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REVIEW ARTICLE

Pharmacokinetics, Pharmacodynamics and Pharmacogenetics of Tacrolimus in Kidney Transplantation

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Abstract: ***Background:*** Tacrolimus (Tac, or FK506), a calcineurin inhibitor (CNI), is the first-line immunosuppressant which consists of the footstone as immunosuppressive regimens in kidney transplantation. However, the drug toxicity and the significant differences of pharmacokinetics (PK) and pharmacodynamics (PD) among individuals are hidden troubles for clinical application. Recently, emerging evidences of Tac pharmacogenetics (PG) regarding drug absorption, metabolism, disposition, excretion and response are discovered for better understanding of this drug.

Method: We reviewed the published articles regarding the Tac PG and its effects on PK and PD in kidney transplantation. In addition, we summarized information on polygenic algorithms.

Results: The polymorphism of genes encoding metabolic enzymes and transporters related to Tac were largely investigated, but the results were inconsistent. In addition to CYP3A4, CYP3A5 and P-gp (also known as ABCB1), single nucleotide polymorphisms (SNPs) might also affect the PK and PD parameters of Tac.

Conclusion: The correlation between Tac PK, PD and PG is very complex. Although many factors need to be verified, it is envisaged that thorough understanding of PG may assist clinicians to predict the optimal starting dosage, help adjust the maintenance regimen, as well as identify high risk patients for adverse effects or drug inefficacy.

Keywords: Pharmacokinetics, pharmacodynamics, pharmacogenetics, Tacrolimus, dosing algorithms, solid organ transplantation.

1. INTRODUCTION

Tacrolimus (Tac, or FK506), a calcineurin inhibitor (CNI), is a 23-membered macrolide lactone isolated from *Streptomyces tsukubaensis* in 1987 for the first time [1]. In 1994, the US Food and Drug Administration firstly approved Tac for liver transplantation. Due to its excellent efficacy, Tac has been extended as a first-line regimen for kidney, heart, lung, intestinal and bone marrow transplantation.

A patient's initial Tac dose is conventionally determined based on body weight and adjusted according to Tac blood concentration. Oral Tac is absorbed in the gastrointestinal tract, and is metabolized by liver enzymes, mainly the cytochrome P450 (CYP450) system, which is easily interacted with many substances. Unfortunately, the therapeutic index of Tac is narrow, and the pharmacokinetics (PK) and pharmacodynamics (PD) features vary dramatically among individuals. As a result, it is often difficult to reach or maintain the target Tac blood concentration, and the patients could be at the risk of either graft rejection or toxicity. Genetic factors including CYP3A5*3, CYP3A4*1B, CYP3A4*22, ABCB1 and POR*28 have been reported frequently for their influence on Tac dose requirement, which reveals the importance of pharmacogenetics (PG) of Tac.

Herein, we summarize the latest research progress of Tac PG, and discuss its effect on PK and PD in kidney transplantation. With thorough understanding of Tac PG, it may assist clinicians to achieve individualized Tac treatment in future.

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2. PHARMACOKINETICS

The average bioavailability of Tac is merely 25%, and it varies dramatically among individuals, ranging from 5 to 90 % [2, 3]. About 99% of Tac binds to erythrocytes after entering the systemic circulation, but only the dissociated portion can enter the lymphatic system and play its major immunosuppressive effect [4]. The first pass effect of absorption in small intestine and liver, and the pumping action of the small intestine contribute to the poor bioavailability. The synergistic effects of CYP3A and P-glycoprotein (P-gp, or ABCB1) can significantly influence the absorption of Tac in the small intestine [4]. P-gp can also inhibit the entry of Tac into organs or septal structures, including blood-brain barrier, testis, placenta, heart and kidney. In P-gp knockout transgenic mice, the Tac concentration in brain cells was significantly increased [5]. This indicates the importance of P-gp in the variability of Tac distribution.

Tac is primarily metabolized by the CYP3A enzyme system, which includes CYP3A5, CYP3A4, CYP3A7 and CYP3A43, and is expressed in small intestine, liver and kidney [6]. Liver is the main site for Tac metabolism, while considerable pre-systemic biotransformation occurs in small intestine [7]. In kidney, the main CYP3A isoform expressed is CYP3A5, which may play an important role in local Tac metabolism [8, 9].

Compared with CYP3A5, the catalytic efficiency of CYP3A4 was relatively low [10]. CYP3A7 has little influence on the metabolism of Tac, while the role of CYP3A43 is unclear [11, 12].

The total body clearance (TBC) of Tac is relatively low, around 0.06 L/(h·kg)-1, while the half-life is long and variable, ranging from 4 to 41 h (about 12 h on average) [2, 3, 13]. Approximately 95% of Tac metabolites are excreted by bile, and urinary excretion is only about 2% [7]. Only 0.5% of the original drug is excreted through urine and feces.

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The metabolites of Tac may also be substrates for potential drug transporters. For instance, metabolites formed by Tac in mucosa may return to the intestinal lumen *via* P-gp transport [14]. In kidney, P-gp expressed on brush border of proximal tubular epithelial cells and more distally on the renal tubule may contribute to renal elimination; by contrast, P-gp on the canalicular surface of hepatocytes controls excretion into bile [15].

Given all the evidences above, it suggests that the expression and/or function of CYP3A5, CYP3A4 and P-gp are closely related to the PK of Tac. Therefore, genetic polymorphism of these proteins or factors that have an impact on them can affect the PK of Tac and lead to inter-individual differences. The relationship between PK and PG is reviewed in Table **1** [6, 8, 11-13, 16-28].

3. PHARMACODYNAMICS

Tac is an effective immunosuppressive drug to prevent rejection. Meanwhile, it also has considerable toxicity and a narrow therapeutic window. In clinic, even though the concentration of some patients is within the therapeutic window, they might also suffer from toxicity or rejection. On the contrary, certain patients do not reject the allografts with a low Tac exposure. The variability between individuals may lie on the genetics polymorphism. The PG-based differences in Tac PD about adverse effects are summarized in Table **2** [11, 24, 25, 27, 29-42].

3.1. Acute Rejection (AR)

The genetics basis associated with acute rejection has been extensively studied [43]. In a cohort study carried out by Oetting WS *et al.*, 969 kidney transplant recipients were recruited and 23 genetic variants which were associated with AR according to previous reports, were analyzed. Interestingly, only one single-nucleotide polymorphism (SNP) within the coagulation factor V gene (rs6025, Leiden mutation), was proved to be significantly associated with AR [44].

Moreover, studies also showed that SNPs of CYP3A and ABCB1 were not the risk factors of rejection [16, 45].

3.2. Nephrotoxicity

CNI-induced nephrotoxicity is likely related to intra-renal concentrations of CNIs, which may not be properly reflected by whole-blood CNI concentrations [29, 46-48]. As mentioned above, the main CYP3A isoform expressed in the kidney is CYP3A5, which contributes to local Tac metabolism and limit the Tac local accumulation [8, 9]. However, contradictory results have been reported on their relationship [30, 31]. Possible reasons for these discrepancies include differences in ethnicity, sample size and the definition of nephrotoxicity. In addition, there is a hypothesis that, it is not Tac itself but its metabolites that are responsible for its nephrotoxicity.

ABCB1 expressed in renal tubules may limit the local accumulation of Tac and its metabolites in kidney through facilitating them into urine [15]. Thus, a lower ABCB1 expression in kidney may be associated with increased risk of chronic kidney damage caused by Tac. However the results of the reported literatures remains inconsistent [32, 49, 50]. One possible explanation is that what really works is the function of ABCB1 other than its expression. Besides, CYP3A5 may have different interplay with ABCB1 in vascular and tubule-interstitial compartments of kidney [30].

In addition to ABCB1 and CYP3A, CYP2C8 is also related to CNI-nephrotoxicity. CYP2C8 is a member of the P450 superfamily which plays a role in the metabolic process of arachidonic acid

Table 1. PK and PG.

Genes		rsID	Alleles	Pharmacokinetic Parameters	References
CYP3A5*3		rs776746	*3/*3	↓ D[a,b] ↓ CL/F ↑C_0/D ↑ C_{max}/D ↑AUC_{12}/D ↑C_0	[12, 13, 27]
CYP3A5*6		rs10264272	*6/*1 *6/*6	↑C_0/D	[18]
CYP3A5*7		rs41303343	*7/*1 *7/*7	↑C_0/D	[18]
CYP3A4*1B[c]		rs2740574	*1B/1 *1B/*1B	↑D ↓C_0/D	[12]
CYP3A4*18[c]		rs28371759	*18/*1 *18/*18	↑CL/F ↓C_0/D ↓C_2/D	[12, 16, 28]
CYP3A4*22		rs35599367	*22/*1 *22/*22	↑C_0/D ↓D	[6, 8, 19]
ABCB1 3435C > T		rs1045642	T-T	↑D ↓D ↑C_0/D	[12, 16, 28]
ABCB1 2677G > T/A		rs2032582	G-T T-T	↑C_0/D ↑D ↓D	[11, 12, 16]
ABCB1 1236C > T		rs1128503	C-T T-T	↑C_0/D	[11, 12, 16]
Haploid	ABCB1 3435C > T	rs1045642	T-T-T	↓D ↑C_0/D (vs. C-G-C)	[11, 12, 16]
	ABCB1 2677G > T/A	rs2032582			
	ABCB1 1236C > T	rs1128503			
PXR 8055C > T		rs2276707	C-T T-T	↑AUC_{12}/D	[26]
POR*28		rs1057868	*28/*28 *28/*1	↓C_0[d] ↓AUC_{24}[d] ↓C_{max}[d] ↑D[d]	[17, 20-25]

AUC_x: Area under the concentration time curve(0~x h); CL/F : Apparent clearance rate; C_0 : Tac trough concentration; Cmax : Maximum blood concentration; D: Dose requirement.
a: An example how to read the table: compared with other genetic variants (*3/*1 or *1/*1), type *3/*3 may decrease the Tac dose requirement; b: in order to make the table legible, only the common parameters mentioned frequently in literature are listed; c: there is Linkage disequilibrium with CYP3A5*3; d: only make sense when the recipient is CYP3A5*1 allele carrier.

Table 2. PD (adverse effects) and PG.

Genes		rsID	Genotype	Tac-induced Adverse Events Risk					
				Acute Rejection	Nephrotoxicity	DGF	PTDM	Hypertension	Neurotoxicity
CYP3A5*3		rs776746	*3/*3		a↑[31, 34] ↓[30]	↑[58]		↓[35, 36]	↓[70]
ABCB1 3435C > T		rs1045642	T-T		↑[50] (D&R) ↓[37] (D)				↓[38]
ABCB1 2677G > T/A		rs2032582	G-(T/A) or (T/A)-(T/A)						↑[38] ↓[11]
ABCB1 1236C > T		rs1128503	C-C						↑[11]
Haploid	**ABCB1 3435C > T**	rs1045642	T-G-C		↑[11]				
	ABCB1 2677G > T/A	rs2032582							
	ABCB1 1236C > T	rs1128503							
PXR 8055C > T		rs2276707	T-T			↑[57] (D)			
POR*28		rs1057868	*28/*28 or *28/*1				↑[17]		
TGF-β1 29T > C		rs1800470	C-T		↑[39-41]				
TGF-β1 74G > C		rs1800471	G-C		↑[39, 40]				
PPARA rs4253728 G > A		rs4253728	A-A or A-G				↑[17]		
CYP2C8*3		rs11572080	*3/*3 or *3/*1		↑[42]	↑[59]			

a: an example to read the table: compared with other genetic variants (*3/*1 or *1/*1), type *3/*3 may increase the risk of Tac-induced nephrotoxicity, investigated in reference 25 and 133.

When there are ↑ and ↓ on a same line, it means there are conflicting results demonstrated by different groups. (D&R): means the genotype of both the donor and recipient is effective in influencing the risk; (D): means only the donor genotype may contribute to the influence. Not all research results are listed, only those seems to be reliable are demonstrated here, for details, readers can refer to the paragraph or the references.

(AA) to epoxyeicosatrienoic acids (EETs) in kidney [51-53]. EETs are biologically active to help the kidneys to counter the vasoconstrictive effects of CNIs, which indicates the beneficial role of CYP2C8 in CNI-nephrotoxicity.

3.3. DGF

Delayed graft function (DGF) is a frequent complication after kidney transplantation which reduces long-term allograft survival. Although the definition may differ, a widely-recognized definition is the need for dialysis within the first week after transplantation [54, 55]. Ischemia/reperfusion injury is the main reason for DGF [54, 56]. Hauser *et al*. reported that PXR significantly increased the risk of DGF [57]. Another study found that DGF was associated with CYP3A5 [58]. Besides, association between DGF and CYP2C8 has also been reported [59].

3.4. Post Transplanted Diabetes Mellitus (PTDM)

New-onset diabetes is another frequent complication after transplantation due to the immunosuppressive drugs, such as glucocorticoids and mammalian target of rapamycin (mTOR) inhibitors. Tac can also cause glycometabolism disorder, and is more diabetogenic than cyclosporine [33]. The mechanisms involve impairment of insulin secretion and insulin gene expression as well as directly toxicity to Langerhans in islets [60]. Recent studies revealed that the genetic background was one of the risk factors for PTDM. The PPARA rs4253728 A>G and POR*28 variant alleles could increase the risk of developing PTDM [60]. Polymorphisms in the genes of vitamin D receptor, promoter region of the IL-6, transcription factor 7-like 2 (rs7903146) and zinc transporter-8 (SLC30A8; rs13266634) have also been reported [17, 61-65].

3.5. Hypertension

Hypertension caused by Tac is due to activating the renal sodium chloride co-transporter, which disturbs the"with-no-lysine"(WNK) kinase network [66].

CYP3A5 and ABCB1 have been reported to play a role in regulating the metabolism of 6β-hydrocortisol and the transport of aldosterone, which influences the metabolism of water and sodium in kidney [67]. The genetic polymorphisms of ABCB1 and CYP3A5 may be related to hypertension, but it needs further research [68].

3.6. Neurotoxicity

Neurotoxic effects of Tac include tremor, headache, insomnia, and peripheral neuropathy [69]. Although the exact pathophysiol-

ogy of Tac-induced neurotoxicity is unclear, how Tac penetrates into the central nervous system (CNS) is the critical step for neurotoxicity. Yanagimachi *et al*. Reported that the CYP3A5*1 allele could increase the risk of neurotoxicity [70]. They also suggested that it might not be Tac itself but its metabolites that caused neurotoxicity. ABCB1, which is expressed in the blood brain barrier, also takes part in Tac transport in CNS. In mice, dysfunction of ABCB1 leaded to accumulation of Tac in the CNS [5, 71]. However, whether ABCB1 genotype has an impact on Tac-induced neurotoxicity in clinic is still unclear.

So far, the genetics of Tac PD has been less well-investigated than that of Tac PK. Tissue concentrations of CNIs have hitherto received little attention due to technical difficulties, although only the intra-renal Tac can play a role. Meanwhile, more attention should be paid to unbound blood Tac concentration, which may have a closer relationship to Tac toxicity [72]. The current evidences of the relationship between PG and PD are summarized in Table **2**. With better understanding of the relation between gene polymorphisms and Tac PD, we might be able to assess the efficacy of Tac through the detection of gene polymorphisms in future.

4. PHARMACOGENETICS

Definitely, the correlation between Tac PK, PD and PG is very complex. Published investigations mainly focused on the polymorphism of genes encoding metabolic enzymes and transporters. In addition to CYP3A4, CYP3A5 and P-gp (also known as ABCB1), there are more SNPs that may affect the PK and PD parameters of Tac as mentioned above. The following is a brief summary.

4.1. CYP3A5

Polymorphisms in the CYP3A5 gene explain 40-50% of the variability in Tac dose requirement [73, 74]. The hottest SNP studied most in CYP3A5 is CYP3A5*3, which is an A to G transition at position 6986 within intron 3 (rs776746) [67]. This mutation leads to alternative splicing, and truncation of the protein, which decreases the function of CYP3A5 enzyme [75]. As a result, CYP3A5 expressers (CYP3A5*1/*1 or CYP3A5*1/*3 genotype) have significantly lower dose-adjusted C_0 compared to CYP3A5 non-expressers (CYP3A5*3/*3 genotype), and the requirement of Tac dose is CYP3A5*1/*1 > *1/*3 > *3/*3 [67]. In Chinese, the frequency of CYP3A5*3 allele is as high as 77.8%, which may be an explanation for the lower dosage required for Chinese people [76]. Meanwhile, as for the postoperative adverse drug reactions including abnormal liver function and renal toxicity, there is a conflicting result that type *1/*3 and *3/*3 are significantly higher than type *1/*1 [30, 77].

Following standard bodyweight-based dosing, the exposure of Tac for CYP3A5 expressers could be insufficient at the early stage post transplantation, so that the risk for AR might increase. MacPhee *et al*. demonstrated that even under the therapeutic drug monitoring (TDM), CYP3A5 expressers did achieve the target Tac concentration with a delay [78]. However, no evidence supports the hypothesis that this delay would increase rejection. It was reported that CYP3A5 expressers only had an earlier onset of AR compared with non-expressers (median time, 7 days versus 13 days), but the rate of biopsy-proven acute rejection had no significant difference [77]. This is in consistent with some other investigations [11, 79-86].

Meanwhile, the CYP3A5 genotype-based Tac initial dose has been verified extensively. Several randomized-controlled clinical trials (RCT) suggested that CYP3A5 genotypes could be helpful in predicting the initial dose of Tac [87-89]. However, it is still unclear whether this strategy was superior in terms of efficacy when compared with conventional TDM [90]. Nevertheless, recipients who received a CYP3A5 genotype-based Tac dose needed significantly less time and fewer dose adaptations to reach target, which, in our view would be helpful in some potential ways for the recipients.

Other CYP3A5 SNPs include CYP3A5*6 (rs10264272) and CYP3A5*7 (rs41303343). CYP3A5*6 encodes a G to A transition at position 14690, causing a splice variant mRNA and deletion of exon 7, resulting in nonfunctional CYP3A5 protein [18, 75]. CYP3A5*7 denotes a single base insertion at codon 346, causing a frameshift and resulting in a truncated mRNA and nonfunctional CYP3A5 [91].

4.2. CYP3A4

As for CYP3A4 gene, two SNPs in relation to Tac PK have been investigated extensively: CYP3A4*1B SNP (rs2740574) and CYP3A4*22 SNP (rs35599367). The CYP3A4*1B SNP involves an A to G transition at position -392 in the promoter region of CYP3A4, and is associated with an increase of CYP3A4 activity [92]. It showed that the C_0/D ratio of Tac in patients with the *1B mutation was reduced by 35% compared with that of wild-type homozygotes [93]. However, there is a linkage disequilibrium(LD) between CYP3A4*1B and rs776746 of the CYP3A5 gene. It is possible that the effect of CYP3A4*1B on Tac PK and PD is caused by rs776746, which has been shown in several published studies [12, 94]. Therefore, the exact effect of CYP3A4*1B alone on Tac is still unclear. The CYP3A4*22 SNP (rs35599367) contains a transition of C to T in intron 6 and is associated with reduced CYP3A4 mRNA expression and CYP3A4 enzyme activity *in vitro* [95]. In clinic observation of kidney transplantation, the CYP3A4*22 required less Tac dose to achieve the target exposure. What's more, it was not influenced by the CYP3A5 genotype [6]. Similar result was observed in pediatric heart transplant recipients [96]. To reach similar target concentrations, the requirement of Tac dose was 30% less in CYP3A4*22 carriers than that in CYP3A4*1/*1 carriers.

CYP3A4 * 18 (rs28371759) may also have an impact on Tac PK. This SNP is located in intron 10, with a transition of T to C at position 878. This mutation may increase the activity of CYP3A4 enzyme, and thereby increase the Tac clearance rate and plasma drug concentration [97].

Recently a new and rare CYP3A4 variant was found, which is now designated as CYP3A4*26 [98]. This variant is a c.802C>T transition and results in a premature stop codon at position 268 in exon 9 (R268*) [98]. The truncated CYP3A4 protein is nonfunctional. Werk *et al*. [99] first identified this mutation when they observed an unusually low Tac dose requirement in a kidney transplant recipient. This patient had very high Tac exposure following standard Tac dosing and only reached the therapeutic window once the Tac dose was reduced to 0.5 mg thrice weekly. This patient was a CYP3A5*3 homozygote and was also homozygous for CYP3A4*26, and therefore experienced complete failure of CYP3A enzyme activity.

When combining CYP3A4 and CYP3A5 genotypes, Elens *et al*. [19] were able to predict Tac dose requirements better compared with the CYP3A4 or CYP3A5 genotype alone. Based on these observations, it has been proposed to prescribe different Tac doses for ultra-rapid (CYP3A5 expressers and CYP3A4 *1/*1), intermediate (CYP3A5 non-expressers and CYP3A4*1/*1) and poor (CYP3A5 non-expressers and CYP3A4*22 carriers) CYP3A metabolizers, respectively [100].

4.3. ABCB1 Gene

P-gp, also known as ABCB1 or MDR1 is a glycoprotein encoded by human ABCB1 gene. As discussed above, it serves as drug transporter of Tac, and plays an important role in Tac PK. Recently, P-gp has been found to contain more than 50 SNPs. Among them, the ABCB1 3435C>T (rs1045642), 1236C>T (rs1128503) and 2677G>T/A (rs2032582; Ala893Ser/Thr) SNPs have drawn the most attention after intensive investigation [101-103].

The ABCB1 3435C＞T (rs1045642) might be the hottest locus among all the ABCB1 gene SNPs. Reportedly, the frequency of this mutation in Orientals is 37-49% [104]. The variation of rs1045642 locus might reduce the expression and function of P-gp in the duodenum, and thus potentially affect the bioavailability of Tac [16].

Another retrospective study recruited 81 recipients and found that after one month of renal transplantation, the daily Tac dose and the concentration/dose ratio were highly associated with 2677G＞T/A SNP [105]. In detail, wild-type patients required 40% higher Tac dose compared with homozygous carriers of 2677G＞T/A SNP ($P \leq 0.05$), while the concentration/dose ratio was 36% lower in the wild-type patients ($P \leq 0.02$). The haplotype analysis further confirmed the results and suggested that 3435C>T and 2677G>T/A SNPs were associated with daily Tac dose requirements.

In addition, the study of these three SNP haploid (1236C＞T, 2677G＞T/A and 3435C＞T, which are in linkage disequilibrium) found that C-G-C (haplotype 1) and T-T/A-T (haplotype2) accounted for 45.4% and 36.2% of the haplotypes, respectively; individuals with haplotype 1 required significantly higher daily doses of Tac than those with haplotype 2 [105].

Because lymphocytes also express ABCB1 on the membrane, the activity of ABCB1 may affect the intracellular accumulation of Tac where the drug exerts its biologic effect as well. Vafadari *et al*. found that patients with the ABCB1 3435CC genotype needed more Tac for inhibition of IL-2 production in T-cells compared with 3435TT genotype patients [106]. Capron *et al*. found that patients with the ABCB1 3435T or the 2677T/A allele had 1.3-fold higher Tac concentrations within circulating lymphocytes compared with wild-type homozygotes [107]. These studies provide evidences that ABCB1 3435C>T and 2677G>T/A affect Tac distribution into lymphocytes with the variant alleles which are associated with an increased pharmacodynamic effect of Tac. Therefore, ABCB1 SNPs may also play a role in Tac-induced nephrotoxicity, as tissue concentrations of Tac are believed to be more related to its renal side effects.

Although there are many studies on the association of ABCB1 gene polymorphism with Tac PK or PD, the results remain inconsistent. To further confirm the association, large-scale genotype-phenotype correlation trials are encouraged.

4.4. POR

POR is essential for CYP-mediated drug oxidation as an electron donor [108]. POR*28 (rs1057868; A503V) is a coding variant in POR gene, which is believed to be effective in increasing the activity of POR and thus leads to the increasing activities of CYP3A4 and CYP3A5 [17, 28]. An investigation demonstrated that the POR*28 cloud lead to an increase of CYP3A5-mediated Tac metabolism, but in CYP3A5 non-expressers, there was no increase of CYP3A4-mediated Tac metabolism, which indicated a possibility of interaction between POR, CYP3A5 and Tac [109].

In addition, it has also been reported frequently that POR*28 carriers have lower adjusted Tac C_0 and Tac C_0/Tac dose in heart or kidney transplantation, no matter for the adult or the pediatric [21-24]. Although the strength of this association seems weak and has limited clinical impact on Tac dose requirements (15%-20%), POR*28 may explain a part of Tac variability, and POR*28 carriers may experience faster Tac metabolism [21, 23, 25].

4.5. PXR

As a nuclear transcription, the human pregnane X receptor (PXR), which is encoded by NR1I2, regulates the expression of CYP3A and ABCB1. Polymorphisms of NR1I2 have been reported, but the results regarding their association with Tac dose requirement are conflicting [26, 73, 100].

The six-base pair deletion mutation (rs3842689, -/GAGAAG) in the NR1I2 promoter region was first discovered by Uno *et al*. [110, 111], which occurs in a potential liver nuclear factor (HNF-1) binding site. Research indicated that the PXR Six-base deletion mutation could reduce the expression of PXR mRNA, and thus, significantly reduce the expression of CYP3A4 and ABCB1 [112]. However, Z.P. Wang *et al*. reported that the PXR rs3842689 native homozygous WW genotype was only a risk factor for gastrointestinal reactions, and the other genotypes seemed to play a minor role in Tac-induced adverse reactions [113].

4.6. PPAR-α

The expression and activity of CYP3A is also related to the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-α). Two sequence variants in the PPAR-α gene (PPARA), PPARA c.209-1003G>A and c.208+3819A>G, can reduce the PPAR-α expression and contribute to the intra- and inter-individual variability of CYP3A [114]. In one study with 229 kidney transplant recipients, the Tac C_0/D ratio was significantly higher in patients with one or more PPARA variant alleles [94]. Patients who were homozygous for PPARA-α c.209-1003G>A showed significantly higher Tac exposure, which was consistent with the reduced CYP3A4 protein and activity observed *in vitro* [114]. At present, PPARA c.208+3819A>G appears to have the strongest influence on Tac PK, though it still needs confirmation.

As always the case, there are opposite findings, which show that the PPARA c.209-1003G A has no effect on Tac C_0/D [115, 116]. These paradoxical results need further investigation.

4.7. Other SNPs

The multidrug resistance-associated protein 2 (MRP2), which is encoded by the ABCC2, may also be associated with Tac metabolism [117]. Reportedly, ABCC2 c.3972C>T (rs3740066) SNP significantly increased the dose-normalized concentration of Tac, whereas ABCC2 c.-24C>T (rs717620) SNP had no influence on it [117]. Genvigir *et al*. also showed that the ABCC2 c.3972C>T polymorphism affected Tac C/D in Brazilian kidney transplant recipients [118]. However, Renders *et al*. showed that there was no association between the ABCC2 c.3972C>T polymorphism and the Tac concentration in German patients [82].

The CYP2C8 enzyme, which is highly expressed in the liver, can also be found in extrahepatic tissues like kidney [119]. Reported by Suarez-Kurtz *et al*. [120], The CYP2C8*3 was associated with higher Tac C_0/D, but only in CYP3A5 none-expressers. Furthermore, CYP2C8*3 and CYP2J2 c.-76G>T SNPs were reported to influence the renal function of the patients and the occurrence of adverse events during treatment with Tac and mycophenolate sodium [118].

Genetic polymorphisms in IL-18 (*e.g*., rs5744247) and IL-10 (*e.g*., -819 C/T and -592 C/A) can also affect Tac dose requirements [81, 94]. However, the exact mechanism by which they affect Tac dose requirements is unknown [121, 122]. Recently, our group also demonstrated that IL-3 rs181781 and CTLA4 rs4553808 genetic polymorphisms probably influence the Tac dose requirements in Chinese kidney transplant recipients [123].

5. CLINICAL APPLICATION

The metabolism of Tac can be influenced by many factors, including ethnicity, age, gender, concomitant medication, hepatic and renal dysfunction, and genetic factors such as CYP3A5, CYP3A4 and ABCB1 SNPs [12, 16, 124]. Among them, CYP3A5 genotype is associated with a remarkable impact on Tac PK, while the effects of other genetic polymorphisms are limited or even contradictory [125-127]. A number of algorithms containing clinical and/or PG factors have been constructed to predict the requirement of Tac dose; meanwhile, retrospective and prospective trials have been conducted to verify these algorithms [87, 125, 128-134].

The first dosing algorithm was created by Passey *et al*. in 2011. The CYP3A5 genotype was the only genetic factor included in the algorithm [130], while this dosing algorithm was not able to predict estimated Tac clearance accurately in another study in the UK in 2013 [135]. Another dosing algorithm reported by Passey *et al*. was improved by incorporating the CYP3A4*22 allele [136]. There are also other dosing algorithms reported by different groups demonstrating their successful performance [87, 125]. In general, PG factors guided Tac dosing enabled more renal recipients to achieve target Tac trough (C_0) levels. What's more, it took less time for these patients to reach the target concentration with fewer dose modifications. These successes in clinic revealed the possibility to improve clinical outcomes of Tac therapy by taking PG factors into account.

In our previous study, we collected the clinical data of 1045 renal transplant patients from multiple transplant centers in the past 7 years, developed machine-learning models to predict Tac stable dose(TSD) in renal transplant recipients [124]. To our knowledge, this is the first study using machine-learning models to predict TSD. Comparing conventional dosing algorithms performed by multiple linear regression with the eight new techniques of machine learning, we demonstrated that the technique of regression tree was the best to predict TSD. With the highest ideal rate, the algorithm performed by this technique might provide a more accurate approach which could help achieve personalized medicine in clinic. One concern for our study is that only the data from the Chinese was analyzed; studies in other ethnic groups may come to different results.

Algorithms that are widely accepted in clinic should be validated in populations of different ethnicity. Genetic variations of drug-metabolizing enzymes show remarkable differences between different peoples. For example, the allelic frequency of the CYP3A5*3 allele, which is common among Caucasian patients (90-93%), is less frequently seen in Asian (60-73%) or African (32%) descent [137, 138]. When it comes to a particular group, the situation may be much more complicated. In a study of six different Chinese ethnic groups, Lai *et al*. [128] reported the frequencies of CYP3A5*3 variant alleles differed dramatically in Uygur Chinese (88.1%), Kazakh Chinese (84.5%), Tibetan Chinese (80.3%), Han (67.3%), Bai Chinese (70.2%) and Wa Chinese (56.3%). More details about the allelic frequencies of the most common SNPs in CYP3A5, CYP3A4, ABCB1 and POR*28 in various ethnic groups were summarized by J.T. Tang *et al*. [139].

Although it is still a question whether genotype testing would improve clinical outcome, it is definitely true that this technique is effective on Tac pharmacokinetic parameters. At present, the TDM is still the indispensable part in current management of Tac, which obviously cannot be replaced by polygenic algorithms. However, more and more evidences show the association between the genotypes and Tac PK parameters in recent years, which suggests the potential for greater predictive value of polygenic algorithms. In fact, many centers have already established or applied some dosing algorithms, which are primarily based on CYP3A5 genotype. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has also published Tac dosing guidelines based on CYP3A5 genotype expression [140, 141]. Unfortunately, it is still questionable whether these techniques have been widely used in standard practice to guide Tac dosing. So far, the evidence has been limited for us to provide an appropriate genotype testing strategy for each ethnic group, and the Tac dosing guidelines based on CYP3A5 genotype published by CPIC seem to be the only one which is relatively authoritative. But we do hope that more and more clinicians could try to use the genotype-guided dosing followed by TDM and pay more attention on Tac adverse effects simultaneously. If so, we may get more valuable evidence to achieve the optimal individual therapy.

CONCLUSION AND FUTURE PROSPECTS

In order to better understand the individual differences of Tac, tremendous efforts have been made. The genetics polymorphisms, including SNPs of CYP3A4, CYP3A5, ABCB1 etc., play an important role in the variability of Tac. Although it is not sure whether genotype testing of these alleles would improve clinical outcome of kidney transplantation, this technique is definitely effective in depicting the PK parameters of Tac. Algorithms based on multiple genotypes have a better performance in predicting the required dose, which helps recipients achieve target Tac concentration faster with fewer dose adjustments. It is inspiring that the transplant community devotes such great efforts to the PG research. We believe that, by combining genetics with demographic, clinical, epigenetic and environmental information, predictive algorithms may be developed to achieve more reliable dosing, thereby avoiding patients exposing to ineffective or overly toxic regimens.

Furthermore, if the intra-cellular or tissue drug quantification can be carried out in daily clinical practice, and novel techniques such as mass spectrometry can be applied, we may soon clarify the significance of Tac metabolites and tissue Tac concentrations.

To achieve Tac tailored treatment, another obstacle in the development of PG in China is the cost of genetic testing which has not been covered by insurance. Economic condition has limited the routine clinical practice of genotyping. All in all, we still have a lot of difficulties to overcome. But considering that Tac is likely to be around for the next decade, all the efforts are worthy.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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