been dramatic reductions in the incidence of AR related to the introduction of more effective immunosuppressive medications (such as mycophenolate mofetil), robust induction regimes and desensitization.

Development of NODAT has been associated with Tac exposure.[20] NODAT increases the risk of cardiovascular events, graft failure and mortality.[21] In our study, 4.4% developed NODAT within three months after transplantation. This low frequency is comparable to those in the Symphony study (10.6% in the first year) and Kamar'study.[4,22] These percentages may roughly be compared since most cases of NODAT often occurs in the first 3 post-transplantation months.[23] Risk factors for new-onset diabetes mellitus after kidney transplantation may make a difference in proportion of NODAT. Our patients were younger (35.4 ± 8.98 *vs.* 45.4 ± 14.7 and 46.4 ± 13.59 years), lower BMI (20.0 ± 3.26 *vs.* 23.4 ± 3.95 kg/m²), lower proportion of HCV infection (2.6% *vs.* 3.7%), different ethnicity and lower Tac concentrations in the first three months (6.7 (4.5 – 10.2) *vs.* > 7 and 10 ng/ml).

In our study, the incidence of opportunistic infections including CMV, BKV, HBV and HCV were low and similar or lower than those in other reports.[24-27] We hypothesized that low proportion of post-transplant infections may be partly due to our lower Tac levels and careful pre-transplant screening, immunization, and post-transplant prophylactic

antimicrobials. These preparation may reduce the risk for post-transplant infection.[28]

CONCLUSION

This observational study provided a realistic Tacrolimus therapeutic drug monitoring transplantation in Vietnamese renal transplant recipients. Main clinical outcomes were acute rejection, post-transplant viral infections, neurotoxicity, NODAT, CKD and Tac-associated nephrotoxicity.

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AUTHOR'S CONTRIBUTIONS

Study design: Van Anh T. Nguyen, Lien Huong T. Nguyen, Thang Viet Le, Manh Van Bui

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Data interpretation: Lien Huong T. Nguyen, Thang Viet Le, Manh Van Bui

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CONFLICTS OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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GRAPHICAL ABSTRACT
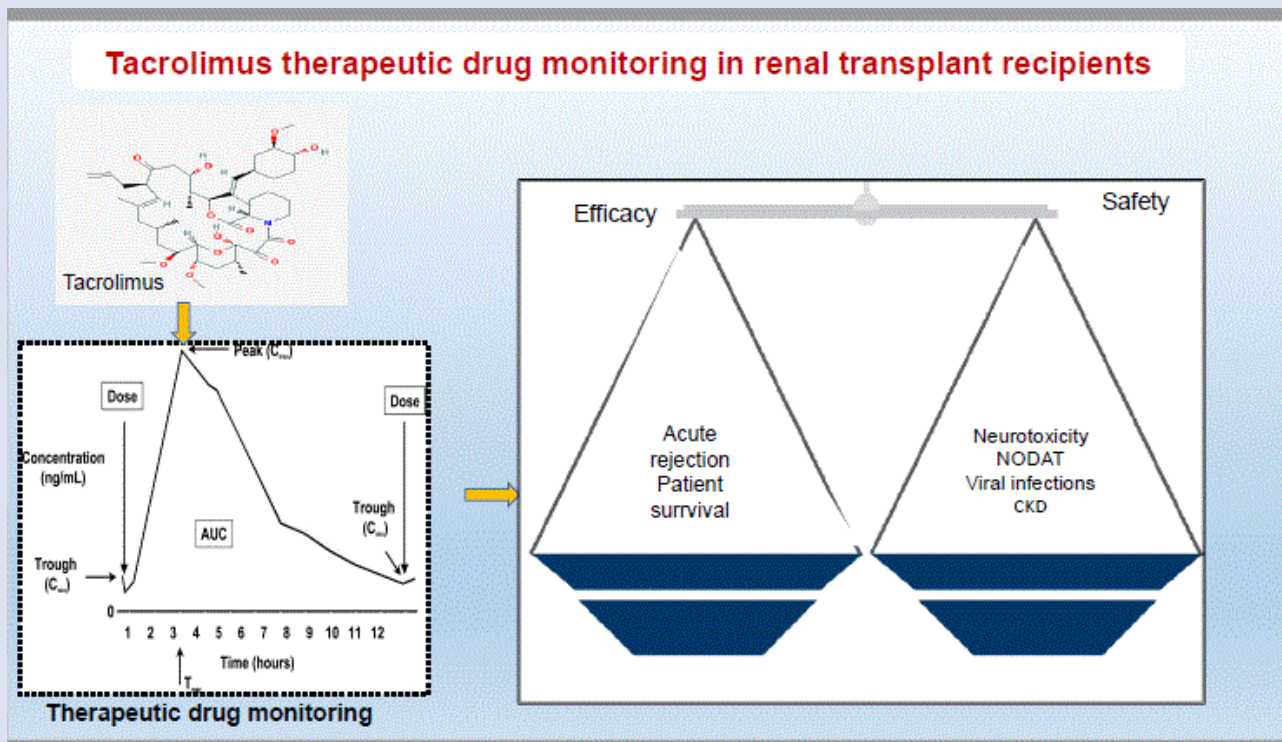
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