The impact of cytochrome P450 3A5 genotype on early tacrolimus metabolism and clinical outcomes in lung transplant recipients

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Abstract
Background Tacrolimus (Tac) is the cornerstone of immunosuppressant therapy after lung transplantation (LTx). It shows great inter-individual variability in pharmacokinetics, which could partly be explained by pharmacogenetic factors. Aim We aim to investigate the influence of cytochrome P450 3 A5 (CYP3A5) genotypes on early post-LTx Tac metabolism and whether it is affected by concomitant use of azole antifungals. Also, we explored the association between CYP3A5 genotype and clinical outcomes. Method 90 recipients who underwent LTx from 2017 to 2019 were enrolled in the study. The effect of CYP3A5 genotype on Tac metabolism and interaction with azole antifungals were assessed during week 1–4 after transplantation. Associations between CYP3A5 genotype and the incidence of acute kidney injury (AKI), length of hospital stay and mortality were analyzed. Results CYP3A5*1 carriers had lower dose adjusted concentration (C/D) than CYP3A5*3/*3 group at all time points (p < 0.05). The dose ratio of CYP3A5*1 carriers to CYP3A5*3/*3 was between 1.3 and 2.4 when comparable concentrations were reached. Use of azole antifungals did not blunt the effect of CYP3A5 genotypes on Tac metabolism. Logistic regression showed Tac concentration ≥ 7.5 ng/mL at week 1 was associated with higher incidence of AKI. No statistically significant difference was found between CYP3A5 genotypes and the length of hospital stay. Kaplan–Meier analysis showed no statistically significant difference between 30-day or 1-year mortality and CYP3A5 genotype. Conclusion CYP3A5 genotype could affect Tac metabolism early after LTx. However, it had no influence on the incidence of AKI, length of hospital stay and mortality.

Keywords AKI · CYP3A5 genotype · Lung transplantation · Mortality · Tacrolimus

Impacts on practice
- Genetic polymorphism of CYP3A5*3 could affect tacrolimus metabolism early after lung transplantation and hence transplant pharmacists may use this genetic information to guide personalized dosing of tacrolimus.
- Genetic polymorphism of CYP3A5*3 did not seem to be directly associated with incidence of AKI and mortality in lung transplant recipients.
- Rather than considering CYP3A5*3 genotype, transplant pharmacists should pay more attention to tacrolimus concentration at week 1, which seems more relevant in determining patient at higher risk of AKI after lung transplantation.

Introduction
Tacrolimus (Tac) is the cornerstone of immunosuppressant therapy after lung transplantation (LTx) [1]. It is mainly metabolized by cytochrome P450 3 A (CYP3A) enzymes after oral administration [2]. CYP3A5*3 (rs776746) mutation results in non-functional protein, leading to reduction in CYP3A5 activity [3]. The association between CYP3A5 genotype and Tac metabolism has been consistently observed among kidney, liver, and heart transplant recipients, with CYP3A5*1 carriers requiring higher doses, and exhibiting lower dose adjusted trough concentration (C/D) compared to CYP3A5*3/*3 genotype [4–6]. In LTx, similar results have been reported, but the study population mainly consisted of Caucasians [7–9]. Except for a different frequency
of $CYP3A5^*3$ allele from Caucasians, males and older recipients seems to account for the majority of Chinese LTx population [10, 11]. Till now, studies in this population are limited and usually conducted in small sample sizes, leaving a major void in this area [12, 13].

Whether $CYP3A5$ genotype affects the clinical outcomes of transplant recipients has been controversial. Rojas et al. conducted a meta-analysis including 21 kidney transplant studies, and summarized $CYP3A5^*1$ carriers might be associated with a higher risk for rejection and tended to suffer from chronic nephrotoxicity [14]. However, Woillard later reported no association between $CYP3A5$ and allograft loss in renal transplant recipients [15]. Also, random control trials comparing between $CYP3A5$ genotype guided Tac dosing and fixed dosing showed no differences in patient survival, nephrotoxicity, or acute rejection [16, 17]. Thus, there is no definitive answer to this question and more studies are warranted.

**Aim of the study**

Based on current status, our study was designed to investigate two key questions. First, whether $CYP3A5$ genotype plays a role in Tac metabolism and whether it is affected by concomitant use of azole antifungals early after LTx. Second, whether there is association between $CYP3A5$ genotype and clinical outcomes.

**Ethics approval**

All procedures in this study were in accordance with the 1964 Helsinki declaration and its amendments, and was approved by the Ethics Committee of China-Japan Friendship Hospital in May, 2019 (No. 2019-65-K45). All recipients signed informed consent when undergoing lung transplantation, in which they gave permission for use of anonymized medical data by scientists.

**Method**

**Patients**

Recipients who undergone LTx during 2017 to 2019 in China-Japan Friendship Hospital were enrolled in this study. The inclusion criteria were: (1) LTx for the first time; (2) received Tac-based immunosuppressive regimen; (3) age $\geq$ 18. The exclusion criteria were: (1) received cyclosporin in the first month; (2) survived less than 24 h after surgery. During this time, 150 patients received LTx. From this study population, 51 were excluded due to not available for genetic testing, 3 were excluded due to missing data, 3 were excluded due to use of cyclosporin, 2 were excluded for death within 24 h and 1 was excluded due to less than 18 years old, leaving 90 for final analysis.

**Immunosuppressive and anti-fungal regimens**

Per protocol in our center, most recipients used a triple maintenance immunosuppressive regimen consisting of Tac, mycophenolate mofetil (MMF) and prednisone. Tac was given on post-operative day (POD) 1. Starting dose was 2 mg/d in 2 divided doses, except those with exceptionally high or low body weight were given a personalized dose per attending physician’s judgement. Dose adjustments were made according to whole-blood trough concentration, determined using micro-particle enzyme immunoassay (ARCHITECT i1000SR immunoassay analyzer, Abbott U.S.). The target range of concentration was 8–10 ng/mL in the first month after LTx. The initial dose of MMF was 1000 mg/d in 2 divided doses. Dose adjustments were made based on area under curve (AUC) calculations. Prednisone was given intravenously at 1 mg/kg/d during POD 1–3, and then switched to oral administration at 0.5 mg/kg/d, and gradually tapered to 5–10 mg/d for long-term maintenance.

In addition to immunosuppressive therapy, voriconazole or posaconazole were administrated for prophylaxis or treatment of invasive aspergillus. Voriconazole was started with a loading dose of 800 mg/d in 2 divided doses, either intravenously or oral. Then dose adjustments were made according to trough concentration measurements and maintenance dose was 300–400 mg/d. Posaconazole was given in suspensions, and started at 800 mg/d, in 4 divided doses. Then dose adjustments were made according to trough concentration and maintained at 600 or 800 mg/d, in 3 or 4 divided doses, respectively.

**Genotype determination**

Genomic DNA was extracted from EDTA-anticoagulated peripheral blood samples by a commercially available DNA purification kit (EasyPure Blood Genomic DNA Kit, Transgene Biotech, Beijing, China). The quality of genomic DNA was verified with Multiskan GO Microplate Spectrophotometer (Thermo Fisher Scientific, Waltham, MA), using the absorbance ratio at A260/A280 (1.8–2.0). For $CYP3A5^*3$ (rs776746) genotype determination, the Sanger dideoxy DNA sequencing method was adopted. Genomic DNA samples were then amplified by polymerase chain reaction (PCR) and sequenced by the ABI 3730XL DNA Sequencer (ABI Co; Majorbio Biotechnology Co., Ltd., Beijing, China). The forward primer is 5’-CAGCATTAGTC CTTGTGAG-3’, and the reverse primer is 5’-ACGACA CACAGCAACCTTAG-3’. The Chromas software (Tecnelysium, South Brisbane, Australia) was used for DNA
data analysis. Patients with CYP3A5*1/*1 and *1/*3 were grouped as CYP3A5*1 carriers.

**Data collection**

Patients’ data were extracted by reviewing electronic medical records. Information including basic demographics (age, sex, height, weight, diagnosis, comorbidities, and transplant type), baseline laboratory test results (serum creatinine (SCr), anine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Tbil), direct bilirubin (Dbil), urea, uric acid, red blood cells (RBC), hemoglobin, hemocrit, and glucose) and post-operative data (Tac dose (mg/d), corresponding body weight (kg), trough concentration (ng/mL), use of azole antifungals (voriconazole or posaconazole), and SCr) were obtained. C/D (ng/mL per mg/kg/d) was calculated by dividing concentration by the corresponding body weight adjusted daily dose (mg/kg/d).

**Outcome definitions**

Pharmacokinetic outcomes of interest were Tac concentration, dose, and C/D. Clinical outcomes were incidence of AKI, length of hospital stay, 30-day and 1-year mortality. AKI was determined and staged according to the ‘Kidney Disease: Improving Global Outcomes’ (KDIGO) Clinical Practice Guideline, basing on SCr obtained from the transplantation day until 7 days after transplantation [18].

**Statistical analysis**

The normality distribution of data was assessed using the Shapiro–Wilk test. Chi-square test was performed to assess the deviation of gene frequencies from Hardy–Weinberg equilibrium. Descriptive statistics were expressed as mean ± standard deviation (SD) for normally distributed continuous variables or median (interquartile range, IQR) for non-normally distributed continuous variables. Categorical variables were presented as count (percentage). Comparisons between continuous variables were analyzed by Student’s t test or Mann–Whitney U test. Pearson’s chi-square test or Fisher’s exact test was used to compare differences in categorical variables. Logistic regression was performed to study factors associated with incidence of AKI. Potential risk factors with a $p < 0.20$ in univariate analysis were incorporated into multivariate logistic regression, which adopts a forward LR strategy. 30-day and 1-year survival rates stratified by CYP3A5 genotype was analyzed by Kaplan–Meier analysis and compared using the log–rank test. $P < 0.05$ was considered of statistical significance. Data was processed using Statistical Package for Social Science (SPSS) 19.0.

**Results**

**Patients’ characteristics**

Table 1 shows the demographics of the study population. Median (IQR) age was 60 (56–64) years old, and male patients (79 cases, 87.8%) accounted for a large proportion. Median (IQR) hospital stay length was 46 (35–60) days and follow-up time was 1 year.

For CYP3A5 genotypes, *1/*1, *1/*3 and *3/*3 were detected in 6, 36 and 48 patients, respectively. The frequency of CYP3A5 genotypes were in accordance with Hardy–Weinberg equilibrium ($p > 0.05$). CYP3A5*1 carriers and CYP3A5*3/*3 group differed in baseline BMI, Dbil and pre-operative diabetes mellitus status.

**Influence of CYP3A5 genotype on Tac metabolism**

Figure 1a shows the Tac concentration trend-lines of all patients. Individual concentration fluctuated considerably in the early post-operative period, with only a small portion of patients reaching the target range on POD 3 after receiving a standardized starting dose. CYP3A5*1 carriers exhibited statistically significant lower concentration level than CYP3A5*3/*3 group (Fig. 1b) at comparable dose levels at week 1 (Fig. 1c). When comparable concentrations were reached at week 2–4, CYP3A5*1 carriers required higher Tac doses compared with CYP3A5*3/*3 group (Fig. 1). Lower C/D in CYP3A5*1 carriers were observed at all time points (Fig. 1d).

**Relationship between azole antifungals, CYP3A5 genotype and Tac metabolism**

Patients who underwent concomitant azole antifungals and Tac therapy showed significantly lower dose requirements and higher C/D of Tac at week 1–4 (Table 2) compared to those who received Tac only. When further stratified by CYP3A5 genotype, CYP3A5*1 carriers still showed lower C/D than CYP3A5*3/*3 group at all time points (Fig. 2).

**Influence of CYP3A5 genotype on AKI**

Five variables, including age, baseline SCr, uric acid, RBC and week 1 Tac concentration $\geq 7.5$ ng/mL, showed $p < 0.20$ in univariate analysis and were further assessed in multivariate model (Table 3). Only week 1 Tac concentrations $\geq 7.5$ ng/mL (OR 5.38; 95% CI 1.40–20.69; $p =$
0.014) was associated with increased risk of AKI. CYP3A5 genotype showed no significance in both univariate and multivariate analysis.

**Influence of CYP3A5 genotype on length of hospital stay and mortality**

Of our study population, no statistically significant difference was observed in the length of hospital stay between CYP3A5*1 carriers and *3/*3 group: 48 (37–68) vs. 46(32–57) d, \( p = 0.264 \). Thirty-day and 1-year survival rates of the study population were 94.4% and 88.9%, respectively. According to Kaplan-Meier analysis, although CYP3A5*1 carriers showed higher survival rates than *3/*3 group at both 30-day and 1-year, no statistical significance was achieved (Fig. 3).

**Discussion**

**Statement of key findings**

In this study, the influence of CYP3A5 genotype on Tac metabolism and clinical outcomes in Chinese LTx population was discussed. We drew three major conclusions from the data: (1) patients bearing CYP3A5*1 allele showed significantly lower Tac C/D and higher dose requirement compared with *3/*3 genotype in the early post-operative period; (2) the use of azole antifungals did not change the influence of CYP3A5 genotype on Tac metabolism; (3) CYP3A5 genotype had no effect on the incidence of AKI, length of hospital stay or mortality.

Consistent with previous literature in lung and other organ transplantations, we observed higher C/D and lower
dose requirements for \textit{CYP3A5}*3/*3 carriers [6, 8, 14]. \textit{CYP3A5}*3/*3 carriers exhibited roughly 1.5–2.5 times higher C/D compared with \textit{CYP3A5}*1 carriers in prior studies [8, 13], whereas in our study the C/D ratio was slightly higher, varying from 2 to 2.9.

We calculated the dose ratio of \textit{CYP3A5}*1 carriers to \textit{CYP3A5}*3/*3 at week 2–4 when comparable concentration levels were reached, and it was between 1.3 and 2.4. The 2015 CPIC guideline recommended a 1.5–2 folds increase in dose followed by TDM for \textit{CYP3A5}*1 carriers [1]. The 2019 TDM guideline summarized \textit{CYP3A5}*1 carriers require approximately 50% higher Tac dose to reach the target therapeutic range compared with \textit{CYP3A5}*3/*3 [10]. Basing on these data, a 1.5–2 folds increase in Tac dose for \textit{CYP3A5}*1 carriers seems safe and appropriate for our patients. However, Tac metabolism is complex and influenced by both clinical and genetic factors, especially in the early periods of LTx, when patients’ clinical status is unstable [19]. So, we must interpret dose recommendation carefully and take into account other possible influential factors, like age, hematocrit and concomitant drugs when making decisions [20–22].

Previous studies have reported a major drug-drug interaction between Tac and azole antifungals, which leads to higher C/D and 50–75% dose reduction of Tac in transplant patients [9, 23, 24]. Similarly, lower dose requirements of Tac and elevated C/D were observed in patients using...
azole antifungals in our study (Figs. 2 and S1). Besides, CYP3A5*3/*3 carriers still exhibited higher C/D and lower dose requirement compared with CYP3A5*1 carriers regardless of using azole antifungals or not, suggesting the effect of CYP3A5 genotype on Tac metabolism was not blunted by azole antifungals.

We further explored if a direct association existed between CYP3A5 genotype and clinical outcomes. In analysis of risk factors for AKI, Tac concentration ≥ 7.5 ng/mL in the first week, not CYP3A5 genotype, was associated with the incidence of AKI. Previous reports also mentioned supra-therapeutic tacrolimus trough concentration in the first week as a risk factor for AKI [25, 26]. Interestingly, 7.5 ng/mL in our study was slightly lower than the therapeutic range. We attributed this finding to the demographic characteristics of our population. Around half of them were over 60 years old, who might be more vulnerable to AKI [11]. So, clinical pharmacists should pay more attention to their concentrations even when they are within therapeutic range.

Similarly, Woodahl et al. reported no correlation between CYP3A5 genotype and AKI in hematopoietic cell transplantation patients [27]. One possible explanation for this lack of correlation is common genetic polymorphisms of CYP3A5 tested in blood samples did not reflect its expression profile in the kidney. In distal tubules, CYP3A5 expression may be protective against the nephrotoxicity of Tac, whereas in proximal tubules its was associated with increased nephrotoxicity [28].

CYP3A5 genotypes did not alter the length of hospital stay in our study. Bosó et al. reported increased hospital stay in kidney transplant recipients with CYP2C19*2/*2 genotype [29]. They attributed the difference to CYP2C19*2/*2 carriers’ higher median Tac C/D during the first week. Judging from our data, CYP3A5*3/*3 group also exhibited higher median Tac C/D at week 1, however, no difference in hospital stay were found. Considering the small number of patients (n=4 in CYP2C19*2/*2 group) in Bosó’s study, the correlation might lack potency and needs further validation. Furthermore, no correlation between CYP3A5 genotype and mortality was found, which was in consistence with previous studies in kidney and heart transplant population [6, 30].

**Strengths and weaknesses**

In summary, despite the large number of studies addressing the influence of CYP3A5 genotype on Tac metabolism, whether it plays a role in clinical outcomes remains controversial. Several meta-analysis and studies have reported no significant association between CYP3A5 genotype and adverse outcomes [15, 31]. Instead, Tac C/D has been proposed as a stronger prognostic marker for poor outcomes recently. Though closely related to CYP3A5 genotype, Tac C/D is also affected by other factors, including the use of

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**Table 2** Influence of use of azole antifungals on Tac metabolism

| Week 1 (n = 81) | Week 2 (n = 81) | Week 3 (n = 80) | Week 4 (n = 81) |
|----------------|----------------|----------------|----------------|
| **Antifungals (–)** | **Antifungals (+)** | **Antifungals (–)** | **Antifungals (+)** |
| n (%) | 70 (86.4) | 11 (13.6) | 67 (83.3) | 17 (20.2) | 63 (78.8) | 23 (29.1) | 55 (67.9) | 26 (32.1) |
| Concentration | 5.8 (2.4–10.2) | 11.0 (9.3–17.4) | 5.6 (2.3–9.0) | 10.4 (7.1–13.0) | 6.6 (4.9–10.9) | 7.4 (6.2–9.9) | 8.4 (6.9–10.9) | 0.188 |
| Dose (mg/dL) | 20.0 (10.0–30.0) | 10.0 (5.0–20.0) | 0.5 (0.5–20.0) | 10.0 (5.0–20.0) | 0.5 (0.5–20.0) | 10.0 (5.0–20.0) | 0.5 (0.5–20.0) | 0.188 |
| C/D (ng/mL per mg/d) | 134.10 (68.42–238.99) | 693.00 (417.60–1000.50) | 129.00 (71.84–230.14) | 745.20 (506.35–1148.35) | 122.01 (62.66–215.78) | 678.00 (320.17–938.40) | 121.60 (59.40–187.25) | 98.40 (48.00–193.70) |

Categorical data are presented as number (%), continuous data presented as mean with SD or median with IQR, depending on variable distribution. 

Mann–Whitney U test
corticosteroids and non-adherence, and therefore, may be better in reflecting immunosuppressive status [32, 33].

There are certain limitations in our study. Firstly, it was a retrospective study with a relatively small sample size, therefore, the conclusions might need confirmation in prospective studies. Secondly, our population mainly consisted of male adults, limited females and no pediatric patients were included. They might possess different physiological characteristics, such as liver function, hemoglobin concentration and hematocrits, and hence further studies in a more diverse population are warranted. Thirdly, we only validated the influence of CYP3A5 genotype on Tac metabolism. Since other influential factors were not considered, it is unrealistic to give a precise dosing recommendation.

Conclusion

In this study, we investigated the influence of CYP3A5 genotype on Tac metabolism and clinical outcomes in Chinese LTx recipients. As with other types of transplantation, CYP3A5*1 carriers exhibited significantly lower C/D and higher dose requirements compared to CYP3A5*3/*3 group in the early post-operative period. Concomitant use of azole antifungals did not blunt the influence of CYP3A5 genotype on Tac metabolism. We also found CYP3A5 genotype was not associated with clinical outcomes, including incidence of AKI, length of hospital stay, 30-day and 1-year mortality.
Table 3  Odds ratio (OR) with 95% confidence interval (CI) for risk factors of AKI incidence

| Variables                | Univariate analysis | Multivariate analysis |
|--------------------------|---------------------|-----------------------|
|                          | OR (95% CI)         | p                     |
| Age                      | 0.96 (0.91–1.02)    | 0.179                 |
| Sex                      | 1.42 (0.28–7.18)    | 0.668                 |
| BMI (kg/m²)              | 1.03 (0.91–1.17)    | 0.617                 |
| **Diagnosis**            |                     |                       |
| COPD                     | Reference           |                       |
| ILD                      | 1.36 (0.41–4.56)    | 0.615                 |
| PH                       | 7.34×10⁸ (0.00–.)   | 0.999                 |
| Others                   | 1.36 (0.11–16.58)   | 0.808                 |
| **Comorbidities**        |                     |                       |
| Hypertension             | 1.39 (0.36–5.44)    | 0.634                 |
| Diabetes mellitus        | 0.76 (0.28–2.10)    | 0.598                 |
| Hyperlipidemia           | 1.90 (0.22–16.78)   | 0.562                 |
| **Transplant type**      |                     |                       |
| Unilateral               | Reference           |                       |
| Bilateral                | 1.07 (0.38–3.00)    | 0.903                 |
| SCr (µmol/L)             | 0.98 (0.95–1.01)    | 0.192                 |
| ALT (IU/L)               | 0.98 (0.96–1.01)    | 0.206                 |
| AST (IU/L)               | 1.01 (0.96–1.06)    | 0.756                 |
| Tbil (µmol/L)            | 1.06 (0.94–1.20)    | 0.355                 |
| Dbil (µmol/L)            | 0.99 (0.66–1.48)    | 0.959                 |
| Urea (mmol/L)            | 1.39 (1.04–1.87)    | 0.027                 |
| Uric acid (µmol/L)       | 1.00 (1.00–1.01)    | 0.088                 |
| RBC (× 10¹² cells/L)     | 1.71 (0.80–3.66)    | 0.165                 |
| Hemoglobin (g/L)         | 1.01 (0.99–1.04)    | 0.329                 |
| Hematocrit (%)           | 1.04 (0.95–1.13)    | 0.379                 |
| Glucose (mmol/L)         | 0.98 (0.83–1.17)    | 0.868                 |
| **Week 1 Tac concentration** ≥ 7.5 ng/ml | 5.38 (1.40–20.69) | 0.014 | 5.38 (1.40–20.69) | 0.014 |

Fig. 3  Kaplan-Meier survival curves stratified by CYP3A5 genotypes at 30-day (a) and 1-year (b). CYP3A5*1 carriers tended to show higher survival rates than *3/*3 group at 30-day (97.6% vs. 91.7%) and 1-year (92.9% vs. 85.4%), however, no statistical significance was achieved (p = 0.218 and p = 0.262, respectively). Comparisons were made by log–rank test.
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Conflicts of interest All authors report no conflict of interest.

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