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Indonesian Journal of Kidney & Hypertension InaKidney

Original Article

Effect of Tacrolimus Once Daily XR on Variance of Blood Tacrolimus Concentrations in Comparison with Twice Daily Tacrolimus in Kidney Transplant Recipients

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ARTICLE INFO

Article history:
Received: May 21, 2025
Accepted: August 12, 2025
Published Online: August 24, 2025

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ABSTRACT

Background: Variability of tacrolimus concentration in the plasma of recipients is associated with nephrotoxicity, acute rejection, and affects graft survival.
Objective: To test the hypothesis that the coefficient variation of plasma tacrolimus in new tacrolimus XR (extended-release) once daily is lower than conventional twice daily.
Methods: The study was conducted in two phases. Phase 1, a comparative observational analysis with a single-group crossover, comparing periods of divided-dose treatment with crossover to prolonged-dose treatment. Phase 2, a cross-sectional design, is used to correlate IVP and serum creatinine variation.
Results: A total of 19 kidney post-transplant recipients were included. There was a significant difference in blood tacrolimus CoV between XR tacrolimus and divided dose therapy (22.22±7.39% vs 44.32±15.54%, p<0.001). A significant linear correlation was observed between blood tacrolimus CoV and serum creatinine CoV in all patients (r=0.74; r^2= 0.54; b=1.15; p<0.001). Subgroup analysis revealed a significant correlation between blood tacrolimus CoV in divided dose tacrolimus therapy subgroup (r=0.58; r^2= 0.33; p=0.02) but not in the XR group (r=0.06; r^2= 0.004; p=0.84). Multivariate ANCOVA showed serum CoV was associated with CoV of blood tacrolimus (B=0.72; r^2= 0.255; p=0.01). Furthermore, XR tacrolimus was associated with lower serum creatinine CoV (B= -20.7; r^2=0.20; p=0.02).
Conclusion: XR tacrolimus therapy produces significantly lower variance of blood tacrolimus concentrations in kidney transplant recipients. This variance is associated with serum creatinine variance, especially in divided-dose tacrolimus therapy. Serum creatinine variance is linked to variances in blood tacrolimus levels, and XR tacrolimus therapy is associated with lower serum creatinine variance.
Keywords: Tacrolimus Extended Release, Variance of Blood Tacrolimus, Variance of Serum Creatinine, Kidney Transplant Recipients.

Introduction

Kidney transplantation is one of the replacement therapies for kidney failure. It has several advantages over other replacement therapies, including a better quality of life and independence from regular dialysis treatment.[1] The goal of immunosuppressive therapy is to maintain graft survival by preventing allograft rejection while reducing the risks of drug nephrotoxicity and infection. After transplantation, immunosuppressive management, including dosing and monitoring, particularly in tacrolimus regimens, plays a central role in increasing organ survival, maintaining long-term organ function, and preventing rejection and allograft loss. Most of the transplantation centers use triple immune-suppressive agents during induction, maintenance, and reversal when rejection occurs.[2] The use of mycophenolate mofetil (MMF), tacrolimus (Tac), and sirolimus

Cite this as:
Widiana IGR, Putra IMR, Wahyuningrum SA. Effect of Tacrolimus Once Daily XR on Variance of Blood Tacrolimus Concentrations in Comparison with Twice Daily Tacrolimus in Kidney Transplant Recipients. InaKidney. 2025;2(2):63-72. doi:10.32867/inakidney.v2i2.190

combination has become increasingly common in recent years.[3]

Tacrolimus belongs to the immunophilin calcineurin inhibitor class, which strongly inhibits the activation of T lymphocytes. The intracellular transduction pathway of T cells is inhibited by binding of tacrolimus and FK506-binding proteins (FKBP), forming a tacrolimus-FKBP complex. This complex molecule is a strong inhibitor of the transcription gene of T cells that produces interleukin (IL)-2, other growth factor cytokines, TNF-α, and protooncogenes. It also suppresses the expression of IL-2 and IL-7 receptors. Tacrolimus also has inhibitory properties on mixed lymphocyte reaction, cytotoxic T cell generation, and T cell-dependent B cell activation. Tacrolimus has no inhibitory activity on T cell proliferation due to its lack of effect on T cell activation by IL-2, antigen presentation, mononuclear phagocytic function, and natural killer cell activity.[4]

The variability of tacrolimus concentrations in the plasma of recipients is associated with nephrotoxicity, a side effect of tacrolimus, and affects graft survival and patient prognosis. This variability has also been linked to acute rejection and long-term prognosis of transplant recipients.[5] Histopathologic features of this nephrotoxicity of tacrolimus are supported by histopathologic findings of interstitial fibrosis, tubular injury, and arteriolopathy. Some cytokines may mediate these processes, such as growth factor TGF-β.[6,7] An extended-release of tacrolimus is an alternative preparation to the older divided-dose tacrolimus for immunosuppressive treatment of kidney transplant recipients. Some reports have shown that divided-dose tacrolimus is associated with a higher risk of acute rejection compared to prolonged-release tacrolimus.[8]

This study aims to test the hypothesis that the coefficient of variation (CoV) of plasma tacrolimus in new extended-release (XR) tacrolimus is significantly lower than that in conventional twice-daily immunosuppressive regimens among kidney transplantation recipients. In addition, this study also aims to determine the correlation between plasma CoV of tacrolimus and CoV serum creatinine concentrations in those patients.

Methods

Design and participants

The study design is divided into Phase 1, a comparative observational analysis with a single-group pre- and post-test design, comparing the CoV of tacrolimus between the period of divided dose treatment (first period) and the period of crossover to XR (second period) of tacrolimus treatment. A phase 2, cross-sectional design is used to correlate the CoV of tacrolimus and the CoV of serum creatinine.

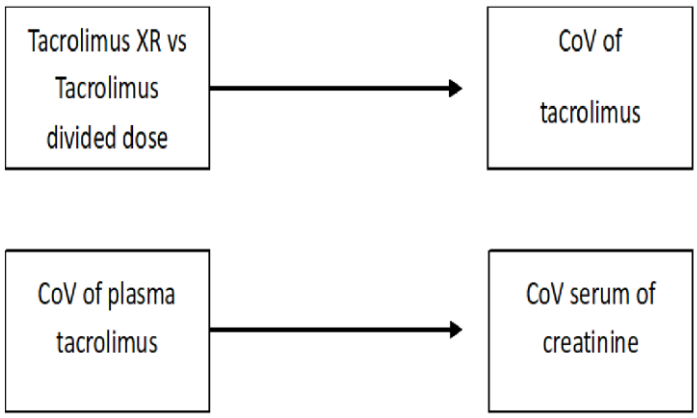

Figure 1. Diagram of study design

This study was conducted at the Transplant Outpatient Clinic, Prof. dr. I.G.N.G. Ngoerah Central General Hospital, Bali, Indonesia, from March 2019 to August 2021. Study variables are divided into:

Phase 1 study:

- Dependent variable was the CoV of tacrolimus
- Independent variable was intervention: tacrolimus XR vs tacrolimus divided dose (twice daily tacrolimus)

Phase 2 study:

- Dependent variable CoV of serum creatinine.
- Independent variable was the CoV of plasma tacrolimus

Controlled variables were: age, gender, body mass index, ischemic time.

CoV of tacrolimus plasma concentrations is the standard deviation divided by the mean of plasma tacrolimus concentrations, and expressed as a percentage value (%). The formula can be expressed as: CoV = SD/Mean × 100%. Tacrolimus concentrations were measured from blood samples taken 12 hours after the first dose, just before the following scheduled doses of the day. Concentrations were examined by Chemiluminescent Microparticle Immunoassay (CMIA) assay and expressed in units of ng/L. The CoV will be categorized into a quartile range (percentile 25). Serum creatinine concentrations were examined using the Cobas Integra 401 method and expressed in mg/dL.

All kidney post-transplant recipients were evaluated for tacrolimus treatment, blood tacrolimus, and serum creatinine concentrations. Data from patients who visited the transplant polyclinic were openly evaluated regarding both the study drugs and the data from the Hospital Information Management System's medical records. We have re-evaluated the data of some patients who received a divided dose and found that CoV was high. Information about these results was notified to the Hospital Department of Pharmacy and the Hospital Director. After the evaluation, it was decided that Astellas would supply Tacrolimus Extended Release to curb the potential long-term harmful effects of kidney grafts caused by the use of divided-dose tacrolimus immunosuppressive treatment.

Tacrolimus immunosuppressive treatment is divided into two periods. The first period was considered a time when divided dose (conventional) tacrolimus was used for immunosuppressive treatment. The second period is a period during which tacrolimus XR was replaced and used for immunosuppressive treatment. All patients underwent regular visits for clinical evaluation, including dose adjustments of tacrolimus treatment, blood tacrolimus concentration measurements, and serum creatinine examinations. All clinical data, including gender, age, body weight, and height, as well as ischemic times, were extracted. Additionally, lab data on plasma tacrolimus and serum creatinine concentrations were collected and analyzed. The CoV plasma tacrolimus and CoV creatinine concentrations during the first and the second period are calculated and compared.

Statistical analysis

Descriptive analysis to describe patient characteristics such as age, gender, of the donors and recipients, body weight and height, co-treatment (antihypertensives, immune-suppressive combination), and information of transplantation operation (ischemic times). CoV of tacrolimus and quartile distribution will be analyzed and expressed as mean and percentage. The Shapiro-Wilk test is used to analyze the normalcy of numeric data.

An independent t-test is used to compare the coefficient of variance of tacrolimus and quartile distribution between the tacrolimus XR group during the first and second periods. Pearson's correlation and linear regression analysis between the CoV of tacrolimus and the CoV of serum creatinine will be done when appropriate. Significance level (alpha) is set on p-value < 0,05. Data precision is set at a 95% confidence interval. The ethical committee of the Medical Faculty of Udayana University has approved this study.

Results

During the study, 15 patients were treated with a divided dose, n=15, and patients were treated with an extended-release dose, n=15 (Figure 2). Table 1 presents the characteristics of patients included in the study.

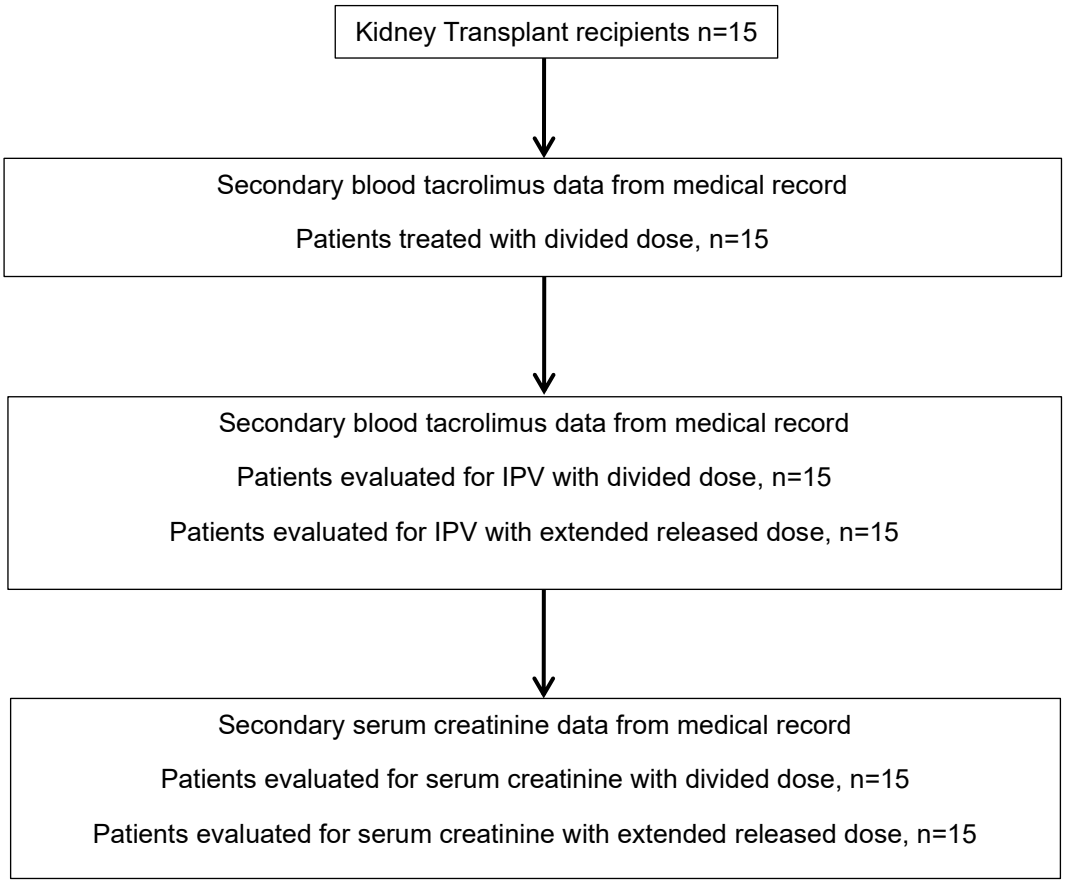

Figure 2. Flow diagram of the study

Table 1. Characteristics of patients included in baseline (n=15)

Variables	mean±SD	n (%)
Age (years)	31±8	
Gender		
Males		13 (87)
Females		2 (13)
Body weight (kg)	61±11	
Body height (cm)	167±6	
Body mass index (kg/m2)	21.7±2.8	
Albumin (g/dL)	3,84±0,53	
Blood sugar (mg/dL)	99,47±33,78	
ALP (U/L)	32,30±33,66	
ALT (U/L)	61,97±88,40	

There was a significant difference between blood tacrolimus CoV of patients with tacrolimus XR and divided dose tacrolimus therapy (22.22± 7.39% vs 44.32±15.54%, $p<0.001$). There was a half lower of blood tacrolimus CoV in patients with tacrolimus XR than divided dose tacrolimus therapy. In general, the median CoV of tacrolimus was 29.79% with

an interquartile range between 20.51% and 45.80%. If this CoV is divided between groups, the median tacrolimus CoV value was 21.02% with an interquartile range between 17.96% and 27.73% in patients with tacrolimus XR, and the median value was 45.65% with an interquartile range of 32.51% to 48.39% in divided dose tacrolimus. This data showed that the median tacrolimus coefficient of variance value was more than twice as high in patients receiving extended-release compared to those receiving divided doses (Figure 3).

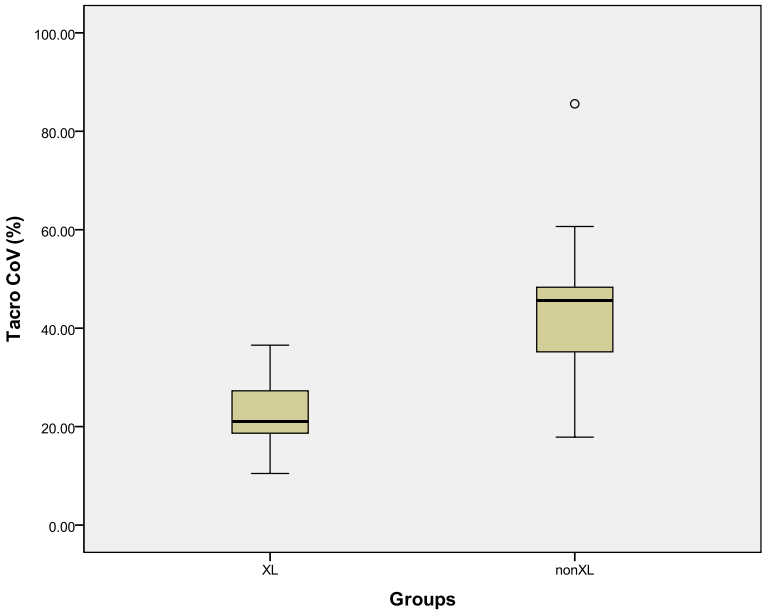

Figure 3. Diagram box plot of the mean of blood tacrolimus CoV (coefficient of variation) between XR (extended-release) and divided dose tacrolimus treatment

If we divide association between treatment with tacrolimus XR and divided dose tacrolimus and quartile (25 percentile) of blood tacrolimus CoV, it was showed that there was significant association between treatment with groups of tacrolimus XR or divided dose and quartile (25 percentile) of blood tacrolimus CoV (p=0.001), where, 6 (85.6%) vs 1 (14.3%) of patients with tacrolimus XR and divided dose tacrolimus were in quartile 1 and none vs 7 (100%) of patients with tacrolimus XR to divided dose tacrolimus treatment (Table 2).

Table 2. Quartile Coefficient of variance of Tacrolimus in Extended Release (XR) and Divided Dose Tacrolimus Therapy

		Group of tacrolimus therapy		
		XR	Divided dose	Total
CoV	1st quartile	6	1	7
	2nd quartile	7	1	8
	3rd quartile	2	6	8
	4th quartile	0	7	7
Total		15	15	30

X2=17.1; df=3; p=0.001

Figures 4,5, and 6 show that there was a significant linear correlation between blood tacrolimus CoV and serum creatinine CoV in all patients (r=0.74; r^2= 0.54; b=1.15; p<0.001). However, if this association was analyzed in a subgroup of therapy, there was only a significant linear correlation between blood tacrolimus CoV in the subgroup with divided dose tacrolimus therapy (r=0.58; r^2= 0.33; p=0.02) and none in patients with tacrolimus XR therapy (r=0.06; r^2= 0.004; p=0.84).

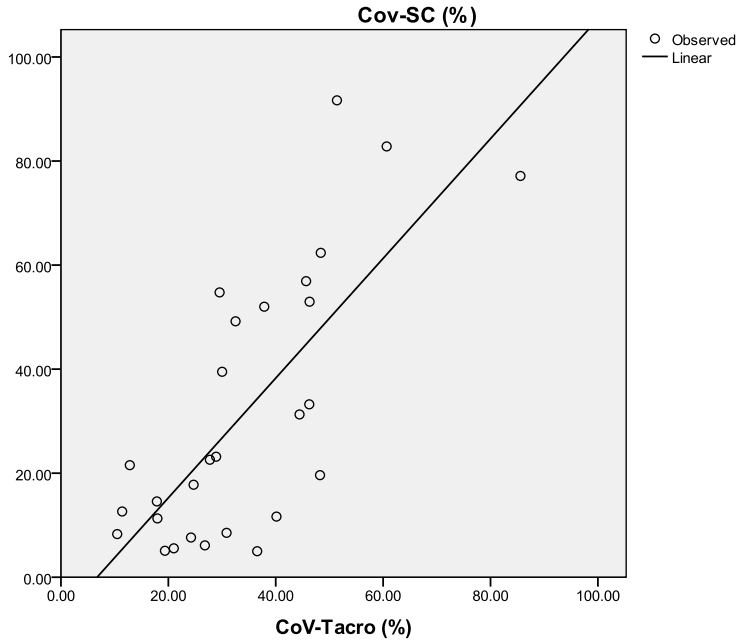

Figure 4. Scatter diagram and linear association between blood tacrolimus covariance and serum creatinine covariance in all patients (r=0.74; r^2= 0.54; b=1.15; p<0.001)

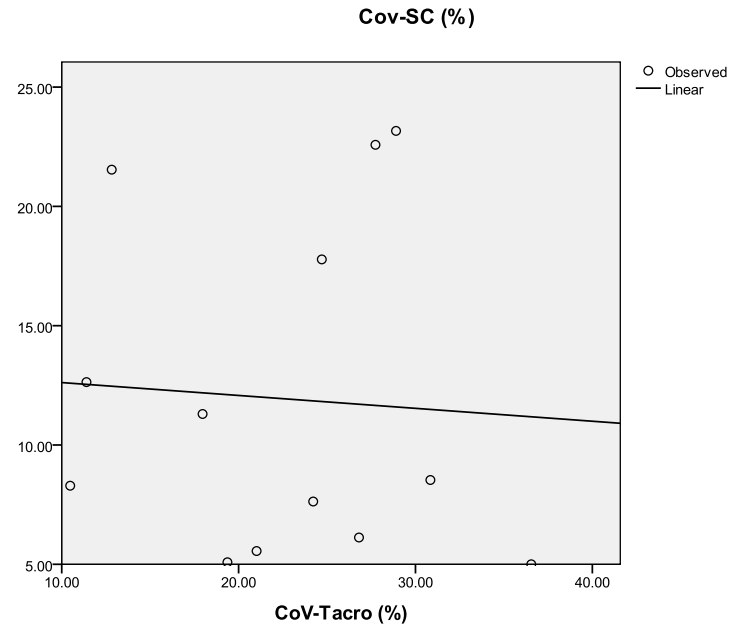

Figure 5. Scatter diagram and linear association between blood tacrolimus coefficient of variance and serum creatinine covariance in extended-release patients (r=0.06; r2 = 0.004; p=0.84)

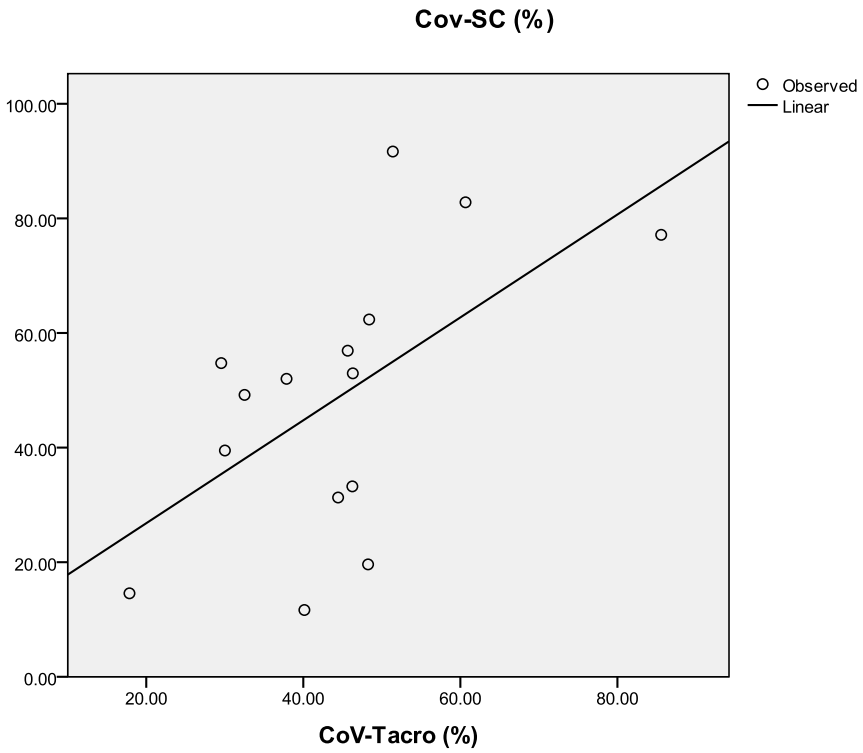

Figure 6. Scatter diagram and linear association between blood tacrolimus coefficient of variance and serum creatinine coefficient of variance in divided dose patients (r=0.58; r^2= 0.33; p=0.02)

Discussion

Variability of tacrolimus concentrations in plasma of the recipient, namely intra-patient variability (IPV), is frequent during tacrolimus therapy and is measured by its CoV.[9] Nephrotoxicity is one of the main side effects of tacrolimus, which may affect graft survival and patient prognosis. Histopathologic features of this nephrotoxicity include interstitial fibrosis, tubular injury, and arteriolopathy, which may be mediated by several cytokines, such as the growth factor TGF-β.[5] The renin-angiotensin system may also contribute significantly to the pathogenesis of tacrolimus nephrotoxicity.[7] This IVP is strongly associated with acute rejection and long-term prognosis of transplant recipients.[6] This study showed that there is a linear correlation between blood tacrolimus CoV and serum creatinine CoV in all patients. The present findings suggest that an unstable concentration of tacrolimus may produce nephrotoxicity, as indicated by variability in serum creatinine concentration. When tacrolimus target levels are less than 5 ng/mL, the impact of this IVP on acute rejection will become obvious.[10] On the other hand, high IVP may produce an increased risk of over-immunosuppression, when tacrolimus concentration exceeds the target of treatment, which results in nephrotoxicity and risk of infection. On the contrary, those with under-immunosuppression due to fewer treatment targets may cause allograft rejection.[4,11] The delay of blood test for tacrolimus concentration and adjusting the doses may result in a high degree of variability and increased risk of nephrotoxicity and rejection. During the Phase 1 period of the study, using a divided dose of tacrolimus treatment, the variance of blood tacrolimus is high (mean value 45%). The introduction of tacrolimus XR therapy in Phase 2 results in a lower half of its covariance coefficient. The decrease in variance of blood tacrolimus with extended release may be able to lower the risk of rejection and/or drug toxicity.

This study showed that, firstly, the CoV in blood tacrolimus is a half lower in patients with

extended-release (XR) tacrolimus than those with divided-dose tacrolimus therapy. The second finding is that the association between CoV of blood tacrolimus and CoV of serum creatinine is significant in the subgroup receiving divided-dose tacrolimus therapy, but not in patients receiving extended-release therapy. These findings may support the concept that slow-release tacrolimus therapy can stabilize blood concentration and blunt the variation of tacrolimus. Each unit of tacrolimus CoV increases 0.7 serum creatinine CoV. In addition to tacrolimus CoV, the use of tacrolimus XR blunts the variation of serum creatinine.

The common method to evaluate the effectiveness of immunosuppression and patient compliance with tacrolimus treatment is to monitor its plasma concentrations and calculate the IVP. The IVP is influenced by genetic factors, the interaction of tacrolimus with food and other drugs in the gut, and can be used to assess patients' compliance with the treatment.[12] We may not be able to explain whether high variation in the phase study is caused by genetic variation in our patients or lack of close monitoring and prompt adjustment of tacrolimus doses.

A prolonged-release tacrolimus may be an alternative preparation to a divided dose for immunosuppressive treatment of the recipients after kidney transplantation. Peak plasma concentrations and the time interval are expressed as the area under the curve (AUC) and over the dosage time interval (AUCT). The under the curve (AUC) over the dosage time interval (AUCT) is reported to be a good marker of systemic exposure of tacrolimus and has a strong association with clinical efficacy outcomes. Due to the lower tacrolimus time interval, divided-dose tacrolimus is associated with a higher risk of acute rejection than prolonged-release tacrolimus. Intestinal absorption of prolonged-release tacrolimus is slower than immediate-release, divided-dose tacrolimus, resulting in a longer time interval than immediate-release.[8]

Intestinal absorption of tacrolimus depends on the presence of food in the gut lumen, bile acids, and intestinal motility.[5] In blood circulation, tacrolimus strongly binds to erythrocytes and plasma proteins. Tacrolimus is broadly distributed across various tissues, including the lungs, heart, brain, spleen, kidneys, pancreas, muscles, and liver. It passes through the placental barrier, resulting in a concentration that is approximately one-third of the plasma concentrations in the umbilical cord. Tacrolimus is also detected in low concentrations in breast milk.[13] Tacrolimus is metabolized mainly in the liver and to a lesser extent in the intestinal mucosa. CYP3A4 isoenzymes mediate its metabolism. Its major metabolite is 13-O-dimethyl-tacrolimus. Inhibitors of CYP3A4 can increase tacrolimus blood concentrations, while CYP3A4 inductors can reduce its concentrations.[14] Interaction between tacrolimus and affecting factors may occur at the level of absorption, distribution, metabolism, and excretion.[12] Variability of blood concentrations depends on gastrointestinal motility, primarily due to phase 1 metabolism. Individual variation of blood concentration also depends on the variability of absorption and bioavailability. Fatty food, magnesium oxide, aluminum oxide, and sodium bicarbonate in the gastrointestinal lumen can reduce its absorption. Finally, variability of intestinal absorption is affected by genetic polymorphism of CYP3A or P-glycoprotein.[2,15]

Conclusion

Extended-release tacrolimus therapy produces significantly lower variance of blood tacrolimus concentrations in kidney transplant recipients. The variance in blood tacrolimus concentrations is associated with the variance in serum creatinine, especially in divided-dose tacrolimus therapy.

Limitations of the Study

This study is subject to some limitations, most notably the small sample size, which may result in a lack of statistical power. A single-group pre- and post-test design, which inherently carries over the effect of the first treatment to the second treatment, cannot be ruled out. Larger sample sizes are needed for more generalized and robust

conclusions. This study was a retrospective analysis taken from hospital medical records; therefore, several drawbacks arose from the study design, retrospective evaluation, and controlled variables, which may have confounded the conclusions.

Declarations

Ethics approval and consent to participate

This study adhered to the guidelines for clinical research and received approval from the Ethics Committee of the Prof. dr. I.G.N.G. Ngoerah Central General Hospital Denpasar under reference number : 1366/UN14.2.2.VII.14/LP/2019.

Competing interests

There are no conflicts of interest in writing this article.

Funding source

Not applicable.

Acknowledgments

We acknowledge the Medical Record Office of Prof. dr. I.G.N.G. Ngoerah Hospital for the use and analysis of the data for publication.

Author's Contribution

Idea/concept: IGRW. Design: IGRW. Control/supervision: IGRW. Data collection/ processing: IMRP, SAW. Analysis/ interpretation: IGRW. Literature review: IGRW, IMRP. Writing the article: IGRW. Critical review: IGRW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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