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REVIEW ARTICLE

Biomarkers for individualized dosage adjustments in immunosuppressive therapy using calcineurin inhibitors after organ transplantation

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Calcineurin inhibitors (CNIs), such as cyclosporine A and tacrolimus, are widely used immunosuppressive agents for the prevention of post-transplantation rejection and have improved 1-year graft survival rates by up to 90%. However, CNIs can induce severe reactions, such as acute or chronic allograft nephropathy, hypertension, and neurotoxicity. Because CNIs have varied bioavailabilities, narrow therapeutic ranges, and individual propensities for toxic effects, therapeutic drug monitoring is necessary for all CNIs. Identifying the genetic polymorphisms in drug-metabolizing enzymes will help to determine personalized dosage regimens for CNIs, as CNIs are substrates for CYP3A5 and P-glycoprotein (P-gp, MDR1). CNIs are often concomitantly administered with voriconazole or proton pump inhibitors (PPIs), giving rise to drug interaction problems. Voriconazole and PPIs can increase the blood concentrations of CNIs, and both are primarily metabolized by CYP2C19. Thus, it is expected that interactions between CNIs and voriconazole or PPI would be affected by CYP2C19 and CYP3A5 polymorphisms. CNI-induced acute kidney injury (AKI) is a serious complication of transplantations. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) are noninvasive urinary biomarkers that are believed to be highly sensitive to CNI-induced AKI. In this article, we review the adverse events and pharmacokinetics of CNIs and the biomarkers related to CNIs, including CYP3A5, CYP2C19, MDR1, NGAL, and KIM-1. We hope that these data will help to identify the optimal biomarkers for monitoring CNI-based immunosuppressive therapy after organ transplantation.

Keywords: tacrolimus; cyclosporine A; CYP3A5; CYP2C19; MDR1; NGAL

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INTRODUCTION

An organ transplantation is the best method for curing end-stage organ disease, especially in conjunction with the strong immunosuppressive abilities of calcineurin inhibitors (CNIs), such as cyclosporine A (CsA), which was discovered in the 1970s [1]. Subsequently, the more effective and less toxic CNI tacrolimus (TAC) was identified in the 1980s [2, 3], resulting in lower rejection rates and improving the short-term allograft survival rates. Current 1-year graft survival rates are ~90%, and acute rejection rates are below 20% [4–6].

Due to the narrow therapeutic range and large inter-individual and intraindividual variability in the pharmacokinetics of CNIs, the therapeutic drug monitoring of CNIs is considered to be essential for patient management and determining individualized dosage adjustments for the prevention of post-transplant rejection. Despite the large variation in TAC pharmacokinetics, the area under the concentration-time curve (AUC) has a nearly linear relationship with the trough blood concentration among organ transplant patients [7, 8]. CNIs are substrates of P-glycoprotein (P-gp), CYP3A4, and CYP3A5, and therefore, these proteins represent potential pharmacokinetic factors that may help to determine the personalized dosage regimens for these drugs. The effects of single-nucleotide polymorphisms (SNPs) in the genes *MDR1 (*also known as *ABCB1)* and *CYP3A5* on the pharmacokinetics of immunosuppressive drugs have been widely examined. CNIs can induce severe reactions, such as nephrotoxicity that can lead to renal dysfunction and the eventual need for a kidney transplant. Patients with TAC trough concentrations higher than 6 ng/mL have a significantly increased risk of developing adverse events following pediatric liver transplantations [9]. Therefore, genetic polymorphisms may affect CNI pharmacokinetics and affect the risks of experiencing adverse drug reactions. Because of these severe reactions, the long-term use of CNIs is not compatible with good survival. After 10 years, the graft survival rate remains at 50% after a deceased donation in the US and Europe, with approximately 30% of patients returning to dialysis, and 1 in 4 patients dying with a functional graft [10].

Although there are currently no biomarkers that can predict CNI-induced nephrotoxicity early, accurately, and noninvasively, some pharmacokinetic biomarkers, such as CYP3A5 and CYP2C19, and kidney damage markers, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), can still be used to predict CNI-induced nephrotoxicity.

In this article, we review the adverse events and pharmacokinetics of CNIs and the biomarkers related to adverse drug

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reactions to CNI, including CYP3A5, CYP2C19, MDR1, NGAL, and KIM-1. We hope that this information will lead to the identification of the optimal biomarkers for monitoring CNI-based immunosuppressive therapy.

THE IMMUNOSUPPRESSIVE MECHANISM

CsA acts by binding to molecules of the cyclophilin family, with a high affinity for calcineurin, which is the key protein phosphatase for the activation of T cells. Calcineurin is a serine/threonine phosphatase that is widely distributed in mammalian tissues and is able to sense Ca^{2+} through its activation by calmodulin. TAC is a macrolide, containing a 23-membered lactone ring, whose mechanism of action is similar to that of CsA. TAC becomes biologically active only after forming a complex with the cytosolic FK-binding protein (FKBP). Several FKBP family members, such as FKBP12, FKBP12.6, and FKBP51, are expressed in T cells. However, no pharmacological effect of TAC was observed in T cells derived from FKBP12-deficient mice [11]. CNIs prevent the dephosphorylation of nuclear factor of activated T cells (NFAT) proteins by binding to cytosolic immunophilins (cyclophilin A and FKBP12), which, in turn, bind to and inhibit calcineurin, which inhibits NFAT activity [12, 13]. An NFAT has two subunits, one of which is confined to the cytoplasm, while the other has a predominantly nuclear localization. In resting T cells, NFAT proteins are hyperphosphorylated and are retained in the cytosol. The activation of T-cell receptors activates calcineurin, which dephosphorylates NFAT, allowing for its translocation to the nucleus, where it activates the expression of a range of genes [14]. The calcineurin–NFAT pathway was initially described in T cells, where NFAT acts as a master regulator of lymphocyte development and the expression of proinflammatory cytokines, such as interleukin (IL)-2, IL-3, IL-4, IFN-γ, and TNF-α. The classic calcineurin-NFAT signaling pathway can be described as follows. When receptors accept an antigen, phospholipase C-γ is activated and hydrolyzes phosphatidylinositol-4,5-bisphosphate into inositol-1,4,5-trisphosphate (IP3) and diacylglycerol. Next, IP3 binds to specific receptors on the endoplasmic reticulum and drives Ca^{2+} release from the endoplasmic reticulum into the cytoplasm, which triggers the opening of Ca^{2+} release-activated Ca^{2+} channels. As a result of the increased intracellular Ca^{2+} levels, the calcineurin enzyme becomes active and dephosphorylates NFAT, allowing for the translocation of NFAT into the nucleus and the subsequent regulation of gene expression [15]. NFAT signaling was later identified in other immune cells, including B cells, dendritic cells, and megakaryocytes [16, 17]. CNIs have therefore been regarded as inhibitors of immune-cell functions. TAC and CsA limit the immune response through the inhibition of calcineurin activity, using similar but slightly different mechanisms. In vitro, the pharmacological effect of TAC was approximately 100-fold greater than that of CsA [18]. According to the maximum effect model, the population mean estimates of the blood concentrations that yield a half-maximal effect (EC_{50}) for TAC and CsA were 26.4 and 200 ng/mL, respectively [19]. Although FKBP12 is the only known drug target in T cells that mediates the pharmacological actions of TAC [11], the results of Xu et al. suggest that TAC may have one or more unknown molecular mechanism(s) that reduce immunological activity, which are distinct from the classical calcineurin inhibitory pathway.

ADVERSE EFFECTS

All adverse events and adverse drug reactions were coded using the coding system described in the Medical Dictionary for Regulatory Activities (MedDRA 21.0, March 2018).

Acute kidney injury

The characteristic feature of acute CNI nephrotoxicity is reversible tubular dysfunction [20]. Several studies have indicated that vascular dysfunction results from the upregulation of vasoconstrictor factors, including endothelin and thromboxane, the activation of the renin-angiotensin system (RAS), and the downregulation of vasodilating factors, such as prostacyclin, prostaglandin E2, and nitric oxide [21, 22]. CNIs can activate the RAS through both direct effects on juxtaglomerular cells [23] and indirect effects related to hemodynamic changes in the renal vasculature (arteriolar vasoconstriction), leading to the downregulation of vasodilating factors and the upregulation of endothelin [24]. Moreover, CNIs also augment the vasoconstricting effects of angiotensin II in smooth muscle cells by influencing intracellular calcium stores and smooth-muscle cell phenotypic maintenance and contractility [25]. In addition, CsA induces imbalances in the vasodilator/vasoconstrictor ratio of arachidonic acid metabolites (eicosanoids), which ultimately promotes renal vasoconstriction. In addition, the inhibition of calcineurin–NFAT signaling by CNIs inhibits COX-2, which promotes renal vasoconstriction and reduces the glomerular filtration rate [26, 27]. Because this vasoconstriction is dose-dependent and reversible, the withdrawal of CNIs is sufficient to cure this nephrotoxicity [28, 29].

Chronic allograft nephropathy

Chronic CNI nephrotoxicity is a more serious problem. In 1984, Myers et al. were the first to demonstrate chronic CNI nephrotoxicity after the long-term use of CsA. In heart transplant recipients, this nephrotoxicity was associated not only with a reversible decrease in the glomerular filtration rate but also with irreversible renal functional deterioration as a result of irreparable and progressive tubulointerstitial injury and glomerulosclerosis [30].

The initial phase (year 1) of the development of chronic allograft nephropathy is characterized by early tubulointerstitial damage from ischemic injury, prior to severe rejection, and subclinical rejection. These findings are present in 94.2% of patients [31].

Chronic CNI use not only contributes to late allograft loss but may also be the major cause of chronic renal allograft damage, which is characterized by the progressive and irreversible deterioration of renal function, in conjunction with interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, and glomerulosclerosis [32].

The exact mechanism of nephrotoxicity induced by CNIs remains unknown. Tolou-Ghamari et al. [33] suggest that it may result from alterations in the production of vasoactive substances by mesangial and endothelial cells, which are contributing factors to decreased renal blood flow and glomerular thrombosis.

Hypertension

Given that CNIs can lead to vasoconstriction by many mechanisms, as mentioned above, hypertension is a common reaction to CNIs. The de novo development or aggravation of hypertension is common and can pose a significant hazard, both early and late, after all types of solid-organ transplantations. Hypertension can promote or aggravate cardiovascular risk factors, which are associated with poor long-term outcomes in patients [34, 35]. Opelz et al. [36] showed that a lower systolic blood pressure is associated with improved patient and graft survival.

Research has shown that TAC is associated with a slower reduction in cardiac output, lower systemic vascular resistance, and less rapid increases in arterial pressure and that hypertension significantly decreases when CsA is replaced with TAC [37–40].

Neurotoxicity

Neurotoxicity is a well-recognized adverse effect of CNIs, although the mechanism remains obscure. Although this reaction is uncommon and is often resolved after withdrawal, Chohan et al. [41] reported that CNI-induced neurotoxicity is frequently associated with a poor prognosis. Some studies have shown that mTOR treatment can recover neurological functions and can be combined with low doses of CNIs to prevent rejection [42, 43].

Table 1. Influence of CYP3A5 SNPs on the pharmacokinetics of cyclosporine or tacrolimus in organ transplant recipients

Drug	Ethnicity	Treatment	Genotype–phenotype relationship	References
Cyclosporine	Asian (Chinese)	Liver transplantation $N = 339$	NS	Xin et al. [49]
	Asian (Malaysian)	Renal transplantation $N = 67$	*3/*3 required lowest dosage	Eng et al. [46]
	Caucasian (Netherlanders)	Renal transplantation $N = 171$	NS	Bouamar et al. [48]
	Caucasian (Spainish)	Heart transplantation $N = 26$	NS	Jordán de Luna et al. [50]
Tacrolimus	Asian (Japanese)	Liver transplantation $N = 50$	C/D ratio was decreased in *1/*1	Goto et al. [47]
	Asian (Japanese)	Liver transplantation $N = 410$	*3/*3 had higher C/D, and *1 allele showed a higher rate of acute rejection	Uesugi et al. [54]
	Caucasian (Swiss)	Heart transplantation $N = 52$	*1 required 2.2- to 2.6-fold higher daily TAC doses to reach the targeted C0 concentration	Lesche et al. [56]
	Indian	Renal transplantation $N = 25$	In *3/*3, the trough level was almost two-fold higher than in *1	Nair et al. [45]
	American	Lung transplantation $N = 83$	*3/*3 had a higher level/dose ratio than *1	Zheng et al. [57]
	Asian (Chinese)	Renal transplantation $N = 67$	*3/*3 required lowest initial dosage, and blood concentration and C/D were increased in *3/*3	Chen et al. [51]
	Caucasian	Heart transplantation $N = 76$	C/D was 1.8-fold lower in *1	Deininger et al. [53]

NS there was no significant influence on drug pharmacokinetics, *C/D* concentration/dose ratio

Efforts to achieve the maximal CNI dose reduction and the careful monitoring of CNI serum levels are important for the prevention of these irreversible changes. However, the administration of CNIs is complicated by variable pharmacokinetics, narrow therapeutic ranges, and individual sensitivities to toxic effects [44]. To help strike a balance between the immunosuppressive and toxic effects, identifying a good biomarker is key.

BIOMARKERS

SNPs and pharmacokinetics

CYP3A5. In general, drug–drug interactions involving CNIs occur most frequently when potent CYP3A4/5 inhibitors, such as macrolide antibiotics, azole antifungals, and calcium channel blockers, are combined with CYP3A4/5-metabolized CNIs. Because CYP3A5 is an important intestinal and hepatic enzyme for CNI metabolism, CYP3A5 polymorphisms are believed to be the primary cause for the interindividual variability in CNI pharmacokinetics and affect the risk of experiencing adverse drug reactions.

The presence of an SNP in intron 3 of *CYP3A5*, 6986A>G, results in the absence of a functional CYP3A5 protein in homozygous carriers (poor metabolizer phenotype). *CYP3A5* has 2 alleles (**1* and **3*), and patients can therefore be subdivided into three groups: *CYP3A5*1/*1* (expressers), *CYP3A5*1/*3* (expressers) and *CYP3A5*3/*3* (nonexpressers). Nonexpressers are believed to have a higher bioavailability of (and exposure to) CNIs, in part due to increased intestinal absorption, and thus require lower doses to achieve the target concentration in comparison to expressers. Some studies have shown that expressers require approximately double the starting dose of CNIs, indicating that nonexpressers have an almost 2-fold higher trough level of CNIs than expressers [45–47]. However, the CYP3A5 polymorphism only appears to have a measurable effect on TAC therapy, and many studies have revealed that there is no relation between the CYP3A5 polymorphism and CsA activity [48–50].

In addition, many reports suggest that CYP3A5 is related to the mean concentration/dose ratio (C/D) of CNIs. Some researchers have reported that nonexpressers exhibit greater renal CNI metabolism; thus, even though nonexpressers require a lower initial dose, they have higher CNI blood concentrations and C/D values [51–55]. These results suggest that expressers experience the increased metabolic clearance of TAC and low trough concentrations, which results in a high incidence of acute rejection. Therefore, the *1 genotype may increase the risk of acute cellular rejection [54].

These findings are summarized in Table 1 [56, 57]. One hypothesis is that the polymorphism in the *CYP3A5* gene affects the nephrotoxicity of TAC and acute rejection; however, because the mechanism of TAC-induced chronic allograft nephropathy is still unknown, and the definition of chronic allograft nephropathy varies across the world, studies in this area have not been consistent.

Kuypers et al. [58] found that *CYP3A5*1* genotypes are significantly more frequently associated with the development of biopsy-proven TAC-related nephrotoxicity than are *CYP3A5*3* genotypes. However, this result contradicts the findings of Chen et al. [51] and de Denus et al. [59], who found that nephrotoxicity was the greatest in the *CYP3A5*3/*3* group. Queineh et al. [60] found that the *CYP3A5* genetic polymorphism was not associated with TAC nephrotoxicity. Further research is required to elucidate these conflicting results.

CYP2C19. Because immunosuppressive agents reduce the activity of the immune system, transplant recipients have increased risks of infections. CNIs are often combined with an antifungal agent, such as voriconazole, to prevent fungal infections early after transplantation, thus introducing drug interaction problems. Many researchers have demonstrated that when a CNI is combined with voriconazole, the blood concentration of the CNI increases [61–65].

Voriconazole is a strong inhibitor of CYP3A4/5 [66] and is primarily metabolized by CYP2C19. Thus, it is expected that the interaction between CNIs and voriconazole may be affected by CYP2C19 polymorphisms, as the magnitude of CNI inhibition due

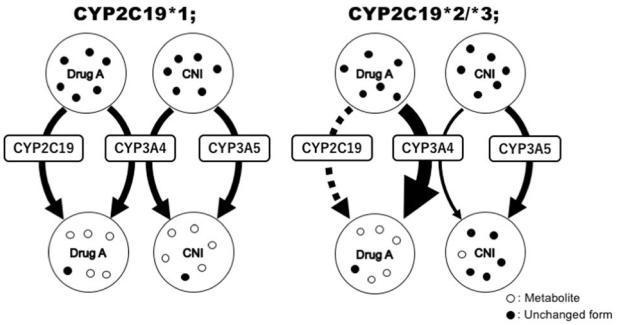

Fig. 1 The mechanism underlying the influence of CYP2C19 polymorphisms on CNI effects. Drug A is voriconazole or a PPI. Black dots represent the blood concentration, and white dots denote a drug metabolite

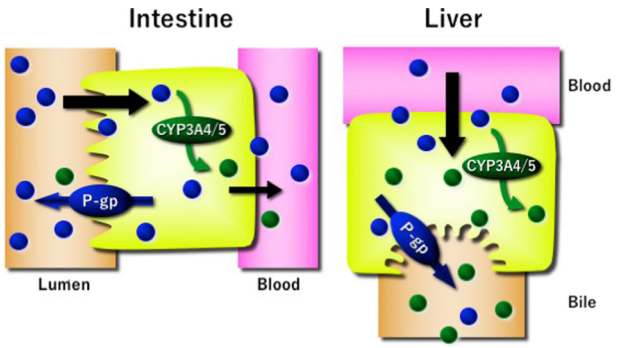

Fig. 2 The role of P-glycoprotein (P-gp; also known as MDR1 or ABCB1) and CYP3A4/5 in the enterohepatic processing of tacrolimus and cyclosporine A. Blue and green symbols represent the unchanged form and metabolite, respectively. (Adapted from the article by Masuda S. and Inui K. [2006], with permission from Elsevier.)

to metabolism by CYP3A4/5 has been found to be dependent on the concentration of voriconazole, within a specific range, in human liver microsomes in vitro [62].

The gene *CYP2C19* is located in chromosomal region 10q24.2 and consists of nine exons. *CYP2C19* contains many SNPs, and its variants can be categorized into three groups, based on the ability to metabolize voriconazole: poor metabolizers (*CYP2C19*2/*2*, *CYP2C19*3/*3*, and *CYP2C19*2/*3*, PMs), intermediate metabolizers (*CYP2C19*1/*2* and *CYP2C19*1/*3*, IMs) and extreme metabolizers (*CYP2C19*1/*1*, EMs). PMs and IMs experience 4- and 2-fold higher voriconazole exposure (AUC), respectively, than EMs; therefore, when a CNI is combined with voriconazole, CYP2C19 polymorphisms should be considered [66]. A few studies have indicated that the AUC0-24 of a CNI (primarily TAC) in IMs and PMs was significantly higher than that in EMs when the CNI is combined with voriconazole [66, 67].

Similar to voriconazole, proton pump inhibitors (PPIs) can affect the blood concentrations of CNIs through CYP2C19. In contrast to voriconazole, PPIs inhibit the metabolism of CNIs only in patients who carry variant alleles of *CYP2C19* (EMs have the wild-type allele) because PPIs are metabolized by both CYP3A4/5 and CYP2C19. Therefore, CYP2C19 polymorphisms can also increase the blood concentrations of a CNI [68, 69]. The interactions between CNIs and voriconazole/PPIs is illustrated in Fig. 1.

Because the contribution of CYP2C19 to the metabolism of omeprazole is greater than that to lansoprazole and rabeprazole [70], some researchers have reported that the C/D ratios of CNIs co-administered with lansoprazole or rabeprazole were less strongly associated with CYP2C19 polymorphisms, although lansoprazole can increase the C_{max} of TAC [71–73]. Overall, the blood concentration of CNIs that are co-administered with PPIs is higher in EMs and IMs than in PMs, especially for the co-administration of omeprazole [68, 74]. In addition, Chiu et al. [75] have reported that CYP2C19 polymorphisms do not affect the expression of *CYP3A4*18*, *CYP3A5*3*, or *MDR1-3435* variants and, therefore, are independent factors.

MDR1/ABCB1. P-gp, the product of the ATP-binding cassette transporter gene (*ABCB1;* also known as *MDR1*), acts as an efflux transporter and decreases the blood concentration of CNIs [76]. The contributions of intestinal P-gp and/or CYP3A4 to CNI therapy are presented in Fig. 2. There are three factors that are believed to affect P-gp expression, which influences the blood concentration of CNIs: (1) the expression level of MDR1 mRNA; (2) MDR1 polymorphisms; and (3) MDR1 haplotype. In this article, we focus on the influence of MDR1 polymorphisms and the expression level of MDR1 mRNA on CNI effects.

MDR1 has multiple polymorphisms; 1236C>T, 2677G>T/A, and 3435C>T were identified as better predictors of the blood concentration of CNIs than 1236C>T and 2677G>T/A [77, 78]. It has been reported that the 3435C>T polymorphism is associated with higher CNI concentrations [79–82], but many studies suggest that MDR1 polymorphisms (even 3435C>T) do not influence the CNI concentrations in Asian patients [47, 83–87]. Consequently, ethnicity may be a stronger factor affecting the association between the MDR1 polymorphisms and CNI concentrations in blood. Similarly, a meta-analysis of studies showed no significant effect of the 3435C>T polymorphism on the pharmacokinetics of digoxin [88]. The literature data are summarized in Tables 2–4 [89–93].

In contrast, studies have shown that the expression level of P-gp is strongly related to the trough levels of CNIs [47, 94, 95], and because the expression level of P-gp may depend on the expression level of MDR1 mRNA, the latter could be a useful biomarker for monitoring CNI therapy. Studies have shown that high expression levels of MDR1 mRNA are associated with a higher target concentration of TAC, a high risk of acute rejection, a lower C/D ratio of CNIs, and reduced survival rates [96–98]. All these data suggest that MDR1 mRNA is a good molecular marker for determining the oral dosage regimen of TAC. However, because studies on MDR1 mRNA in Caucasians are limited and there are no studies on MDR1 mRNA in relation to CsA, more research is required in this field.

Urinary biomarkers and nephrotoxicity

Kidney Disease Improving Global Outcomes defines acute kidney injury (AKI) as any of the following: (1) an increase in serum creatinine concentration of 0.3 mg/dL within 48 h; (2) an increase in the serum creatinine level of up to 1.5 times the baseline, which is known or presumed to have occurred within the previous 7 days; and (3) a urine volume of 0.5 mL/(kg·h) for 6 h. However, serum creatinine fails to be a sensitive and specific marker of renal injury [99]. In most cases, the signal is delayed and manifests when 70–80% of renal epithelial mass is already lost [100]. In addition, serum creatinine levels are affected by nonrenal factors, such as age, sex, body weight, muscle mass, total body volume, and protein intake [101].

Therefore, biomarkers that are more sensitive and specific for the prediction of renal function are required. There are many biomarkers used to predict renal function, including albumin, α-GST, α_1-microglobulin, β_2-microglobulin, clusterin, cysteine-rich protein, cystatin-C, exosomal fetuin-A, heart-type fatty acid-binding protein, hepatocyte growth factor, interleukin-18, liver-type fatty acid-binding protein, *N*-acetyl-β-glucosaminidase, netrin-1, osteopontin, retinol-binding protein, sodium/hydrogen exchanger isoform 3, NGAL, and KIM-1 [102]. Here, we will discuss two of these factors: NGAL and KIM-1.

Table 2. Influence of MDR1 cDNA C1236T SNPs on the pharmacokinetics of cyclosporine or tacrolimus in organ transplant recipients

Drug	Ethnicity	Treatment	Genotype–phenotype relationship	References
Cyclosporine	Asian	Heart transplantation $N = 14$	NS	Chowbay et al. [83]
	Caucasian (French)	Renal transplantation $N = 106$	1236CC had lower dose-adjusted peak drug concentrations (−16%) and dose-adjusted AUC values over the first 4 h (−14%)	Anglicheau et al. [89]
	Caucasian (Italian)	Renal transplantation $N = 154$	1236TT required a significantly higher CsA oral dose	Saracino et al. [90]
Tacrolimus	Asian (Chinese)	Renal transplantation $N = 60$	NS	Sun et al. [84]
	Caucasian (Spanish)	Renal transplantation $N = 91$	NS	Kravljaca et al. [78]
	Caucasian (Portuguese)	Renal transplantation $N = 30$	Heterozygous showed concentrations 44.4% higher than 1236CC	Mendes et al. [91]
	Caucasian (Italian)	Renal transplantation $N = 154$	NS	Saracino et al. [90]

NS there was no significant influence on drug pharmacokinetics, *AUC* area under curve

Table 3. Influence of MDR1 cDNA G2677T/A SNPs on the pharmacokinetics of cyclosporine or tacrolimus in organ transplant recipients

Drug	Ethnicity	Treatment	Genotype–phenotype relationship	References
Cyclosporine	Asian (Japanese)	Renal transplantation $N = 97$	NS	Kuzuya et al. [85]
	Caucasian (Egyptian)	Renal transplantation $N = 50$	Daily dose requirements were significantly higher for 2677GG	Sharaki et al. [92]
Tacrolimus	Asian (Chinese)	Renal transplantation $N = 60$	NS	Sun et al. [84]
	Asian (Japanese)	Liver transplantation $N = 181$	NS	Goto et al. [47]
	Caucasian (Egyptian)	Liver transplantation $N = 41$	NS	Fathy et al. [77]
	Caucasian (Spanish)	Renal transplantation $N = 91$	2677TT required significantly higher doses and had a lower level/dose ratio	Kravljaca et al. [78]

NS there was no significant influence on drug pharmacokinetics

Table 4. Influence of MDR1 cDNA C3435T SNPs on the pharmacokinetics of cyclosporine or tacrolimus in organ transplant recipients

Drug	Ethnicity	Treatment	Genotype–phenotype relationship	References
Cyclosporine	Asians (Chinese)	Renal transplantation $N = 106$	NS	Hu et al. [86]
	Caucasian (Egyptian)	Renal transplantation $N = 40$	NS	Mostafa-Hedeab et al. [93]
	Caucasian (Canadian)	Renal transplantation $N = 69$	AUC (0–4)/mg dose CsA/kg was significantly higher in 3435CC	Foote et al. [79]
	Caucasian (Spanish)	Heart transplantation $N = 14$	The 3435C allele is associated with a higher cyclosporine concentration	Isla Tejera et al. [80]
	American	Renal transplantation $N = 60$	Oral clearance was 1.5-fold higher in subjects with at least one 3435T allele	Yates et al. [81]
Tacrolimus	Asian (Japanese)	Liver Transplantation $N = 69$	NS	Goto et al. [87]
	Asian (Chinese)	Renal transplantation $N = 60$	NS	Sun et al. [84]
	Caucasian (Spanish)	Renal transplantation $N = 35$	3435CC showed 40% lower concentration/dose ratios	López-Montenegro Soria et al. [82]

Table 5. Urinary biomarkers of kidney toxicity

Biomarker	Treatment	Result	References
Neutrophil gelatinase-associated lipocalin (NGAL)	Liver transplantation $N = 31$	Urinary NGAL, was significantly higher in patients with AKI than in those without AKI	Tsuchimoto et al. [101]
	Renal transplantation $N = 25$	NGAL staining contributed to the characterization of renal damage post-transplant	Mishra et al. [110]
	Renal transplantation $N = 50$	Plasma NGAL was significantly higher in the DGF group. NGAL increased after TAC introduction	Cantaluppi et al. [112]
	Renal transplantation $N = 80$	Serum NGAL was significantly higher among kidney allograft recipients and patients with CKD	Malyszko et al. [118]
	Heart transplantation $N = 88$	Plasma NGAL levels correlate with renal dysfunction	Gustafsson et al. [103]
	Renal transplantation $N = 94$	Significantly higher levels of NGAL on day 1 following transplant in patients who developed acute rejection	Field et al. [104]
	Liver transplantation $N = 26$	Plasma NGAL detected AKI with an optimal AUC at 8 h after admission and at 4 h after admission for urinary NGAL	Dedeoglu et al. [105]
Kidney injury molecule-1 (KIM-1)	Renal transplantation $N = 145$	Urinary KIM-1 is an independent predictor of long-term graft loss	van Timmeren et al. [122]
	Renal transplantation $N = 94$	Higher KIM-1 levels on days 0, 1, and 4 were significantly associated with lower probabilities of rejection-free survival	Jin et al. [106]
	Renal transplantation $N = 56$	At 18 h after transplantation, urinary KIM-1 can predict DGF with 100% specificity and 89.9% sensitivity	Yadav et al. [107]

AKI acute kidney injury, *DGF* delayed graft function, *CKD* chronic kidney disease

CNIs cause structural damage to the straight segment of the proximal tubule and renal vasoconstriction, which is mediated by the renal sympathetic nervous system [20]. Therefore, biomarkers synthesized both in the proximal and distal tubules, such as NGAL and KIM-1, may be well associated with renal vasoconstriction and the interstitial fibrosis caused by CNI-induced nephrotoxicity. A summary of the available literature data on NGAL and KIM-1 is provided in Table 5 [103–107].

NGAL. NGAL is a small protein belonging to the lipocalin family [108–110]. This ubiquitous 25 kDa protein is secreted by various human tissues, including those of the gastrointestinal tract, respiratory tract, and kidneys, and because of its small molecular size, NGAL easily passes filtration and can be readily detected in urine [111]. When kidney function is essentially normal, the concentration of NGAL should be undetectable in the urine and serum; however, NGAL is rapidly induced in kidney tubule cells in response to ischemic injury [112]. The early appearance of NGAL in urine and serum is independent of the glomerular filtration rate but is highly predictive of a drop in this rate, which may happen up to several days later [109]. NGAL levels in urine and plasma may undergo a 100- to 10,000-fold concentration increase compared to normal levels in cases of renal injury [113]. Furthermore, NGAL was expressed during renal failure caused by ischemia-reperfusion injury in a mouse model [114]. A clinical study showed that NGAL staining contributed to the characterization of renal damage after kidney transplantation [115] and that NGAL could predict the development of AKI approximately 2 days before a rise in serum creatinine was observed [116].

One research group studied TAC-induced AKI in liver transplant patients and identified seven biomarkers, including monocyte chemotactic protein 1, liver-type fatty acid-binding protein, interleukin-18, osteopontin, cystatin-C, clusterin, and NGAL. This group showed that NGAL was superior to the other six urinary biomarkers, as high urinary levels of NGAL correlated with the probability of AKI [101].

Many studies have confirmed the sensitivity and specificity of urinary NGAL for the early diagnosis of AKI [109, 111, 112, 117], and NGAL not only has the potential to predict AKI but may also be a biomarker of chronic kidney disease, with high sensitivity and specificity, suggesting that NGAL is an early and accurate biomarker of renal function [112, 118].

KIM-1. KIM-1 is a type 1 transmembrane protein expressed in the proximal tubules that is cleaved from the surface of activated tubular cells and released into urine by a metalloproteinase. KIM-1 staining is detectable in proximal tubule epithelial cells and is sensitive to drugs and their metabolites [102, 113, 119]. The KIM-1 gene is located in human chromosomal region 5q33.2, and the KIM-1 protein is undetectable in healthy kidneys or in normal urine but is released into urine after proximal tubular kidney injury [120, 121]. A clinical study showed that urinary KIM-1 could predict the development of graft loss after kidney transplantation [122]. Therefore, KIM-1 has been consistently demonstrated to be an early indicator of kidney injury and is considered a highly sensitive and specific urinary biomarker for monitoring drug-induced kidney injury [123–126].

Studies have revealed that urinary KIM-1 protein concentrations are significantly higher in patients with AKI [123, 124], but increased KIM-1 expression can also be an early marker for identifying renal tubular damage. Nogare et al. [125] have reported that KIM-1 protein expression is increased in biopsies with interstitial fibrosis and tubular atrophy, implying that KIM-1 can serve as a biomarker of chronic kidney injury (CKI) induced by CNIs. Thus, KIM-1 expression is significantly related to kidney function, which makes KIM-1 a sensitive and specific marker of both AKI and CKI.

CONCLUSION

In summary, although CYP3A5, CYP2C19, and MDR1 can affect the CNI concentration, more information is available regarding CYP3A5 and CYP2C19 polymorphisms in relation to TAC, in the absence of differences in patient ethnicity. In contrast, MDR1 has a stronger relationship with ethnicity than CYP3A5 polymorphisms. NGAL and KIM-1 are sensitive and specific biomarkers of CNI toxicity, but other immunosuppressive drugs (e.g., everolimus) do not have similar biomarkers and will also induce toxicity; therefore, the identification of a more effective biomarker is required.

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ADDITIONAL INFORMATION

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