ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2018; 23: 300-309
DOI: 10.12659/AOT.907666

Received: 2017.10.22
Accepted: 2017.12.29
Published: 2018.05.08

A Low Fixed Tacrolimus Starting Dose Is Effective and Safe in Chinese Renal Transplantation Recipients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACE 1 Jiang-Tao Tang*
BC 1,2 Lin Yan*
AG 1 Lan-Lan Wang
E 1 Yang-Juan Bai
BC 1 Ya-Mei Li
A 1 Yuan-Gao Zou
BC 1,3 Yi Li
ACE 3,4 Teun van Gelder
AEF 5 Yun-Ying Shi

1 Department of Laboratory Medicine/Research Centre of Clinical Laboratory Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China
2 Sector Nephrology and Transplantation, Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
3 Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
4 Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
5 Department of Nephrology, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China

* Jiang-Tao Tang and Lin Yan contribute equally to this work

Corresponding Author: Yun-Ying Shi, e-mail: yyshi0130@163.com

Source of support: This study was funded by the Natural Science Foundation of China (81571561)

Background: We investigated whether a low fixed Tac starting dose regimen could lead to a better achievement of Tac target concentrations, as well as an effective immunosuppressive treatment, in Chinese kidney transplant recipients (KTRs).

Material/Methods: We collected whole-blood and serum samples from 189 KTRs and the Tac starting dose was 2, 2.5, or 3 mg/day. Information on Tac C_0, dose, body weight, body mass index (BMI), Scr, eGFR, and *CYP3A5* genotypes were collected from a routine therapeutic drug monitoring database. The correlation between Tac C_0 and body weight (or BMI) was investigated by calculating the goodness of fit. Multivariable logistic regression was performed to estimate the independent associated factors.

Results: The patients with 3 mg per day of Tac had higher C_0 at day 7 compared to those with 2 or 2.5 mg. For patients receiving the same Tac starting dose, no significant difference was found in Tac C_0 at day 7 among different body weight or BMI groups. There was no significant difference in Scr or eGFR at 1 year after transplant, nor was there a significant difference in the rates of DGF or AR at post-transplant day 30 among different Tac starting dose groups or among the 3 Tac C_0 range groups. *CYP3A5* genotype and Tac initial dose were independently associated with Tac C_0.

Conclusions: *CYP3A5* genotype and Tac initial dose were independently associated with Tac C_0 in renal transplant recipients. Our results suggest that a low Tac target C_0 range (5–8 ng/ml) with a low fixed starting dose (3 mg/day) would be safe and effective among Chinese KTRs.

MeSH Keywords: Body Mass Index • Body Weight • Kidney Transplantation • Tacrolimus

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/907666

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Tacrolimus (Tac) has a narrow therapeutic window and displays large pharmacokinetic variability [1]. Even with therapeutic drug monitoring (TDM), it can take up to 14 days to reach target concentrations [2]. Based on animal studies [3,4], the initial oral starting dose of Tac in the first clinical trials in humans was 0.15 mg/kg. At present, oral Tac therapy is initiated with a daily dose ranging from 0.10 to 0.20 mg/kg administered in 2 equally divided doses [5]. In most transplant centers, the Tac starting dose is calculated based on body weight [5]. However, dosing algorithms have demonstrated that body weight does not seem to have a statistically significant influence on Tac clearance [6,7], and the evidence that Tac elimination is linearly related to total body weight remains weak.

Underexposure to Tac may result in under-immunosuppression and acute rejection in transplant recipients, and overexposure puts patients at risk of Tac-related toxicity. The KDIGO Transplant Workgroup states that dosing of Tac is important and relatively under-investigated [3]. More and more studies proved that underexposure of Tac could be related to low body weight and overexposure to higher body weight in kidney transplant recipients if the Tac starting dose is only based on body weight [8–11]. With global obesity on the rise, the number of overweight patients is likely to increase even further, raising questions whether it is wise to continue to base the Tac starting dose on body weight. Chinese patients generally weigh less and have smaller, less various body mass index (BMI) compared to white people. Furthermore, there are more cytochrome enzyme P 450 (*CYP3A5*) expressers in the Chinese population than in white cohorts [12]. Hence, the decision to select a Tac starting dose for Chinese renal transplant recipients might need to follow a different strategy. In this study, we aimed to investigate whether a low fixed Tac starting dose regimen could lead to a better achievement of Tac target concentrations, as well as an effective immunosuppressive treatment in Chinese renal transplant recipients.

Material and Methods

Patients

This was a retrospective study including 189 patients (146 males and 43 females) who underwent living donor renal transplantation in West China Hospital, from January 2014 to May 2015. Most of the patients (n=175) received either basiliximab or rabbit antithymocyte globulin (rATG) as induction treatment. All patients received a Tac-based immunosuppressive regimen (Tac+mycophenolate mofetil+prednisone) for maintenance treatment. The Tac starting dose was 2, 2.5 or 3 mg/day according to recipient hepatitis B status and the preference of the renal transplant team. There are 2 teams of doctors in our renal transplant center; one group prefers lower Tac starting dose (2 or 2.5mg per day) while the other one prefers a higher dose (3 mg per day). There were 17 recipients co-infected with hepatitis B virus (defined as hepatitis B surface antigen-positive), for whom the Tac starting dose was determined according to their hepatitis B virus e (HBe) antigen status. If the recipient's HBe antigen was positive, then we gave 2 mg/day of Tac; otherwise, we gave 2.5 or 3 mg/day. Tac was always dosed twice daily. Since more than 300 renal transplants are performed annually in our center, the routine blood tests including Tac C_0 are performed once every week during the post-transplant hospitalization to insure an efficient sequence. Hence, Tac C_0 was measured for the first time on the morning of post-operative day 7 after patients had received 12 unaltered doses of Tac. After day 7, the physicians could adjust the Tac dose based on whole-blood Tac trough concentration measurements to reach the target Tac pre-dose concentration range (5–8 ng/ml) at first steady-state. Delayed graft function (DGF) was defined as the need for dialysis within the first week after transplantation. Acute rejection (AR) was proved by renal allograft biopsy, or defined as acutely increased serum creatinine (Scr) level exclusive of other possible causes, which could be effectively treated by high-dose oral glucocorticoid or methylprednisolone pulse therapy. The AR data within the first year after transplantation of all the included recipients were recorded.

The markers of renal function, liver enzymes, blood glucose, and Tac blood concentration measurements

Blood samples were collected before the morning dose of Tac. The Tac trough concentration (C_0) was measured in whole blood by the enzyme-multiplied immunoassay on a V-Twin device (Syva Company/SIMENS). Scr levels were measured by turbidimetric immunoassay on a COBAS device (Roche Diagnostics Limited Company, Germany). The estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: eGFR (ml/min/1.732)=a×(serum creatinine/b)c×(0.993) [13].

Genomic DNA extraction

Preoperative blood samples (3 mL) were collected in EDTA tubes from the renal transplant recipients, and genomic DNA was isolated from the whole-blood samples using the whole-blood DNA kit (Biotake corporation, Beijing, China) and DNA was extracted according to the manufacturer's protocol. The concentration of DNA was diluted to 10 ng/μL for working solution and the isolated DNA was stored at –20°C.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 1. Demographic characteristics among patients with different Tac starting dose.

	2 mg n=70	2.5 mg n=15	3 mg n=104	*P*
Recipient gender (Male/Female)	56 (80.0%)/14 (20.0%)	11 (73.3%)/4 (26.7%)	79 (76.0%)/25 (24.0%)	0.563
Age of recipient (years)	30.8±9.2	29.6±9.3	32.3±9.3	0.256
Ethnicity				
Han	67 (95.7%)	15 (100%)	96 (92.3%)	0.365
Tibetan	2 (2.9%)	0	5 (4.8%)	
Yi	1 (1.4%)	0	3 (2.9%)	
Bodyweight (kg)	57.1±9.4	55.4±8.7	59.9±10.6	0.723
Height (cm)	166.5±7.3	166.0±6.9	166.5±7.8	0.256
BMI (kg/m^2)	20.5±2.8	20.1±2.9	21.6±3.2	0.569
MMF daily dose (mg/day)	1984±170	1981±161	1988 ±188	0.756
No. of recipients on dialysis (hemodialysis/peritoneal/none)	63/4/3	15/0/0	96/2/6	0.256
Duration of dialysis before transplantation(months)	10 (6.0–12.0)	11.0 (6.0–12.1)	11.0 (6.0–12.2)	0.568
Total HLA mismatches	3.8±1.7	3.7±1.7	3.5±1.3	0.546
Panel reactive antibodies (%)	24.3 (17/70)	20.0 (3/15)	21.2 (22/104)	0.745
DSA pre-transplantation (%)	1.4 (1/70)	0.0 (0/15)	0.96 (1/104)	0.785
Co-infection with Hepatitis B (%)	12.9 (9/70)	6.7 (1/15)	6.7 (7/104)	0.032*
No. of recipients on induction treatment (anti-CD25/rATG/none)	63/1/6	11/2/2	91/7/6	0.025*

* p<0.05

CYP3A5 single nucleotide polymorphism (SNPs) measurements

CYP3A5 SNPs (6986A>G) was analyzed by polymerase chain reaction (PCR) and melting curve analyses under the same conditions in a 96-well plate on a Light Cycler480 device (Roche Diagnostics, Penzberg, Bavaria, Germany). The genotype of subset was defined according to known genotypes of controls.

Statistical analysis

Categorical variables are reported using frequency tables and percentages, and continuous variables are expressed as medians with ranges. Tac overexposure was defined as a Tac trough concentration above 8 ng/mL, and underexposure was defined as below 5 ng/mL. The correlation between Tac C_0 and body weight (or BMI) was investigated by calculating the goodness of fit. Data was analyzed using IBM SPSS version 21 (SPSS Inc., Chicago, IL). Descriptive statistics were generated. Multivariable logistic regression was performed to estimate the independent associated factors.

Results

Patient characteristics

For this post hoc analysis, data were available for 189 kidney transplant recipients. The median body weight was 58.5 kg with a range of 38.0–95.0 kg, whereas the median BMI was 21.2 kg/m^2 with a range of 15.2–31.0 kg/m^2. The demographic characteristics among patients with different Tac starting doses were comparable except for the percentage of co-infection with hepatitis B and the distribution of different induction treatment (Table 1).

When the Tac C_0 at day 7 is compared between the 3 Tac dosing groups, it is clear from Table 2 that, on average, the C_0 was higher in patients who started with a daily dose of 3 mg Tac compared to patients who started with 2 mg or 2.5 mg. It is also clear that the lower starting dose of 2 mg led to a very high proportion (91.4%) of patients with a C_0 below the lower limit of the target range (5 ng/mL), and very few (1.4%) with a C_0 above 8 ng/mL. In contrast, for the patients who started

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2. Tac C_0 in the 3 groups of patients with different Tac starting dose.

	2 mg n=70	2.5 mg n=15	3 mg n=104	*P*
Tac C_0 at day 7	3.2±2.2	5.7±2.7	6.2±2.8	0.039*
<5 ng/ml	64 (91.4%)	7 (46.7%)	36 (34.6%)	0.038*
5–8 ng/ml	5 (7.1%)	6 (40.0%)	40 (38.5%)	
>8 ng/ml	1 (1.4%)	2 (13.3%)	28 (26.9%)	

* p<0.05

Table 3. Demographic characteristics and Tac C_0 according to *CYP3A5* genotype.

	CYP3A5 non-expressers (*CYP3A5 *3/*3*) n=93	*CYP3A5* expressers (*CYP3A5*1/*3* and **1/*1*) n=96	*P*
Recipient gender (Male/Female)	73 (78.5%)/20 (21.5%)	73 (76.0%)/23 (24.0%)	0.879
Age of recipient (years)	30.1±8.4	32.9±9.9	0.675
Ethnicity			
Han	85 (91.4%)	93 (96.8%)	0.567
Tibetan	6 (6.5%)	1 (1.1%)	
Yi	2 (2.1%)	2 (2.1%)	
Bodyweight (kg)	58.7±11.6	58.7±8.4	0.779
Height (cm)	167.5±7.8	165.5±7.1	0.812
BMI (kg/m^2)	20.7±3.2	21.4±2.9	0.345
Tac starting dose (mg/day)	2.5±0.5	2.6±0.5	0.366
Tac C_0 at day 7	5.7±3.4	4.4±3.3	0.032*
<5 ng/ml	49 (52.7%)	58 (60.4%)	0.045*
5–8 ng/ml	20 (21.5%)	31 (32.3%)	
>8 ng/ml	24 (25.8%)	7 (7.3%)	

* p<0.05

with 3 mg per day, the proportions of patients with Tac C_0 below or above the target range is almost equal (34.6% and 26.9%).

According to recipients' *CYP3A5* genotype, we divided the recipients into *CYP3A5* expressers (*CYP3A5 *3/*3*, n=93) and non-expressers (*CYP3A5 *1/*3 and *1/*1*, n=96). A significant difference was found in Tac C_0 at day 7, with more underexposed patients among the *CYP3A5* expressers and more overexposed patients among *CYP3A5* non-expressers (Table 3).

Bodyweight

We divided the 189 patients into 7 groups according to their body weight (<45 kg, 45–49 kg, 50–54 kg, 55–59 kg, 60–64 kg, 65–69 kg, and ≥70 kg). Patients with different Tac starting doses (2 mg/kg and 3 mg/kg) were analyzed separately. For patients who received the same Tac starting dose, no significant difference was found in Tac C_0 at day 7 among different body weight groups. More than 80% of the patients who received Tac with a starting dose of 2 mg/day were underexposed regardless of the body weight. In comparison, patients with a Tac starting dose of 3 mg/day had a much lower percentage of underexposure (20–58.8%) and a higher percentage of target range achievement in each body weight group (0–61.1%). The highest percentage of patients within the target range was found in the 55–59 kg group (61.1%).

We further analyzed the achievement of Tac target range in each body weight group based on the recipients' genotype. For patients who received Tac with a starting dose of 2 mg/day, 84.6% of *CYP3A5* non-expressers and 100% of *CYP3A5* expressers were underexposed. For patients receiving 3 mg/day as the Tac starting dose, 44.6% of *CYP3A5* non-expressers were overexposed, while 42.1% of *CYP3A5* expressers were underexposed. Among *CYP3A5* non-expressers, the Tac C_0 at day 7 decreased as the bodyweight increased (Figure 1). This trend

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

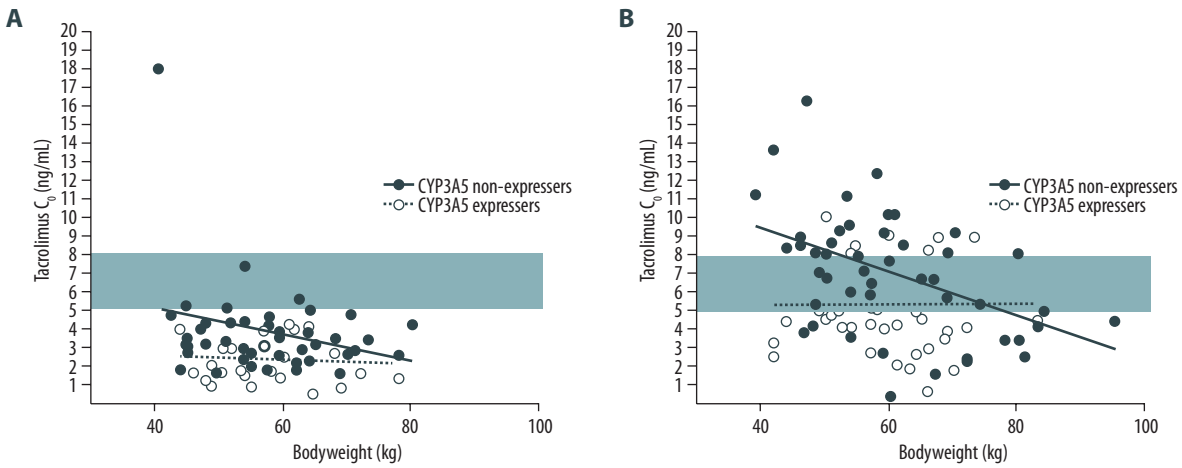

Figure 1. The association between body weight and Tac C_0 on day 7 after transplantation among patients with different *CYP3A5* genotypes. (**A**) Patients who received 2 mg/day as Tac starting dose. (**B**) Patients who received 3 mg/day as Tac starting dose. Shaded part is the target Tac C_0 range (5–8 ng/ml).

Table 4A. The achievement of Tac target C_0 level among patients with 2 mg/day starting dose.

BMI (kg/m²)	n	Dose	C_0 (ng/ml)	*P*	<5 ng/ml	5–8 ng/ml	>8 ng/ml	*P*
<18.5	17	2.0±0.0	3.7±3.8		16 (94.1%)	0 (0.0%)	1 (5.9%)	
18.5–23.9	43	2.0±0.0	3.1±1.4	0.235	38 (88.4%)	5 (11.6%)	0 (0.0%)	0.336
≥24	10	2.0±0.0	2.6±1.1		10 (100.0%)	0 (0%)	0 (0%)	

Table 4B. The achievement of Tac target C_0 level among patients with 2.5 mg/day starting dose.

BMI (kg/m²)	n	Dose	C_0 (ng/ml)	*P*	<5 ng/ml	5–8 ng/ml	>8 ng/ml	*P*
<18.5	2	2.5±0.0	7.8±3.7		0 (0.0%)	1 (50.0%)	1 (50.0%)	
18.5–23.9	12	2.5±0.0	5.4±2.7	0.532	6 (50.0%)	5 (41.7%)	1 (8.3%)	0.456
≥24	1	2.5±0.0	4.8		1 (100.0%)	0 (0%)	0 (0%)	

Table 4C. The achievement of Tac target C_0 level among patients with 3 mg/day starting dose.

BMI (kg/m²)	n	Dose	C_0 (ng/ml)	*P*	<5 ng/ml	5–8 ng/ml	>8 ng/ml	*P*
<18.5	17	3.0±0.0	7.5±3.9		6 (35.3%)	4 (23.5%)	7 (41.2%)	
18.5–23.9	62	3.0±0.0	6.1±2.4	0.289	19 (30.6%)	28 (45.2%)	15 (24.2%)	0.352
≥24	25	3.0±0.0	5.9±2.4		11 (44.0%)	8 (32.0%)	6 (24.0%)	

was not found among *CYP3A5* expressers (Figure 1). However, there was no correlation between Tac C_0 and the bodyweight in either *CYP3A5* non-expressers or *CYP3A5* expressers (P>0.05).

BMI

We divided the 189 patients into 3 groups according to the BMI criteria published by National Health and Family Planning Commission of China. Underweight was defined as BMI <18.5 kg/m², while overweight and obese were defined

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

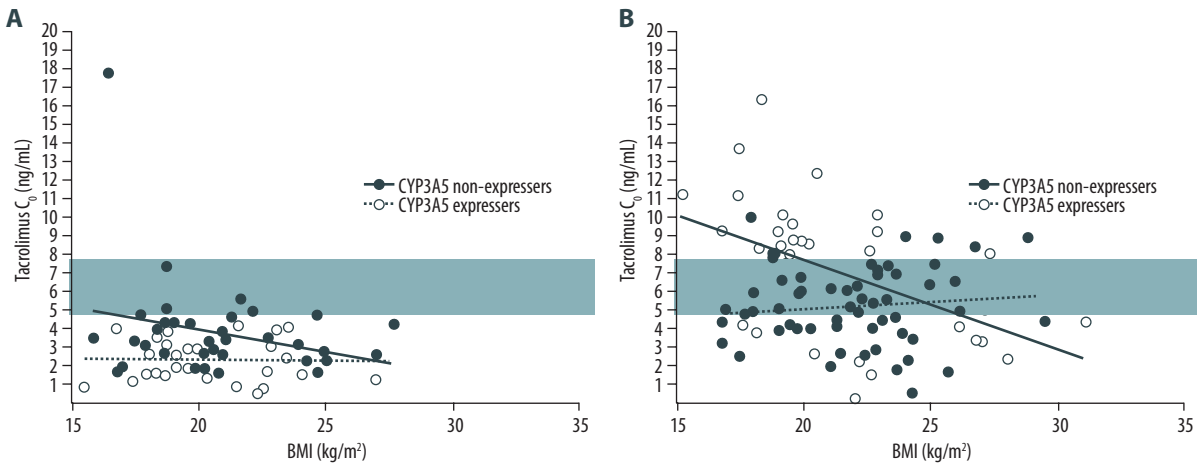

Figure 2. The association between BMI and Tac C_0 on day 7 after transplantation among patients with different *CYP3A5* genotypes. (**A**) Patients who received 2 mg/day as Tac starting dose. (**B**) Patients who received 3 mg/day as Tac starting dose. Shaded part is the target Tac C_0 range (5–8 ng/ml).

as BMI ≥24 kg/m^2. The achievement of Tac target C_0 in each BMI group was analyzed based on the different Tac starting doses (Table 4A–4C). For patients who received the same Tac starting dose, no significant difference was found in Tac C_0 at day 7 among different BMI groups (Table 4A–4C). The percentages of underexposed patients, patients within the target range, and overexposed patients were comparable among underweight, normal, and overweight patients. However, more than 80% of the patients who received a Tac starting dose of 2 mg/day were underexposed regardless of their BMI group (Table 4A). In comparison, patients with a Tac starting dose of 3 mg/day had a much lower percentage of underexposure and a higher percentage of target range achievement in each BMI group (Table 4C). For the association between BMI and Tac C_0 on post-transplant day 7 among patients with different *CYP3A5* genotypes, a similar trend was found as that found between body weight and Tac C_0 on day 7 (Figure 2). However, no correlation was found between Tac C_0 and the BMI in either *CYP3A5* non-expressers or *CYP3A5* expressers (P>0.05).

Kidney function, Tac adverse effects, and the rate of acute rejection among renal transplant recipients

We classified the patients in 3 ways according to different factors, including Tac starting dose, Tac C_0 range at day 7, and *CYP3A5* genotype. There was no significant difference in the Scr or eGFR at post-transplant day 7, day 30, or 1 year after transplantation among patients with different Tac starting dose, and we found no difference among the 3 Tac C_0 range groups (Tables 5, 6). The rates of DGF and AR within 30 days post-transplant were also comparable among these groups (Tables 5, 6). Although there was a significant difference in the Tac C_0 at day 7 between *CYP3A5* non-expressers and expressers, the renal function after transplantation and the rates of DGF and AR within 30 days after transplant were all comparable between the 2 groups with different *CYP3A5* expression (Table 7).

Multivariate logistic regression model

We chose age, sex, height, body weight, BMI, *CYP3A5* genotype, biopsy-proven acute rejection (BPAR) rate, and Tac initial dose for univariate analysis with Tac C_0. To identify independently associated factors with Tac C_0, we selected a multivariate logistic regression model using these parameters, whose P value was less than 0.3 in the univariate analysis. The multivariate analyses demonstrated that *CYP3A5* genotype and Tac initial dose were independently associated with Tac C_0 in renal transplant recipients (Tables 8, 9).

Discussion

This study demonstrated that dosing Tac at a low, fixed dosage (2 mg/day) resulted in Tac underexposure in many patients, while increasing the Tac starting dose to 3 mg/day (also a low, fixed dosage) improved the achievement of Tac target C_0 and decreased Tac underexposure significantly. Few studies have investigated the association of body weight or BMI with Tac exposure at the first measured steady-state blood sample. Theoretically, for lipophilic drugs such as tacrolimus, the volume of distribution might increase as body weight increases, which would make dosing based on total body weight a reasonable approach. However, the results of several studies show that a Tac starting dose solely based on body weight might not be appropriate for overweight patients. Rodrigo et al. concluded

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 5. Kidney function in different Tac starting dose recipients after transplantation.

	2 mg n=70	2.5 mg n=15	3 mg n=104	*P*
Post-transplant day 7				
Scr (umol/L)	101.8±35.3	112.9±65.6	108.5±60.5	0.443
eGFR (ml/min/1.73 m^2)	99.7±32.7	91.8±42.5	97.9±37.8	0.356
The rate of DGF	18.6% (13/70)	13.3% (2/15)	18.3% (19/104)	0.225
Post-transplant day 30				
Scr (umol/L)	104.2±52.5	114.8±27.2	107.2±26.9	0.336
eGFR (ml/min/1.73 m^2)	95.6±34.5	89.7±25.8	92.9±22.6	0.189
The rate of AR	6.5% (7/107)	2.9% (2/51)	6.5% (2/31)	0.435
Post-transplant one year				
Scr (umol/L)	105.5±50.4	118.1±60.8	109.8±61.6	0.443
eGFR (ml/min/1.73 m^2)	96.6±33.2	82.5±45.9	92.3±37.7	0.132

Scr – serum creatinine; eGFR – estimated glomerular filtration rate; DGF – delayed graft function; AR – acute rejection.

Table 6. Kidney function in different Tac levels recipients after transplantation.

	<5 ng/ml n=107	5–8 ng/ml n=51	>8 ng/ml n=31	*P*
Post-transplant day 7				
Scr (umol/L)	106.8±41.4	118.6±79.2	90.5±28.8	0.137
eGFR (ml/min/1.73 m^2)	98.8±30.7	96.8±35.5	111.7±33.3	0.205
The rate of DGF	18.7% (20/107)	19.6% (10/51)	12.9% (4/31)	0.178
Post-transplant day 30				
Scr (umol/L)	114.8±55.9	115.4±29.4	105.6±25.8	0.523
eGFR (ml/min/1.73 m^2)	89.1±24.1	80.6±17.3	89.9±21.7	0.325
The rate of AR	6.5% (7/107)	2.9% (2/51)	6.5% (2/31)	0.632
Post-transplant one year				
Scr (umol/L)	108.5±31.8	118.8±40.6	95.5±23.5	0.325
eGFR (ml/min/1.73 m^2)	98.6±32.5	97.5±36.9	105.6±35.5	0.256

Scr – serum creatinine; eGFR – estimated glomerular filtration rate; DGF – delayed graft function; AR – acute rejection.

that overweight renal transplant recipients are more prone to develop initial high exposure (C_0 >15 ng/mL) compared to non-overweight recipients [10]. Sawamoto et al. demonstrated that the average Tac maintenance dose in patients with a BMI greater than 25 is significantly lower than in patients with a BMI less than 25 [14]. Recently, Andrews et al. [15] confirmed that dosing Tac based solely on body weight results in overexposure in more than half of overweight or obese patients. Miyamoto et al. [16] reported that the Tac concentration in fat tissue was lower than expected based on the lipophilicity of the drug. These intra-fat tissue measurements also support the *in vivo* findings that dosing Tac entirely based on body weight tends to cause overexposure in obese patients. Tac binds to FK-binding protein (FKBP) to exert its immunosuppressive effect. Erythrocytes contain a high level of FKBP, and thus Tac is extensively distributed to the red blood cell compartment [17]. One could argue that the Tac initial dose should be based on the total number of erythrocytes, instead of the body weight. However, such a theoretical dosing basis is impractical in daily clinical work, especially since during surgery, substantial changes in hematocrit may occur. When deciding on the Tac starting dosage, racial differences are another factor that one

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 7. Kidney function in different *CYP3A5* genotype groups after transplantation.

	CYP3A5 non-expressers (*CYP3A5 *3/*3*) n=93	*CYP3A5* expressers (*CYP3A5*1/*3* and **1/*1*) n=96	*P*
Post-transplant day 7			
Scr (umol/L)	105.8±50.4	108.5±55.8	0.332
eGFR (ml/min/1.73 m^2)	102.6±32.6	98.8±32.9	0.189
The rate of DGF	16.1% (15/93)	19.8% (19/96)	0.608
Post-transplant day 30			
Scr (umol/L)	122.2±108.8	115.6±59.4	0.657
eGFR (ml/min/1.73 m^2)	87.7±23.4	85.7±22.8	0.442
The rate of AR	4.3% (4/93)	7.3% (7/96)	0.448
Post-transplant one year			
Scr (umol/L)	102.8±26.8	109.8±39.5	0.223
eGFR (ml/min/1.73 m^2)	106.8±36.6	97.5±32.7	0.233

Scr – serum creatinine; eGFR – estimated glomerular filtration rate; DGF – delayed graft function; AR – acute rejection.

Table 8. Univariable OR for patients with Tac C_0.

	OR	*P*
Age	0.024	0.745
Gender	–0.095	0.191
Height	–0.100	0.176
Biopsy-proven acute rejection (BPAR) rate	0.036	0.527
Bodyweight	–0.168	**0.021**
BMI	–0.148	**0.044**
CYP3A5 genotype	–0.213	**0.003**
Tac starting dose	0.456	**<0.001**

Table 9. Multivariable model of adjusted OR for patients with Tac C_0.

	Adjusted OR	*P*
Gender	0.007	0.928
Height	0.400	0.398
Bodyweight	–1.050	0.238
BMI	0.675	0.368
CYP3A5 genotype	–0.273	**<0.001**
Tac starting dose	0.511	**<0.001**

should consider. Asian patients, such as Chinese, generally weigh less and have smaller, less various BMIs compared to white people. As shown in our study, the mean bodyweight of the Chinese patients was 58.5±10.1 kg and the mean BMI was 21.1±3.1 kg/m^2, which is much lower and less varied compared with the (largely white) patients in the study by Andrews et al. (with a median body weight of 78.9 (37.6–123.1) kg and a median BMI of 25.6 (17.2–42.2) kg/m^2) [15]. Considering the limited evidence for dosing based on body weight, a low fixed Tac starting dose may be reasonable for Chinese transplant recipients. We showed that in patients who received the same Tac starting dose, no significant difference was found in Tac C_0 at day 7 among different body weight groups. Our results confirm that dosing Tac based on body weight is not a rational approach. We also confirmed the strong impact of *CYP3A5* genotype on Tac pharmacokinetics. Further studies are required to identify the optimal fixed Tac starting dose that could improve the achievement of target Tac concentration among patients with different BMIs.

Many studies have shown that high Tac trough concentrations are associated with drug toxicity and adverse effects [18–23]. Aiming for a lower Tac target concentration did not increase the incidence of acute rejection, although this was initially expected [24–26]. Several investigators have attempted to identify the optimal Tac concentration range with the lowest incidence of rejection and acceptable toxicity [27–29]. The findings of these reports were conflicting and limited by their retrospective design, limited numbers of patients, and different co-immunosuppressive medication. Recently, Bouamar et al. [26] pooled the data of 3 large randomized-controlled trials (RCTs)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

and studied the relationship between Tac exposure and the incidence of BPAR. They demonstrated that there was no association between Tac C_0 and the incidence of acute rejection. At present, the optimal target range of Tac C_0 remains controversial. In our study, a low fixed starting dose (2–3 mg/day) and a low target Tac C_0 range (5–8 ng/ml) were used, and most patients received basiliximab induction therapy. Although many patients (especially those receiving with 2 mg/day) were underexposed at day 7 (more than 50%), the Tac dosage was adjusted according to our target range immediately after the first measurement. Moreover, the eGFR levels, and the rates of DGF and AR within 30 days' post-transplant, among the 3 Tac C_0 range groups were not different. Meanwhile, there was no association of the Tac C_0 on post-transplant day 7 with the serum creatinine, eGFR levels, the rate of DGF, and the rate of AR. The above results indicated that the impact of such short-term (1 week) Tac underexposure on the allograft outcome was limited and could be remedied by TDM. In view of the excellent outcome of patients with a Tac trough below 5 ng/mL on day 7, a lower Tac target concentration should be considered. However, to implement this strategy in clinical practice, such a reduced Tac target protocol first needs to be tested in well-designed clinical trials with sufficiently large sample size and longer follow-up.

A limitation of this study is that it was a post hoc analysis. It was unplanned and therefore the apparent differences and associations could be coincidental. Secondly, the Tac concentrations were measured with immunoassay instead of mass spectrometry, which is now considered the criterion standard. In our center, immunoassay was used for the routine determination of Tac concentration at the start of the trial. Many transplant centers worldwide still rely on immunoassays for TDM of Tac.

Conclusions

CYP3A5 genotype and Tac initial dose were independently associated with Tac C_0 in renal transplant recipients. A low Tac target C_0 range (5–8 ng/ml) with a low fixed starting dose (3 mg/day) might be safe and effective among Chinese kidney transplant recipients, although many recipients showed underexposure. More studies are required to explore the optimal fixed dose for Chinese kidney transplant recipients.

Conflict of interest

None.

References:

1. Staatz CE, Tett SE: Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokin, 2004; 43(10): 623–53
2. Thervet E, Loriot MA, Barbier S et al: Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Therap, 2010; 87(6): 721–26
3. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant, 2009; 9(Suppl. 3): S1–155
4. Starzl TE, Todo S, Fung J et al: FK 506 for liver, kidney, and pancreas transplantation. Lancet, 1989; 2(8670): 1000–4
5. Jusko WJ, Thomson AW, Fung J et al: Consensus document: Therapeutic monitoring of tacrolimus (FK-506). Ther Drug Monit, 1995; 17(6): 606–14
6. Passey C, Birnbaum AK, Brundage RC et al: Dosing equation for tacrolimus using genetic variants and clinical factors. Br J Clin Pharmacol, 2011; 72(6): 948–57
7. Andrews LM, Riva N, de Winter BC et al: Dosing algorithms for initiation of immunosuppressive drugs in solid organ transplant recipients. Expert Opin Drug Metab Toxicol, 2015; 11(6): 921–36
8. Press RR, Ploeger BA, den Hartigh J et al: Explaining variability in tacrolimus pharmacokinetics to optimize early exposure in adult kidney transplant recipients. Ther Drug Monit, 2009; 31(2): 187–97
9. Kausman JY, Patel B, Marks SD: Standard dosing of tacrolimus leads to overexposure in pediatric renal transplantation recipients. Pediatr Transplant, 2008; 12(3): 329–35
10. Rodrigo E, de Cos MA, Sanchez B et al: High initial blood levels of tacrolimus in overweight renal transplant recipients. Transplant Proc, 2005; 37(3): 1453–54
11. Størset E, Holford N, Hennig S et al: Improved prediction of tacrolimus concentrations early after kidney transplantation using theory-based pharmacokinetic modelling. Br J Clin Pharmacol, 2014; 78(3): 509–23
12. Lamba JK, Lin YS, Schuetz EG et al: Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev, 2002; 54(10): 1271–94
13. Stevens LA, Claybon MA, Schmid CH et al: Evaluation of the CKD-EPI equation in multiple races and ethnicities. Kidney Int, 2011; 79(5): 555–62
14. Sawamoto K, Huong TT, Sugimoto N et al: Mechanisms of lower maintenance dose of tacrolimus in obese patients. Drug Metab Pharmacokinet, 2014; 29(4): 341–47
15. Andrews LM, de Winter BC, Tang JT et al: Overweight kidney transplant recipients are at risk of being overdosed following standard bodyweight-based tacrolimus starting dose. Transplant Direct, 2017; 3(2): e129
16. Miyamoto Y, Uno T, Yamamoto H et al: Pharmacokinetic and immunosuppressive effects of tacrolimus-loaded biodegradable microspheres. Liver Transpl, 2004; 10: 392–96
17. Astellas Pharma U, Inc. PROGRAF Tacrolimus capsules, tacrolimus injection (for intravenous infusion only). 2009
18. Sikma MA, Hunault CC, van de Graaf EA et al: High tacrolimus blood concentrations early after lung transplantation and the risk of kidney injury. Eur J Clin Pharmacol, 2017; 73(5): 573–80
19. Sikma MA, van Maarseveen EM, van de Graaf EA et al: Pharmacokinetics and toxicity of tacrolimus early after heart and lung transplantation. Am J Transplant, 2015; 15(9): 2301–13
20. Yates CJ, Fourlanos S, Hjelmesaeth J et al: New-onset diabetes after kidney transplantation-changes and challenges. Am J Transplant, 2012; 12(4): 820–28
21. Bottiger Y, Brattstrom C, Tyden G et al: Tacrolimus whole blood concentrations correlate closely to side-effects in renal transplant recipients. Br J Clin Pharmacol, 1999; 48: 445–48
22. Kershner RP, Fitzsimmons WE: Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney trans-plantation. Transplantation, 1996; 62: 920–26
23. Kuypers DR, Naesens M, de Jonge H et al: Tacrolimus dose requirements and *CYP3A5* genotype and the development of calcineurin inhibitor-associated nephrotoxicity in renal allograft recipients. Ther Drug Monit, 2010; 32(4): 394–404

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

24. Ekberg H, Tedesco-SilvaH, Demirbas A et al: Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med, 2007; 357: 2562–75
25. Gaston RS, Kaplan B, Shah T et al: Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: The Opticept trial. Am J Transplant, 2009; 9: 1607–19
26. Bouamar R, Shuker N, Hesselink DA et al: Tacrolimus predose concentrations do not predict the risk of acute rejection after renal transplantation: A pooled analysis from three randomized-controlled clinical trials. Am J Transplant, 2013; 13(5): 1253–61
27. Borobia AM, Romero I, Jimenez C et al: Trough tacrolimus concentrations in the first week after kidney transplantation are related to acute rejection. Ther Drug Monit, 2009; 31(4): 436–42
28. Staatz C, Taylor P, Tett S: Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol Dial Transplant, 2001; 16(9): 1905–9
29. Nashan B, Saliba F, Durand F et al: Pharmacokinetics, efficacy, and safety of mycophenolate mofetil in combination with standard-dose or reduced-dose tacrolimus in liver transplant recipients. Liver Transpl, 2009; 15(2): 136–47

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]