OPEN

Gene Polymorphisms Play an Important Role in the Drug Interaction Between Posaconazole and Tacrolimus in Renal Transplant Patients

Nan Hu, PhD, Mengmeng Guan, BS,*† Bin Gu, BS,‡ Xuping Yang, MS,* Qing Qian, MS,* Di Zhao, PhD,§ Hui Xue, BS,* and Jingting Jiang, PhD¶*

Background: Posaconazole (POSA), a second-generation triazole antifungal drug, inhibits CYP3A and P-glycoprotein. Here, the interaction between POSA and tacrolimus (TAC) in patients undergoing early renal transplantation was studied.

Methods: Twenty-two renal transplant recipients who received POSA as antifungal therapy were studied. The following indicators were analyzed statistically: the blood concentration (*C*), dose (*D*), and concentration–dose ratio (*C/D*) of TAC before and after introducing POSA; the change of *C/D* (Δ*C/D*) after starting POSA; the genotypes of CYP3A5*3, ABCB1 3435, ABCB1 1236, and POR*28; other routine clinical indicators.

Results: After starting POSA, the *C*, *D*, and *C/D* values of TAC were 1.29, 0.57, and 2.74 times the original values, respectively. A linear correlation was observed between the plasma levels of POSA and Δ*C/D*. The CYP3A5*3 gene polymorphism showed a significant impact on *C*, *D*, and *C/D* of TAC; however, it did not affect the Δ*C/D*. Polymorphism of the ABCB1 3435 gene had a significant effect on Δ*C/D*, and patients with the CC genotype in ABCB1 3435 had significantly lower Δ*C/D* than the CT/TT patients.

Conclusions: In renal transplant patients, considerable interindividual variability was observed in the drug interactions between POSA and TAC. The genotypes of CYP3A5*3 and ABCB1 3435 and the plasma level of POSA had strong impact on the interaction between POSA and TAC.

Key Words: tacrolimus, posaconazole, drug–drug interactions, renal transplantation, gene polymorphism

(*Ther Drug Monit* 2025;47:330–336)

INTRODUCTION

Tacrolimus (TAC) is a first-line immunosuppressive drug commonly used as an antirejection therapy after transplantation of the liver, kidney, heart, lung, and bone marrow. Compared to cyclosporine treatment, TAC treatment was associated with a lower incidence of graft rejection and adverse cardiovascular events.[1,2] The pharmacokinetics of TAC is affected by many factors and often leads to large fluctuations of drug concentration within and between individuals.[3] The therapeutic window of TAC is narrow. Inadequate TAC concentrations can lead to rejection, but a high concentration may produce a series of adverse drug reactions such as nephrotoxicity.[4] Studies have shown that the blood concentration of TAC is significantly correlated with the incidence of adverse reactions, such as acute and chronic rejection, hypertension, blood glucose metabolism disorders, neurotoxicity, gingival hyperplasia, hyperkalemia, hypomagnesemia, etc.[5] TAC is mainly metabolized by cytochrome P450 enzymes (CYP) 3A4 and 3A5 after oral administration, and it is a substrate of P-glycoprotein (P-gp), an energy-dependent transmembrane efflux pump encoded by the ATP binding cassette subfamily B, member 1 (ABCB1) gene in humans.[6] ABCB1 is a transmembrane protein belonging to the ATP-binding cassette family. Cytochrome P450 oxidoreductase (POR) determines the activity of CYP450 enzymes, so it plays an important role in the metabolism of TAC. The most common gene polymorphism site is POR*28. The pharmacokinetic properties of TAC are influenced by polymorphisms in the genes encoding metabolic enzymes and transporters, and it has been demonstrated that genetic mutations in the CYP3A5*3, ABCB1, and POR*28 genes can influence the blood concentration of TAC.[7]

Received for publication July 16, 2024; accepted August 26, 2024.

From the *Department of Pharmacy, The Third Affiliated Hospital of Soochow University, Changzhou; †College of Pharmaceutical Sciences, Soochow University, Suzhou; ‡Suzhou Medical College, Soochow University, Suzhou; §School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing; and ¶Department of Tumor Biological Treatment, The Third Affiliated Hospital of Soochow University, Changzhou, China.

N. Hu and M. Guan designed the study and prepared the manuscript. X. Yang and Q. Qian performed the experiments. D. Zhao, M. Guan, and B. Gu analyzed the data. H. Xue and J. Jiang supervised and edited the manuscript.

The authors declare no conflict of interest.

N. Hu and M. Guan authors should be considered joint first authors.

All data generated or analyzed in this study are included in the published article. In addition, the data are available to interested researchers from the corresponding author upon request.

Correspondence: Hui Xue, BS, Department of Pharmacy, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, 213000, China (e-mail: xuehuicz@163.com) or Jingting Jiang, PhD, Department of Tumor Biological Treatment, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, 213000, China (e-mail: jiangjingting@suda.edu.cn).

Owing to the long-term use of immunosuppressive agents and hormones, patients undergoing organ transplantation have weakened immunity and are susceptible to invasive fungal diseases. Posaconazole (POSA) is a second-generation triazole antifungal agent known for its broad-spectrum activity against various fungal pathogens and offers a potent and versatile option for managing serious fungal infections. It is first metabolized to biologically inactive metabolites by hepatic UDP glucuronosyltransferase and then excreted from the cell through the intestinal P-gp.[8] Because it is an inhibitor of CYP3A4 and P-gp, the interaction between TAC and POSA is clinically a delicate issue when the clinician needs to carefully manage both rejection and fungal diseases and for patients after organ transplantation. The existing guidelines for the administration of TAC advise avoiding potent CYP3A inhibitors such as POSA. If the combined therapy of POSA and TAC is inevitable, TAC should be withheld on the day of initiating POSA therapy and restarted at a reduced dose the next day, depending on the blood concentration of TAC. Currently, the common clinical practice is to reduce the TAC dose to one-third of the original dose when used in combination with POSA,[9] and pharmacogenomics is not considered. However, this empirical dose reduction does not provide consistent results for maintaining the blood concentration of TAC within the therapeutic range, and it is necessary to monitor the therapeutic drug concentration of TAC or develop a new personalized dose reduction plan.

In this study, the interaction between TAC and POSA in renal transplant patients was studied for the first time, and the effects of POSA on the concentration of TAC at an early stage of renal transplantation were analyzed. The effects of CYP3A5*3, ABCB1 3435, ABCB1 1236, and POR*28 gene polymorphisms on individual differences in the drug interactions between TAC and POSA were investigated to provide a reference for the clinical combination of the 2 drugs and to create individualized medication.

METHODS

Subjects

Patients hospitalized at the Third Affiliated Hospital of Soochow University from January 1, 2018, to December 31, 2020 who received their first renal transplantation and POSA for the treatment or prophylaxis of invasive fungal infections were selected as the subjects of the study. All included patients were at least 18 years of age and received a triple immunosuppressive regimen of TAC, mycophenolate mofetil, and glucocorticoids. Patients were excluded if the data on the dose and concentration of TAC and POSA were missing or if they were receiving renal replacement therapy such as hemodialysis and plasma exchange. A total of 22 patients were included in this study. The hospital information system and therapeutic drug testing system were used to retrieve demographic information (Table 1), POSA prescription data, and drug adjustments. This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Soochow University (Approval No. 2024062).

TABLE 1. Summary of Basic Patient Data (n = 22, Mean ± SD)

Parameter	Data
Sex (M/F)	13/9
Age, yr	42.5 ± 12.4
BMI, $kg \cdot m^{-2}$	21.9 ± 3.4
LOS, d	38.5 ± 14.9
History of dialysis, yr	4.3 ± 3.5
Hb, $g \cdot L^{-1}$	102.7 ± 15.4
ALT, $U \cdot L^{-1}$	17.4 ± 10.5
AST, $U \cdot L^{-1}$	22.1 ± 14.9
ALP, $U \cdot L^{-1}$	104.7 ± 147.0
HDL-C, $mmoL \cdot L^{-1}$	1.1 ± 0.4
LDL-C, $mmoL \cdot L^{-1}$	2.1 ± 0.8
Cr, $\mu mol \cdot L^{-1}$	289.0 ± 189.3
Uric acid, $\mu mol \cdot L^{-1}$	358.6 ± 118.9
Urea, $mmoL \cdot L^{-1}$	18.9 ± 8.0
GLU, $mmoL \cdot L^{-1}$	6.1 ± 2.6
Int time, d	16.05 ± 12.40

LOS, length of stay, interval from day of transplantation to discharge from the hospital; Int time, interval time, interval between transplantation and the start of POSA treatment.

Blood Samples

Blood (2–3 mL) was collected intravenously in the morning at 0.5 hours before drug administration in ethylenediaminetetraacetic acid dipotassium (EDTA-K2) anticoagulation tubes. A portion of the blood sample was taken for blood drug concentration determination, and the rest was stored at −80°C for gene sequencing. All patients were in a steady-state during TAC therapy before blood collection.

Blood Concentrations of TAC and POSA

The whole blood concentration of TAC was measured using the homogeneous enzyme multiplied immunoassay technique (EMIT) on a Viva-E drug testing system (Siemens, Erlangen, Germany) using an Emit2000 TAC kit, following the manufacturer's instructions.

The plasma concentration of POSA was determined using liquid chromatography tandem mass spectrometry (LC-MS/MS),[10] and plasma samples were pretreated as follows: the working solution of the internal standard (500 $ng \cdot mL^{-1}$, 150 μL) was added to a 1.5 mL centrifuge tube containing plasma (50 μL). The tube was vortexed for 3 minutes, then centrifuged at 26,272*g* and room temperature for 10 minutes, and an aliquot (20 μL) of the supernatant was drawn and diluted with 1/1 vol/vol MeOH/H_2O (180 μL). The resulting solution was then injected and analyzed using a Jasper HPLC instrument (Sciex, Framingham, MA) on a Kinetex C18 LC column (00D-4462-Y0, Phenomenex, Torrance, CA; 3 mm i.d. × 100 mm, particle size 2.6 μm, pore size 100 Å), with a binary gradient of 0.1% aqueous formic acid (solvent A, supplemented with 5 $mmol \cdot L^{-1}$ ammonium acetate) and 0.1% methanolic formic acid (phase B) as follows: 0.01–0.80 minutes, 40% B; 0.80–1.00 minutes, 40%–90% B; 1.00–3.50 minutes, 90% B; 3.50–4.00 minutes, 90%–40% B; 4.00–5.00 minutes, 40% B. The injection volume was 5 μL, the column temperature was 40°C, and the flow rate was 0.6

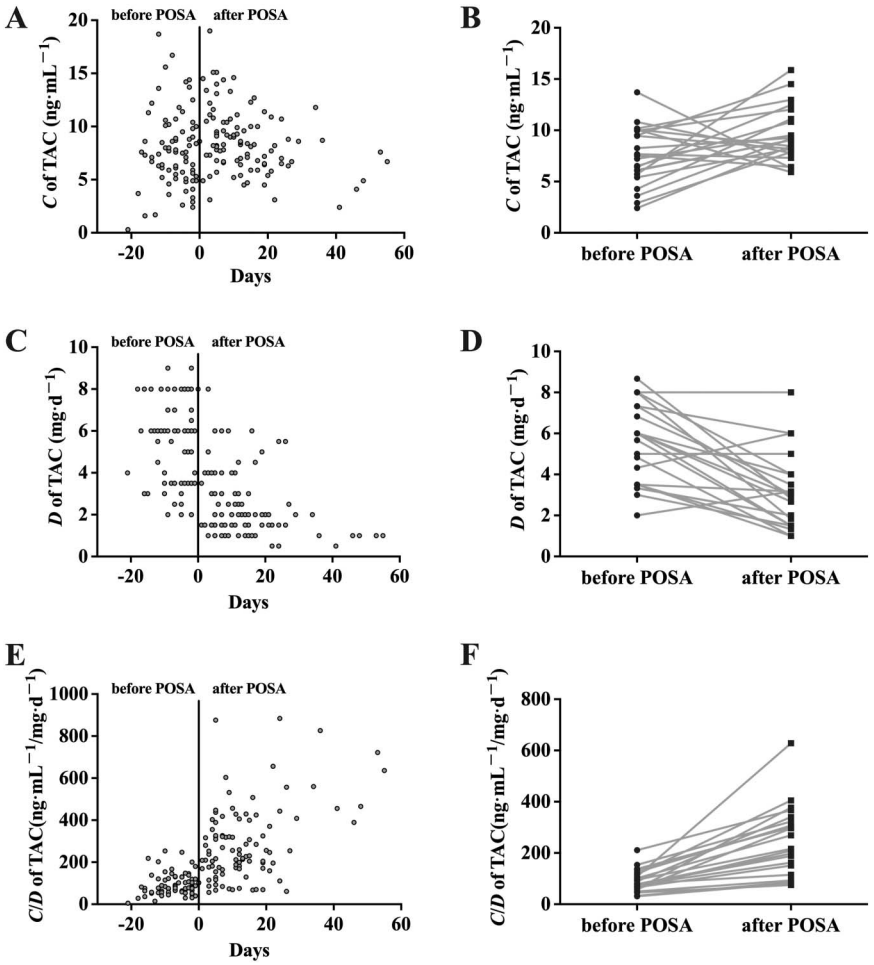

FIGURE 1. *C* (A, B), *D* (C, D), and *C*/*D* (E, F) of TAC in patients before and after the administration of POSA. *C*, whole blood concentration; *D*, dose; *C*/*D*, concentration-to-dose ratio.

mL·minute^{-1}. The MS detection used multiple reaction monitoring, and the quantitative analysis was based on the ion pairs of m/z = 701.4 → 683.2. Other MS parameters were as follows: electrospray ionization, positive ion mode; capillary voltage (IS), 5500 V; ion source temperature, 550°C; nebulizing gas (GS1), 50 psi; auxiliary gas (GS2), 50 psi; curtain gas (CUR), 35 psi; collision gas (CAD), 8 psi; collision voltage, 45 V; and decluster voltage, 170 V.

Genotype Analysis

Genomic DNA was extracted from whole blood using the Axygen AxyPrep MAG Tissue-Blood gDNA Kit (Corning, Tewksbury, MA). After DNA concentration and purity were determined by ultraviolet spectrophotometry, it was amplified by polymerase chain reaction-restriction fragment length polymorphism with the primers using the same protocols described previously.[11,12] The polymerase chain reaction amplification products were sequenced on a DS3000 sequencer (Hitachi High-Tech, Tokyo, Japan) to ascertain the genotypes of CYP3A5*3, ABCB1 3435, ABCB1 1236, and POR*28.

Statistical Analysis

Data are expressed as mean ± SD and were analyzed using SPSS 27.0 (IBM, Armonk, NY). The data were examined using the Shapiro–Wilk test to determine if they conformed to a normal distribution. They were then compared using the Student *t* test and one-way analysis of variance (ANOVA) if they had a normal distribution, or using the Mann–Whitney test if otherwise. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Blood Concentration, Dose, and Concentration–Dose Ratio of TAC After Administration of POSA

The drug–drug interaction between TAC and POSA was significant, with large individual differences (Fig. 1). After POSA was introduced, the whole blood concentration of TAC (*C*) increased significantly (from 7.45 ± 2.85 to 9.58 ± 2.64 ng·mL^{-1}, $P < 0.05$), but the mean daily dose of TAC (*D*) decreased by 43.4% (from 5.46 ± 1.95 to 3.09 ± 1.83 mg·day^{-1}, $P < 0.01$). The median concentration–dose ratio of TAC (*C*/*D*) increased from 90.95 ± 43.19 to 249.58 ± 134.01 ng·mL^{-1}/mg·day^{-1} ($P < 0.01$). After the introduction of POSA, the *C*, *D*, and *C*/*D* values were 1.29, 0.57, and 2.74 times the values before the administration of POSA, respectively. Of the 22 patients in this study,

10 received POSA for fungal treatment and 12 received POSA for prophylaxis. There was no significant difference in *C/D* between patients who received prophylaxis (3.05) and those who received curative treatment (2.60). Only 10 patients who received POSA as a curative treatment had plasma POSA concentrations. The average POSA concentration was 0.49 ± 0.28 mcg·mL^{-1}. A linear correlation was observed between the serum concentrations of POSA and Δ*C/D* (Fig. 2).

Effects of Gene Polymorphism on the Interaction Between POSA and TAC

The effects of gene polymorphisms in CYP3A5*3, ABCB1 3435, ABCB1 1236, and POR*28 on *C*, *D*, and *C/D* ratio in TAC (Fig. 3) were investigated. Table 2 shows the distribution of genotypes. The CYP3A5*3 genotype significantly affected the values of *C*, *D*, and *C/D* ratio (Fig. 3A). Before the administration of POSA, the AG/GG patients had significantly higher *C* values than the AA patients. After the administration of POSA, compared with the AA patients, the AG/GG patients still had significantly higher *C* values but started to have significantly lower *D* values and significantly higher *C/D* ratios. In addition, patients with the CC genotype of ABCB1 3435 had significantly higher *D* values than those with the CT/TT genotype before POSA administration (Fig. 3B).

In terms of the effects of genotypes on the drug interaction, Figure 4 shows that ABCB1 3435 significantly influenced the Δ*C/D*. The Δ*C/D* of patients with the CYP3A5*3 AG/GG genotype was higher than that of patients with the AA genotype; however, the difference was not statistically significant. Patients with the CC genotype in ABCB1 3435 had a significantly lower Δ*C/D* than patients with the CT/TT genotype ($P < 0.05$). The percentage of dose reduction in patients with different ABCB1 3435 genotypes after POSA administration was also calculated. Specifically, the reduction in *D* values after the introduction of POSA was, on average, 24.7% for ABCB1 3435 CC patients and 53.0% for CT/TT patients.

Δ*C/D* were not significantly affected by genotypes CYP3A5*3, ABCB1 1236, and POR*28.

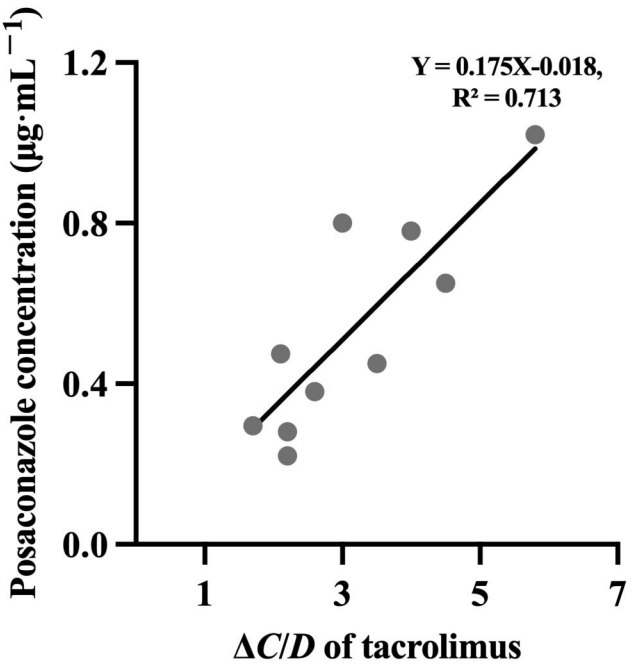

FIGURE 2. Correlation between the plasma level of POSA and the change in the concentration-to-dose ratio of TAC (Δ*C/D*).

DISCUSSION

Extensive use of immunosuppressive therapy in recent decades has markedly enhanced graft survival rates and reduced the incidence of acute rejection after solid-organ transplantation. However, immunosuppressive therapy inevitably results in immunocompromised patients, who are more susceptible to both typical and opportunistic infections. Invasive fungal infections have emerged as a major cause of mortality in patients receiving solid organ transplantations.[13] Currently, clinically used drugs for invasive fungal infections mainly include triazoles, polyenes, echinocandins, and flucytosine. Triazoles are currently the most widely used antifungal agents because they have a wide antifungal spectrum, low toxicity, and better tolerability than polyene amphotericin B.[14] Triazole antifungal agents include fluconazole, itraconazole, voriconazole, POSA, and, most recently, isavuconazole. Triazoles inhibit CYP3A to varying degrees. The in vitro metabolism of testosterone in human liver microsomes revealed that the inhibition of CYP3A activity by triazole antifungals falls in the order of ketoconazole > itraconazole > voriconazole > fluconazole.[15] Triazoles also inhibit the metabolism of midazolam into 1-hydroxymidazolam by CYP3A, and the IC_{50} values rank in the order of ketoconazole (9.1×10^{-8} mol/L) < itraconazole (3.1×10^{-8} mol/L) < POSA (6.8×10^{-7} mol/L) < voriconazole (2.1×10^{-6} mol/L) < fluconazole (8.9×10^{-6} mol/L).[16] When midazolam was coadministered with the oral suspension of POSA (50 mg, 100 mg, and 200 mg), its area under the curve (AUC) increased by 3.1-fold, 4-fold, and 5.7-fold, and the C_{max} increased by 2-fold, 2.4-fold, and 2.7-fold, respectively.[17] Under FDA classification, voriconazole, POSA, and itraconazole are strong inhibitors of CYP3A isoenzymes (increase midazolam AUC by at least 5-fold), whereas isavuconazole is a moderate inhibitor (increase midazolam AUC by at least 2-fold but less than 5-fold).[18] Unlike other triazole antifungals, POSA is hardly metabolized by cytochrome P450 pathways. Approximately 17% of POSA is glucuronidated by UGT1A4, and the rest is eliminated in its original form.[19] Because triazole antifungals have distinct metabolic characteristics, they interact with TAC differently, and an individualized dosing regimen is needed when there is coadministration. Current research on the interaction between TAC and triazoles primarily focuses on voriconazole,[20–22] and there are relatively few studies on the interaction between POSA and TAC. Moreover, to date, there have been no reports on the interaction between POSA and TAC in patients who have undergone renal transplantation.

The present study is the first to evaluate the effects of POSA coadministration on the blood concentration (*C*), dose

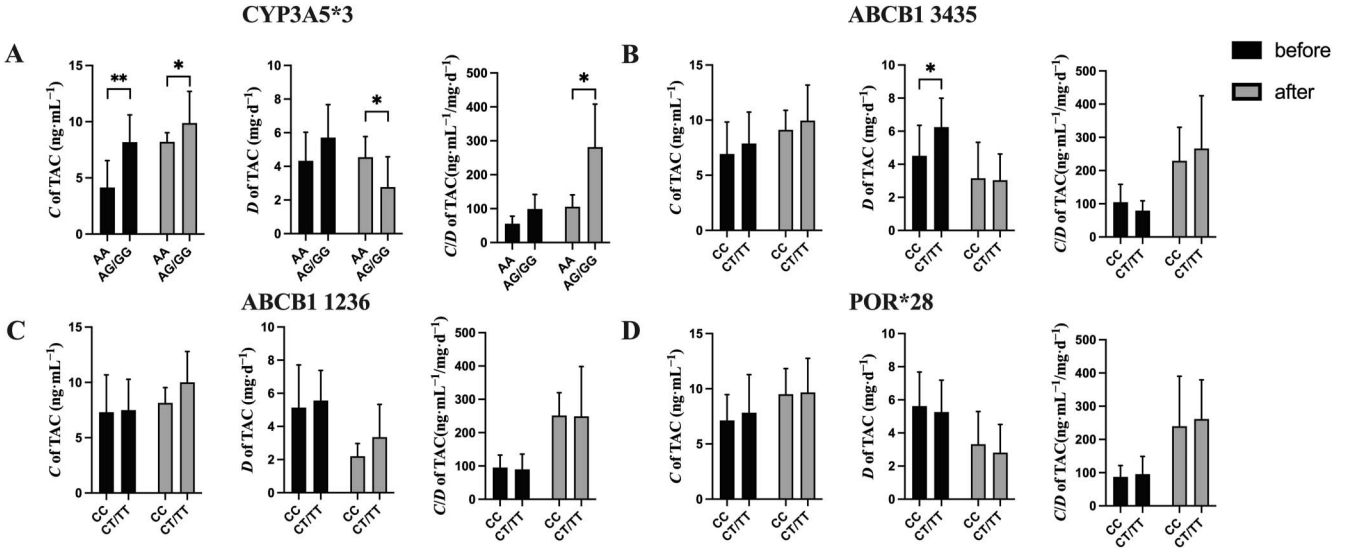

FIGURE 3. The effects of the genotypes of (A) CYP3A5*3, (B) ABCB1 3435, (C) ABCB1 1236, and (D) POR*28 on the whole blood concentration (*C*), dose (*D*), and concentration-to-dose ratio (*C*/*D*) of TAC. *$P < 0.05$, **$P < 0.01$.

(*D*), and concentration–dose ratio (*C/D*) of TAC in renal transplant patients. In the 22 patients included in this study, *C*, *D*, and *C/D* were 1.29, 0.57, and 2.74 times the original values, respectively, after POSA coadministration. Similar changes have been reported in other patients who underwent organ transplantation. Berge et al[23] studied the effect of POSA on the dose, trough concentration, and concentration–dose ratio of TAC in 14 lung transplant recipients and found that in the presence of POSA, the concentration–dose ratio increased significantly ($P < 0.001$) by about 2.29 times (from 1.4 ± 0.3 to 4.6 ± 0.8 $ng \cdot mL^{-1}/mg \cdot day^{-1}$). In studying how POSA affects the pharmacokinetics of TAC in patients undergoing allogeneic stem cell transplantation, Collins et al[24] found that patients who did not receive empirical dose reduction had a significantly longer median time to reach the therapeutic concentration of TAC and a higher overtreatment rate. It was concluded that to reach the treatment level, the empirical oral dose of TAC needs to be reduced from 0.06 to 0.03 $mg \cdot kg^{-1} \cdot day^{-1}$ when it is combined with POSA. Gu et al[25] investigated the effects of isavuconazole, fluconazole, and POSA on the serum concentrations and doses of TAC and cyclosporine in patients receiving allogeneic hematopoietic stem cell transplantation. For the 20 patients included in their study who took POSA and TAC simultaneously, it was found that the initial treatment of fluconazole required a 25% reduction of the TAC dose to maintain the target serum concentration, whereas the needed reduction of TAC dose was 53% and 21% if the patient took POSA and isavuconazole, respectively, at the same time. In addition, Sansone-Parsons et al[26] studied the pharmacokinetics of TAC during the oral administration of POSA in 36 healthy volunteers and found that, compared with day 1, the maximum blood concentration and AUC of TAC increased by 121% and 358%, respectively, on day 14, and the pharmacokinetics of POSA were not affected.

TABLE 2. Summary of Genetic Variants (n = 22)

SNPs	Genotype	No. of Patients
CYP3A5*3(rs776746)	AA (*1/*1)	4 (18.18%)
	AG (*1/*3)	7 (31.82%)
	GG (*3/*3)	11 (50.00%)
ABCB1 C3435T(rs1045642)	CC	10 (45.45%)
	CT	10 (45.45%)
	TT	2 (9.10%)
ABCB1 C1236T(rs1128503)	CC	5 (22.73%)
	CT	9 (40.91%)
	TT	8 (36.36%)
POR*28(rs1057868)	CC	12 (54.54%)
	CT	7 (31.82%)
	TT	3 (13.64%)

Upon administration of POSA, the blood concentration of TAC increased owing to the inhibition of the CYP3A isoenzyme. Current clinical practice guidelines recommend that when it is inevitable to use POSA and TAC simultaneously, TAC should be withheld on the day of starting POSA treatment, and the new TAC dose should be adjusted according to the blood concentration of TAC on the next day. Although the empirical method is to reduce the TAC dose to one-third of the original dose, considerable variation existed among the 22 examined patients in the dose adjustment, and the clinicians initially reduced the TAC dose by 14.3%–66.7% (mean 45.3%). Half of the patients successfully achieved the therapeutic concentration range after adjustment, whereas the other half required at least one additional dose adjustment to reach the therapeutic concentration.

Genetic polymorphisms in drug-metabolizing enzymes and transporters, such as CYP3A5, ABCB1, and POR, have a crucial impact on individual differences in TAC metabolism. In reviewing the association between the pharmacokinetics of TAC and CYP3A5 genotypes, Hesselink et al[27]

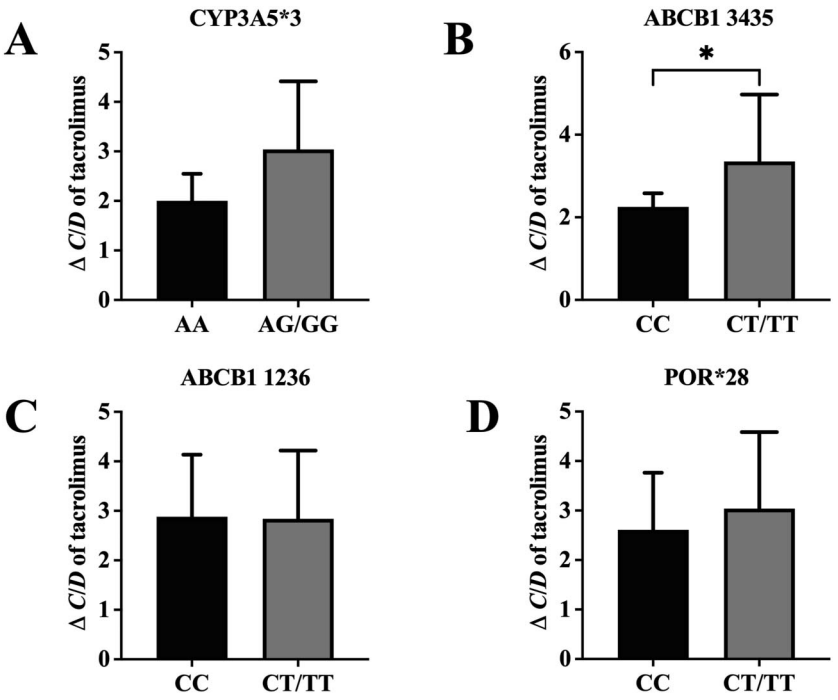

FIGURE 4. The effects of the genotypes of (A) CYP3A5*3, (B) ABCB1 3435, (C) ABCB1 1236, and (D) POR*28 on the change in the concentration-to-dose ratio (Δ*C/D*) of TAC. $*P < 0.05$.

pointed out that patients with the GG genotype have a higher blood concentration of TAC than those with the AA and AG genotypes. POR determines the activity of CYP450 enzymes and plays an important role in CYP450-mediated drug metabolism because it transfers electrons to CYP450 enzymes.[28] The POR*28 gene polymorphism can affect the metabolism of TAC in vivo by influencing the activity of CYP3A.[29] The bioavailability of TAC is affected by the function of the ABCB1 gene as it encodes P-gp, which is a drug efflux transporter.[3] Helal et al[30] reported that the ABCB1 3435C>T gene polymorphism can affect the folding of P-gp and alter substrate specificity, which can potentially contribute to variations in TAC metabolism. Two studies also examined the impact of the ABCB1 1236C>T and 2677G>T/A polymorphisms on the blood concentration levels of TAC.[31,32] The effects of CYP3A5*3 on the concentration and dose of TAC in 400 renal transplant patients were reported previously, showing that ABCB1 1236, ABCB1 3435, and POR*28 significantly affect the concentration of TAC in patients without CYP3A5*3 nonexpression.[11,12] In the present study, it was also found that CYP3A5*3 and ABCB1 3435 significantly affected the dose and concentration of TAC.

Currently, few pharmacogenomic studies have examined how gene polymorphisms in drug-metabolizing enzymes and transporters affect blood concentrations of TAC during the coadministration of POSA and TAC. The results from 22 patients showed that when TAC and POSA were used together, the polymorphisms of CYP3A5*3, ABCB1 1236, and POR*28 were not significantly associated with Δ*C/D*, whereas patients with the CC genotype in the ABCB1 3435 gene had significantly lower Δ*C/D* than CT/TT patients. The Δ*C/D* of CYP3A5*3 in AG/GG patients was higher than that in AA patients, probably because TAC was mainly metabolized by CYP3A4 in AG/GG patients. POSA is a potent inhibitor of CYP3A4 but does not have any significant inhibitory effect on other CYP3A subtypes. However, this may have been limited by the number of patients in this study, as the results were not statistically different. In contrast, the C>T mutation at the 3435 site of ABCB1 can significantly decrease the expression of ABCB1 and impair the function of P-gp.[33] Ciftci et al[34] showed that the ABCB1 3435 genotype affects the blood concentration of TAC in renal transplant patients. Bonhomme-Faivre et al[35] found that, compared with patients with the CC genotype in ABCB1 3435 gene, CT/TT patients had significantly higher blood concentrations of TAC immediately after liver transplantation. In the present study, the reduction in TAC dose after the introduction of POSA in ABCB1 3435 CT/TT patients (53.0%) was also approximately twice the TAC dose of CC patients (24.7%), indicating that POSA had a smaller impact on TAC concentration in ABCB1 3435 CC patients than in CT/TT patients.

In addition, a linear relationship was found between Δ*C/D* and the plasma concentration of POSA, and Δ*C/D* increased with increasing plasma concentration of POSA. In other words, the drug interaction between TAC and POSA became stronger as the POSA concentration increased.

In summary, it was observed that POSA has a significant effect on the pharmacokinetics of TAC in early renal transplant patients. The concentration of TAC after POSA administration varied greatly among individuals, and the key influencing factors were POSA concentration and the ABCB1 3435 and CYP3A5*3 genotypes. The findings of this study can guide dose adjustments when TAC is coadministered with POSA.

ACKNOWLEDGMENTS

The authors would like to thank all patients who participated in this study and acknowledge the funding support from the Changzhou Sci&Tech Program (No. CJ20239010 and CM20223005), Jiangsu Pharmaceutical Association-Aosaikang Clinical Pharmacy Foundation (No. A202327), Jiangsu Pharmaceutical Association-Tianqing Hospital Pharmacy Foundation (No. Q202144), and the Undergraduate Training Program for Innovation and Entrepreneurship, Soochow University (No. 2024C026).

REFERENCES

1. Xue W, Zhang Q, Xu Y, et al. Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis. *Chin Med J (Engl)*. 2014;127:2376–2381.
2. Nogueiras-Álvarez R, Mora-Cuesta VM, Cifrián-Martínez JM, et al. Calcineurin inhibitors' impact on cardiovascular and renal function, a descriptive study in lung transplant recipients from the North of Spain. *Sci Rep.* 2022;12:21207.
3. Yu M, Liu M, Zhang W, et al. Pharmacokinetics, pharmacodynamics and pharmacogenetics of tacrolimus in kidney transplantation. *Curr Drug Metab.* 2018;19:513–522.
4. Brunet M, Van Gelder T, Åsberg A, et al. Therapeutic drug monitoring of tacrolimus-personalized therapy: second consensus report. *Ther Drug Monit.* 2019;41:261–307.
5. Scalea JR, Levi ST, Ally W, et al. Tacrolimus for the prevention and treatment of rejection of solid organ transplants. *Expert Rev Clin Immunol.* 2016;12:333–342.
6. Masuda S, Inui K. An up-date review on individualized dosage adjustment of calcineurin inhibitors in organ transplant patients. *Pharmacol Ther.* 2006;112:184–198.
7. Kuypers DR, De Jonge H, Naesens M, et al. Effects of CYP3A5 and MDR1 single nucleotide polymorphisms on drug interactions between tacrolimus and fluconazole in renal allograft recipients. *Pharmacogenet Genomics.* 2008;18:861–868.
8. Van Daele R, Spriet I, Maertens J. Posaconazole in prophylaxis and treatment of invasive fungal infections: a pharmacokinetic, pharmacodynamic and clinical evaluation. *Expert Opin Drug Metab Toxicol.* 2020;16:539–550.
9. Pu WS, Tao Y. Metabolism and drug-drug interaction of tacrolimus, cyclosporine and triazole antifungal. *Chin J Nephrol Dial Transpl.* 2019;28:63–67.
10. Yang XP, Zhou SL, Jiang Y, et al. Simultaneous determination ofconcentration of six antifungal drugs in human plasma by LC-MS/MS. *Chin J Mod Appl Pharm.* 2021;38:2093–2099.
11. Hu N, Cao JJ, Qian Q, et al. Effect of CYP3A5 and POR gene polymorphisms on dosage and concentration of tacrolimus in renal transplant patients during hospital stay. *Chin J Hosp Pharm.* 2020;40:65–70.
12. Hu N, Tang YF, Qian Q, et al. Effect of CYP3A5 and ABCB1 gene polymorphism on dosage and concentration of tacrolimus and renal function in renal transplant recipients at early postoperative period. *Cent South Pharm*. 2019;17:489–494.
13. Timsit JF, Sonneville R, Kalil AC, et al. Diagnostic and therapeutic approach to infectious diseases in solid organ transplant recipients. *Intensive Care Med.* 2019;45:573–591.
14. Ben-Ami R. Systemic antifungal therapy for invasive pulmonary infections. *J Fungi*. 2023;9:144.
15. Zhang S, Pillai VC, Mada SR, et al. Effect of voriconazole and other azole antifungal agents on CYP3A activity and metabolism of tacrolimus in human liver microsomes. *Xenobiotica*. 2012;42:409–416.
16. Luo X, Li T, Yu Z, et al. The impact of azole antifungal drugs on imatinib metabolism in human liver microsomes. *Xenobiotica*. 2019;49:753–761.
17. Krishna G, Ma L, Prasad P, et al. Effect of posaconazole on the pharmacokinetics of simvastatin and midazolam in healthy volunteers. *Expert Opin Drug Metab Toxicol.* 2012;8:1–10.
18. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. *Transpl Infect Dis.* 2017;19:10.
19. Chen L, Krekels EH, Verweij PE, et al. Pharmacokinetics and pharmacodynamics of posaconazole. *Drugs*. 2020;80:671–695.
20. Chen X, Wang D, Lan J, et al. Effects of voriconazole on population pharmacokinetics and optimization of the initial dose of tacrolimus in children with chronic granulomatous disease undergoing hematopoietic stem cell transplantation. *Ann Transl Med.* 2021;9:1477.
21. Vanhove T, Bouwsma H, Hilbrands L, et al. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ recipients. *Am J Transpl.* 2017;17:2372–2380.
22. Zhao YC, Xiao CL, Hou JJ, et al. The effect of voriconazole on tacrolimus in kidney transplantation recipients: a real-world study. *Pharmaceutics*. 2022;14:2739.
23. Berge M, Chevalier P, Benammar M, et al. Safe management of tacrolimus together with posaconazole in lung transplant patients with cystic fibrosis. *Ther Drug Monit.* 2009;31:396–399.
24. Collins J, Shea K, Parsad S, et al. The impact of initiating posaconazole on tacrolimus pharmacokinetics in allogeneic stem cell transplantation. *J Oncol Pharm Pract.* 2020;26:5–12.
25. Gu TM, Lewis JS II, Le H, et al. Comparative effects of fluconazole, posaconazole, and isavuconazole upon tacrolimus and cyclosporine serum concentrations. *J Oncol Pharm Pract.* 2022;28:1357–1362.
26. Sansone-Parsons A, Krishna G, Martinho M, et al. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. *Pharmacother J Hum Pharmacol Drug Ther.* 2007;27:825–834.
27. Hesselink DA, Bouamar R, Elens L, et al. The role of pharmacogenetics in the disposition of and response to tacrolimus in solid organ transplantation. *Clin Pharmacokinet.* 2014;53:123–139.
28. Nakamura T, Fukuda M, Matsukane R, et al. Influence of POR*28 polymorphisms on CYP3A5*3-associated variations in tacrolimus blood levels at an early stage after liver transplantation. *Int J Mol Sci.* 2020;21:2287.
29. Everton JBF, Patrício FJB, Faria MS, et al. Impact of POR*28 variant on tacrolimus pharmacokinetics in kidney transplant patients with different CYP3A5 genotypes. *Curr Drug Metab.* 2022;23:233–241.
30. Helal M, Obada M, Elrazek WA, et al. Effect of ABCB1 (3435C>T) and CYP3A5 (6986A>G) genes polymorphism on tacrolimus concentrations and dosage requirements in liver transplant patients. *Egypt J Med Hum Genet.* 2017;18:261–268.
31. Mourad M, Wallemacq P, De Meyer M, et al. The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function. *Clin Chem Lab Med.* 2006;44:1192–1198.
32. Provenzani A, Notarbartolo M, Labbozzetta M, et al. Influence of CYP3A5 and ABCB1 gene polymorphisms and other factors on tacrolimus dosing in Caucasian liver and kidney transplant patients. *Int J Mol Med.* 2011;28:1093–1102.
33. Yan L, Li Y, Tang JT, et al. Donor ABCB1 3435 C>T genetic polymorphisms influence early renal function in kidney transplant recipients treated with tacrolimus. *Pharmacogenomics*. 2016;17:249–257.
34. Ciftci HS, Ayna TK, Caliskan YK, et al. Effect of MDR1 Polymorphisms on the blood concentrations of tacrolimus in Turkish renal transplant patients. *Transpl Proc*. 2013;45:895–900.
35. Bonhomme-Faivre L, Picard V, Saliba F, et al. Effect of the ABCB1 3435C>T polymorphism on tacrolimus concentrations and dosage requirements in liver transplant recipients. *Am J Health Syst Pharm.* 2009;66:1645–1651.

