Original Article

Tacrolimus dose prediction during the perioperative period among Thai kidney transplant recipients

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Abstract

Background: Tacrolimus (TAC) is the cornerstone of immunosuppressive drug therapy after kidney transplant (KT). Achieving target TAC concentrations as soon as possible is crucial, especially during the early posttransplant period. Too low or too high tacrolimus exposure can lead to unfavorable complications. This study aimed to develop an equation to predict achieving target tacrolimus dose used at days 3-5 of postKT surgery.

Methods: A retrospective cohort study was conducted at King Chulalongkorn Memorial Hospital, Thailand. We divided subjects in 2 cohorts; the first developmental cohort was KT recipients from 2015-2018 and the second was a validation cohort from 2019-2020. The dose prediction model was developed based on exponential function due to nonlinear association between target TAC dose (mg/kg) and 12-hour level after the first dose (TAC C_{12}).

Results: A total of 206 KT recipients was enrolled, 140 KT recipients in the developmental cohort and 99 (70.7%) deceased donor KT recipients. Mean TAC dose used days 3-5 post-transplant was 5.8 ± 1.9 mg/day in the developmental cohort the same as the TAC dose used in the validation cohort 5.8 ± 2.1 mg/day. We calculated the dose of TAC for achieving an average therapeutic level of 8.5 ng/mL days 3-5 post-transplant involving the equations below.

$$\text{Adjusted TAC dose days 3-5 (mg/kg)} = 0.2588691 * \text{TAC } C_{12}^{(-0.47730647)} * \text{Hemoglobin}^{(-0.03101605)}$$

The R^2 of the developmental cohort was 0.3125 and that of the validation cohort was 0.2929. Mean absolute error (MAE) of TAC dose was 0.0392191 mg/kg.

Conclusion: The TAC dose prediction equation developed from clinical factors, could guide nephrologists to adjust TAC dose during perioperative KT among individual patients and this optimization could reduce both TAC toxicity and KT rejection rates.

Keywords: Tacrolimus, Dose prediction, Perioperative period, Kidney transplantation

Original Article

การทำนายขนาดยาทาโครลิมัส ที่ใช้ในช่วงระหว่างการผ่าตัดปลูกถ่ายไต ในประชากรไทย

อริศรา ฤกษ์ฉวี ณัฐวุฒิ โตวนำชัย

หน่วยโรคไต ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ

บทนำ: ยาทาโครลิมัส (Tacrolimus; TAC) จัดเป็นยากดภูมิที่เป็นรากฐานสำคัญที่ใช้ในผู้ป่วยเข้ารับการผ่าตัดปลูกถ่ายไต การที่ยาทาโครลิมัสบรรลุเป้าหมายสู่ระดับยาที่กำหนดโดยเร็วที่สุดถือเป็นสิ่งสำคัญ โดยเฉพาะอย่างยิ่งระดับยาในช่วงระยะแรกหลังการผ่าตัดปลูกถ่ายไตที่การมีระดับยาต่ำหรือสูงเกินไป อาจนำไปสู่ภาวะแทรกซ้อนอันไม่พึงประสงค์ จุดมุ่งหมายของการศึกษานี้เพื่อพัฒนาสมการสำหรับหาขนาดยาทาโครลิมัสที่บรรลุเป้าหมายในช่วงวันที่ 3-5 หลังการผ่าตัดปลูกถ่ายไต ซึ่งจัดเป็นระยะที่ต้องการระดับของการกดภูมิที่เหมาะสมมากที่สุด

แบบแผนการวิจัย: การศึกษาย้อนหลังจัดทำขึ้นที่โรงพยาบาลจุฬาลงกรณ์ เก็บข้อมูลผู้ป่วยไตวายเรื้อรังทุกรายที่เข้ารับการผ่าตัดปลูกถ่ายไตในโรงพยาบาลจุฬาลงกรณ์ ปี พ.ศ. 2558-2563 แบ่งประชากรออกเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ใช้พัฒนาสมการคือผู้ป่วยที่รับการปลูกถ่ายไตในปี พ.ศ. 2558-2561 และกลุ่มที่สองคือกลุ่มที่ใช้ตรวจสอบประสิทธิภาพของสมการ คือผู้ป่วยที่รับการปลูกถ่ายไตในปี พ.ศ. 2562-2563 คำนวณเพื่อหาสมการพยากรณ์ขนาดยา โดยจะถูกสร้างขึ้นตามฟังก์ชันเอ็กซ์โพเนนเชียลจากความสัมพันธ์ที่ไม่เป็นเส้นตรงระหว่างขนาดยาทาโครลิมัสเป้าหมาย (มก./กก.) และระดับยาทาโครลิมัสที่ 12 ชั่วโมงหลังจากรับประทานยาครั้งแรก (TAC C_{12})

ผลการศึกษา: ผู้ป่วยที่เข้ารับการผ่าตัดปลูกถ่ายไตที่เข้าเกณฑ์การศึกษาทั้งหมด 206 ราย เป็นกลุ่มสำหรับพัฒนาสมการ 140 ราย ลักษณะพื้นฐานของกลุ่มพัฒนาสมการ มีผู้รับไตบริจาคจากผู้เสียชีวิต 99 ราย ปริมาณเฉลี่ยของยาทาโครลิมัสที่ใช้ในวันที่ 3-5 หลังการปลูกถ่ายไตของกลุ่มพัฒนาคือ 5.8 ± 1.9 มก./วัน ซึ่งใกล้เคียงกับในกลุ่มตรวจสอบคือ 5.8 ± 2.1 มก./วัน เราคำนวณหาขนาดยาทาโครลิมัสใน วันที่ 3-5 หลังการปลูกถ่ายเพื่อบรรลุระดับการรักษาที่ระดับยาเฉลี่ย 8.5 นาโนกรัม/มล. ได้เป็นสมการดังต่อไปนี้

$$\text{Adjusted TAC dose at day3-5 (mg/kg)} = 0.2588691 * \text{TAC C12}^{(-0.47730647)} * \text{Hemoglobin}^{(-0.03101605)}$$

ค่า R^2 จากกลุ่มพัฒนาสมการคือ 0.3125 และจากกลุ่มตรวจสอบคือ 0.2929 ค่าเฉลี่ยข้อผิดพลาดสัมบูรณ์ (MAE) ของขนาดยาทาโครลิมัส คือ 0.0392191 มก./กก.

สรุปผลการวิจัย: สมการพยากรณ์ขนาดยาทาโครลิมัสที่ใช้ในช่วงการผ่าตัดปลูกถ่ายไตที่พัฒนาจากปัจจัยทางคลินิก สามารถเป็นแนวทางให้อายุรแพทย์โรคไตใช้เพื่อช่วยในการปรับขนาดยาทาโครลิมัสสำหรับผู้ป่วยแต่ละราย ขนาดยาที่เหมาะสมจะช่วยเพิ่มประสิทธิภาพการรักษา โดยลดทั้งความเป็นพิษจากยาทาโครลิมัส และลดอัตราการปฏิเสธไตได้

คำสำคัญ: ทาโครลิมัส, ทำนายขนาดยา, ระหว่างการปลูกถ่ายไต, การปลูกถ่ายไต

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Background

Kidney transplantation (KT) is another method of renal replacement therapy, significantly improving survival rate of patients with long term, end stage kidney disease. It requires using proper immunosuppressive drugs for KT recipients to reduce the incidence of rejection. In the 1980s, the results of organ transplants, particularly kidney transplants, changed because of developing one of the most crucial immunosuppressive drugs; calcineurin inhibitors. It increases the survival rate of renal allograft and patients undergoing KT.[1] However, calcineurin inhibitors were found to produce significant side effects on the kidneys as well, that is, the occurrence of calcineurin inhibitor nephrotoxicity.[2] This could lead to acute kidney injury and permanent loss of kidney function. Lower tacrolimus trough concentrations were associated with increasing the risk of acute rejection especially mean trough levels within the first week after transplant.[3] When a recipient is required to receive a high dose of calcineurin inhibitor for the first time, it becomes more likely that calcineurin inhibitor nephrotoxicity can easily result creating worse graft outcomes.

Currently, the most commonly used calcineurin inhibitors are tacrolimus (TAC) providing better survival rate and graft function than cyclosporine.[4,5] Because this medication has several important pharmacokinetic characteristics, the narrow therapeutic index and large inter- and intrapatient variability, using this medication with caution is suggested.[6,7] In practice, the blood level of tacrolimus of all patients undergoing KT is required. Many factors may affect tacrolimus levels such as age, sex, ethnicity, body weight, hemoglobin, albumin, use of concomitant drug interactions against tacrolimus such as calcium channel blocker or fluconazole, but not all factors can have significant effect on drug dose.[8,9] In addition, several studies of genetic polymorphism of cytochrome P450 (CYP3A5), indicated its importance for the metabolism of tacrolimus and have been considered one of the important factors affecting the drug level in individual patients.[10] Another factor is TAC C_{12}; tacrolimus levels at 12 hours after taking the first dose, and before receiving the second dose, where studies have found a significant correlation with tacrolimus dose postKT transplant surgery at day 7.[11] Due to significant correlations with TAC dose, so benefits of TAC C_{12} can include posing a good representative factor for predicting TAC dose used during the early postKT period.

According to special pharmacokinetic factors of tacrolimus, this drug needs to be individually adjusted in KT recipients. Therefore, models or equations have been developed to determine the dose of tacrolimus used for patients receiving KT in many studies. The objective of all studies is to increase efficiency in finding the most suitable tacrolimus dose for each patient and providing the therapeutic level as quickly as possible for the best immunosuppressive status in early postKT surgery. Each of the related research results can be applied in a correlation, or model, to predict the dose of the drug. As a result, prediction methods should be used in Thailand. They must be carefully selected. and having a prediction equation that could be especially applied in Thai populations would prove beneficial.

Objective

The current study aimed to develop an equation to predict dose of tacrolimus used during the early postKT period days 3 to 5 for use in Thai patients receiving KT. The study also determined important factors affecting tacrolimus dose during the early KT period requiring high accuracy regarding tacrolimus level to suppress the immune response of patients.

Methods

A retrospective cohort study was conducted at King Chulalongkorn Memorial Hospital, Thailand. Subjects in this study were Thai patients with end stage kidney disease undergoing KT at King Chulalongkorn Memorial Hospital, from January 2015 to August 2020. All KT recipients were ≥18 years of age using tacrolimus-based immunosuppressive regimen at the time of KT. We excluded patients who previously received tacrolimus to treat another disease before KT, patients who received multiple organ transplantation, patients presenting side effects from tacrolimus and those having to change

tacrolimus to other drugs during the early immune suppression period. We also excluded patients receiving preconditioning protocol longer than two days before KT because the patients may have adjusted TAC dose more than once before surgery. The patient's data were retrospectively obtained from medical records for analysis. The study was approved by the institutional review board of Chulalongkorn University (IRB No. 884/63).

All patients received an immunosuppressive regimen based on tacrolimus (PROGRAF®) and mycophenolic acid. We used 0.1 mg/kg of tacrolimus for the starting dose of tacrolimus, then followed by a maintenance dose of tacrolimus twice daily. After the patient received the first loading dose of tacrolimus, we manually tailored the maintenance dose adjusted from TAC C_{12} then followed by first measuring a predose concentration of tacrolimus (C_0) days 3 to 5 after KT. Achieving the target of tacrolimus C_0 level involved 7 to 10 ng/mL at the first week after KT. Demographics and clinical characteristics of the patients were recorded and including the factors affecting tacrolimus dose used during perioperative KT.

For internal validation, we divided this population in two cohorts; the developmental and the validation cohort. We developed a dose prediction model based on the association between target TAC dose days 3 to 5 (mg/kg) and 12-hour level after the first dose (TAC C_{12}). The potential correlation factors of TAC dose such as TAC C_{12}, hemoglobin, serum albumin, serum creatinine, strong concomitant drugs and BSA were selected. Variables were selected and covariates were regularized using a LAZZO regression model. Finally, the model performance was tested in the validation cohort and results were presented in adjusted R-squared (R^2) and Mean Absolute Error (MAE). Statistical analyses were performed using STATA® (StataCorp. Version 16.), R version 4.0

Results

A total of 206 KT recipients were enrolled. The first developmental cohort comprised KT recipients from 2015 to 2018 and the second was the validation cohort from 2019 to 2020, which totaled 140 recipients in the developmental cohort and 66 recipients in the validation cohort. Altogether, 99 (70.7%) deceased donor KT recipients were found, with mean age 44.2 ± 11.8 years, males, 57.1%, body surface area of 1.6 ± 0.2 m^2, hemoglobin of 11.2 ± 1.7 mg/dL and serum albumin, 3.7 ± 0.5 mg/L in the developmental cohort. Mean TAC dose used days 3 to 5 postKT was 5.8 ± 1.9 mg/day in the developmental cohort the same as the TAC dose used in the validation cohort, 5.8 ± 2.1 mg/day. All of the patients' characteristics are shown in **Table 1**.

The study found a nonlinear association between the adjusted target TAC dose days 3 to 5 (mg/kg) and 12-hour level after the first dose (TAC C_{12}). Also, we defined adjusted target TAC dose as a dose normalized with level that achieved the tacrolimus C_0 level of 8.5 ng/mL (average from 7 to 10 ng/mL). Thus, adjusted target TAC dose days 3 to 5 (mg/kg) = (TAC dose x 8.5) /TAC level.

In addition, we found potential covariates including TAC C_{12}, hemoglobin and BSA; all these factors were selected using a stepwise procedure. Intercepts and co-efficients were adjusted using the LASSO regularization technique to identify the most effective factors for use in developing the model. The two significant covariates used in the equation were TAC C_{12} and hemoglobin. Then the dose prediction model was developed based on exponential function due to the nonlinear association between target TAC dose days 3 to 5 (mg/kg) and 12-hour level after the first dose (TAC C12) with selected potential covariate factors.

The results of regression equations to predict TAC dose days 3 to 5 postKT are described below

$$\text{Adjusted TAC dose days 3-5 (mg/kg)} = 0.2588691 * \text{TAC } C_{12}^{(-0.47730647)} * \text{Hemoglobin}^{(-0.03101605)}$$

Table 1 Demographic and Baseline Characteristics of Patients

Characteristic	Total	Developmental cohort	Validation cohort
Number of patients, n	206	140	66
Age (y), mean ± SD	44.3 ± 11.6	44.2 ± 11.8	44.5 ± 11.2
Male, n (%)	113 (54.9)	80 (57.1)	33 (50)
Body weight (kg), mean ± SD	59.1 ± 11.9	57.9 ± 11.3	61.5 ± 13.1
Body surface area (m^2), mean ± SD	1.62 ± 0.2	1.62 ± 0.2	1.62 ± 0.2
Deceased donor KT, n(%)	139 (67.5)	99 (70.7)	40 (60.6)
Hemoglobin, mean ± SD	11.7 ± 1.7	11.2 ± 1.7	11.0 ± 1.7
Serum albumin, mean ± SD	3.7 ± 0.5	3.7 ± 0.5	3.8 ± 0.4
Serum creatinine, mean ± SD	9 ± 3.4	9.2 ± 3.3	8.5 ± 3.7
TAC dose days 3 to 5 (mg/day), mean ± SD	5.8 ± 2.0	5.8 ± 1.9	5.8 ± 2.1
Adjusted TAC dose days 3 to 5 (mg/day), mean ± SD	6.7 ± 5.1	7.2 ± 5.5	5.9 ± 3.9

For internal validation, the model performance was tested in the validation cohort by adjusted R^2 and MAE. The R^2 of developmental cohort was 0.3125 and from validation cohort was 0.2929. MAE of TAC dose was 0.0392191 mg/kg.

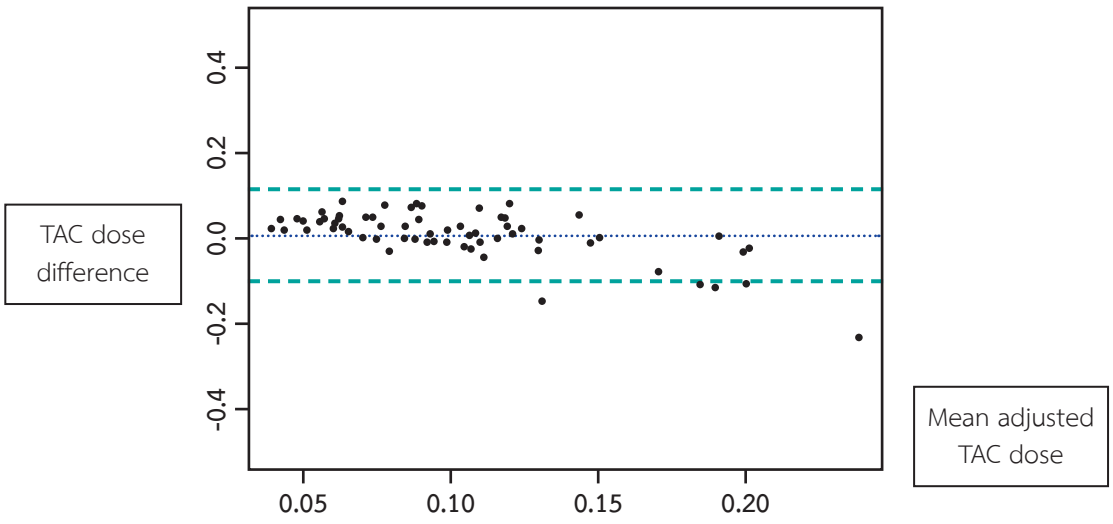

Figure 1. Bland-Altman plot for predicted dose error (mg/kg)

The MAE of the TAC dose is shown in the Bland-Altman plot; **Figure 1**. This plot showed agreement between the adjusted target TAC dose and predicted dose from the equation tested in the validation cohort. The Y-axis shows the TAC dose difference; real TAC dose in the validation cohort – predicted dose from the model equation in the validation cohort; compared with each mean adjusted TAC dose on the X-axis. The mean difference dose or MAE of the TAC dose was 0.0392191 mg/kg and the critical difference dose was 0.1093 mg/kg.

Discussion

Tacrolimus, constitutes the backbone immunosuppressive drug in KT over the past decades. A lower tacrolimus trough level was found to be associated with increased risk of acute rejection especially in the first week after transplant.[3] Achieving the tacrolimus target concentration as soon as possible was preferred; however, tacrolimus overexposure may lead to acute calcineurin inhibitor nephrotoxicity. According to the narrow therapeutic level of tacrolimus and many factors affecting the blood level involving tacrolimus, it becomes important to monitor the drug level to achieve the most suitable target to achieve the best benefit. In worldwide general practice, the most common initial loading dose of TAC is 0.1 to 0.2 mg/kg/day without adjusting with any factor. Moreover, most TAC levels did not achieve the therapeutic target, even when the CYP3A5 genotype factor was added; only one third of patients could achieve the target.[12-15] Due to the higher drug level variability and narrow therapeutic index of this drug, we need to have a precise prediction method of tacrolimus dose to predict the most suitable quantity for use during the early postKT period. In Thailand, most transplant centers did not employ CYP3A5 genotypes due to resource limitation although this constitutes one of the most important factors affecting tacrolimus dosing. However, one related study showed TAC C_{12} presented a significant correlation with TAC dose postTK day 7 as well as for the CYP3A5 factor and may use TAC C_{12} as the simple factor to determine the accurate TAC dose during the early postKT period in transplant centers which cannot access the CYP3A5 genotype.[11] Unfortunately, TAC C_{12} factor alone did not show a good prediction of TAC dose in real life practice. Therefore, this study constitutes the first study in Thailand to use important factors to develop a model for predicting tacrolimus dose to use in Thai KT recipients during the perioperative period days 3 to 5.

We reported the first tacrolimus dosing equation with the most significant correlation factor to TAC dose, developed from the Thai KT recipient's cohort. Our study found TAC dose days 3 to 5 was significantly influenced by TAC C_{12}, hemoglobin level and BSA. Strong concomitant drug factors were not evaluated because no patient received any strong concomitant drug in this study. In addition, when we used intercepts and coefficients to adjust by LASSO regularization technique, the two most influencing factors left included TAC C_{12} and hemoglobin. Regarding TAC C_{12}, our study results found a strong correlation with tacrolimus dose days 3 to 5 corresponding to a related TAC C_{12} study reporting a correlation with tacrolimus dose day 7 and indicating a stable period one to three months posttransplant.[11] It could explain why TAC C_{12} showed a significant correlation to TAC dose. Because TAC C_{12} is a representative loading dose, hemoglobin, serum albumin, other demographic factors and also CYP3A5 genetic polymorphism of the patients can strongly reflect the tacrolimus dose. Some clinical factors in many studies such as serum creatinine or sex were not significantly correlated to TAC dose; thus, we did not evaluate those factors in this study. In developing the prediction equation, many factors were found to be associated with TAC dose days 3 to 5, i.e., TAC C12, hemoglobin level and BSA. However, adding all factors to the equation did not improve the efficacy of prediction and might have made the equation too fit to this population so it could not be widely used in the general population. Therefore, we decided to use only the two most important factors, i.e., TAC C_{12} and hemoglobin in the equation.

The correlation showed R^2 in the developmental cohort was 0.3125 and in the validation cohort was 0.2929. The equation exhibited low R^2, but, in a different perspective, a good predicting performance could show how the test could minimize error of the drug dose needed. Therefore, testing the equation for validation cohort, showed the MAE of the TAC dose was 0.0392191 mg/kg which is not that much in real life concerning the TAC dose used. Moreover, this plot indicated that the prediction dose from the model equation had better prediction among patient requiring lower TAC dose (between 0.05 and 0.1 mg/kg) than among patients requiring higher TAC dose.

One strength of our study, aiming to develop a better model to predict TAC dose, was regarding perioperative

KT using the most important factors affecting real drug dose in Thailand. This constituted the first study enrolling many subjects in a Thai kidney transplant cohort and using many clinical factors to assess the most effective tacrolimus dose for Thai patients. Compared with other related model prediction studies, most were developed in foreign populations such as Caucasians or other Asians so they might not fit Thai patient. Another benefit of our proposed equation was we needed only two simple parameters to find the dose which could be most easily used without need to measure CYP3A5 genetic polymorphism, a limited resource in Thai transplant centers. Furthermore, this study endeavored to determine the most suitable TAC dose at early postKT (days 3 to 5) which was strongly associated with graft outcome compared with most related studies that mainly explored a loading dose of TAC. Therefore, nephrologists could use this to guide adjusting the drug dose that could be better than using manual approximation. However, this study involved a retrospective cohort so it might have encountered limitations such as missing data among recipients. However, the other data were almost complete because this cohort incorporated a valid protocol in the study center for physicians to follow or how to practice when unexpected conditions arose. Hence, the data that we used for analyses were the same and easy to categorize and evaluate.

In conclusion, the TAC dose prediction equation developed from clinical factors, can guide nephrologists to adjust TAC dose during perioperative KT among individual patient and this optimization will reduce both TAC toxicity and KT rejection rates.

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