Zununi Vahed *et al.*, ***BioImpacts,*** 2015, 5(1), 45-54
doi: 10.15171/bi.2015.12
http://bi.tbzmed.ac.ir/

Pharmacogenetics and drug-induced nephrotoxicity in renal transplant recipients

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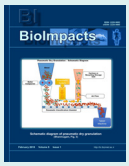
Article Info



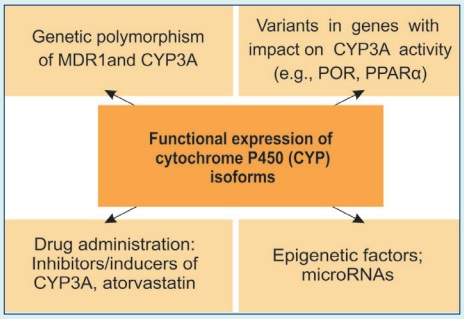
Article Type:
Review Article

Article History:
Received: 15 Mar. 2014
Revised: 07 June 2014
Accepted: 09 June 2014
ePublished: 21 Feb. 2015

Keywords:
Pharmacogenetics
Nephrotoxicity
Renal transplantation
Immunosuppressive agents
Calcineurin inhibitors
Cytochrome P450

Abstract

Introduction: The advent of calcineurin inhibitors (CNIs), as the leading immunosuppressive agents, not only has revolutionized the transplant medicine but also made it a better therapeutic intervention that guarantees the graft outcome and improves the survival rate of patients. However, genetic polymorphism(s) in the CNIs metabolic substrates genes (CYP3A4, CYP3A5) and their transporter such as P-glycoprotein (P-gp) can influence the CNIs metabolism and elicit some possible systemic and intra-renal exposures to drugs and/or metabolites with differential risk of nephrotoxicity, jeopardizing the transplantation.



Methods: In the current study, we review the recent literatures to evaluate the effects of genetic polymorphisms of the genes involved in development of chronic calcineurin nephrotoxicity and progression of chronic allograft dysfunction (CAD) providing an extensive overview on their clinical impacts.

Results: Identifying the inherited genetic basis for the inter-individual differences in terms of drug responses and determining the risk of calcineurin-mediated nephrotoxicity and CAD allow optimized personalized administration of these agents whith minimal adverse effects.

Conclusion: Pharmacogenetics characteristics of CYP isoforms (CYP3A) and efflux transporters (P-gp and MRP), involved in metabolism and extracellular transportation of the immunosuppressive CNIs, can be of pivotal information in the pharmacotherapy of the renal-transplant recipients. Such information can be used for the successes clinical interventions to attain an improved drug administration strategy with reduced rates of rejection and toxicity.

Introduction

Calcineurin inhibitors (CNIs) have widely been used as the immunosuppressive agents to prevent the acute rejection after an organ transplantation. These drugs are highly prolific in preventing the acute graft rejection, even though some genetic variants and polytherapy have resulted in complicated clinical outcomes among individuals undergone such therapy.

In fact, any patient possesses two different genetic entities, namely the donor and the recipient, and accordingly the recipient used drugs can be metabolized by the donor transplanted graft. Furthermore, it should be noted that, because of the polytherapy and drug interactions, each patient possesses variable pharmacokinetics and pharmacodynamics and may respond differently to a given pharmacological treatment modality.[1] Hence, with recommended starting doses, some recipients may not reach the designated concentration(s). It should be highlighted that the under-dosing of CNIs may lead to the acute rejection, while the over-dosing of CNIs can increase the risks of infection/superinfection, malignant disease, and serious drug-specific side effects such as nephrotoxicity, hypertension, hyperlipidemia, and diabetes mellitus.[2]

The frangible equilibrium between the risks and the benefits of suppression of the immune system makes

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the management of immunosuppressive drug therapy a challenging issue, in which the chronic allograft dysfunction (CAD) remains unabated issue that can impose devastating hurdles to individuals undergone the therapy and heavy burdens to the health systems. CAD, as the major hindrance to the long-term graft survival, may be influenced by several parameters and/or issues such as chronic calcineurin nephrotoxicity which is a major factor in CAD development and renal allograft attrition.[3] Different factors involved in CAD may enhance the susceptibility of patients to develop the CNIs-mediated nephrotoxicity. Such factors may include (a) the genetic polymorphisms in genes like CNIs transporters (e.g., P-gp) and metabolizing enzymes (CYP3A4/5), (b) transforming growth factor-β1 (TGF-β1), (c) CCR5 and angiotensin converting enzyme (ACE), (d) tissue concentrations of CNIs and their metabolites, (e) older kidney age, (f) salt depletion, and (g) the use of nonsteroidal anti-inflammatory drugs.[4]

For the success of transplantation, it is conspicuous to search for complementary strategies to manage immunosuppressants beyond therapeutic drug monitoring (TDM) since there exists a poor correspondence between dose, blood concentration and therapeutic response. In recent years, the field of pharmacogenetics has held great promise and potential providing pivotal information upon the role of genes involved in drug metabolism and/or transportation in response to immunosuppressive therapy in the transplant recipients. With an aim to identify the inherited basis for inter-individual differences in drug response and risk of developing calcineurin nephrotoxicity and CAD, pharmacogenetics can allow individualized administration of immunosuppressive agents to optimize/to improve the therapeutic impacts and to minimize the inadvertent adverse effects.[2] Therefore, pharmacogenetics of patients can provide vital information that can be extremely beneficial for the pharmacotherapy and the care of renal transplant recipients. In this review, we will describe the CNIs-mediated nephrotoxicity with a focus on pharmacogenetics and pharmacokinetics.

Pharmacokinetics of immunosuppressive agents

The immunosuppressive property of CNIs such as cyclosporine (CsA) and tacrolimus (Tac) is based on the inhibition of calcineurin which is a key enzyme in T-cell activation. CsA and Tac bind to the cytosolic proteins of the cyclophilin family and FK506-binding protein 12, respectively. Both CsA-cyclophylin and Tac-FKBP12 complexes have a high affinity to calcineurin, resulting in profound inhibition of the phosphatase activity of calcineurin. Thereby, such inhibitory impact(s) prevents the phosphorylation of the nuclear factor of activated T cells (NFAT) responsible for the transcriptional activation of the interleukin-2 (IL2) and IL4 genes and their corresponding receptors.[5] As a result, both humoral and cellular immune responses are diminished, which is deemed to be the main phenomenon for the successful graft acceptance. Nowadays, there exist plethora of compelling evidences that highlight the capability of CsA in inducing and/or suppressing the expression of a wide range of genes in different cell types, in both calcineurin-dependent or -independent manners.[5]

CNI metabolism

CNIs are significantly metabolized in the liver and the gastrointestinal tract by the cytochromes P450 3A enzymes (in particular, CYP3A4 and CYP3A5),[6] which are also subjected to cellular efflux functions mainly by P-gp that is one of the adenosine triphosphate (ATP)-binding cassette transporters, the so-called multidrug resistance 1 (MDR1) or ATP-binding cassette subfamily B 1 (ABCB1).[7] CsA is extensively bio-transformed to approximately 30 metabolites, the primary metabolites appear to be the monohydroxylated AM1 (M-17) and AM9 (M-1) and the N-demethylated AM4n (M-21).[8] These primary metabolites are produced by CYP3A4, whereas only AM9 is produced by CYP3A5.[9] An additional oxidation of AM1 and AM9 were shown to generate the dihydroxylated AM19 (M-8), AM49 (M- 10) and AM69 (M-16).[8] It has also been reported that the dissemination of cyclosporine and/or its major metabolites in the blood are CsA (27%), AM1 (24%), and AM9 (14%).[8]

CNIs nephrotoxicity

As matter of fact, the use of CNIs transfigure significant decrease in the incidence of acute rejection and also enhanced success of the short-term outcome of the renal allograft. Nonetheless, the acute and chronic nephrotoxicity of these drugs are deemed to be the Achilles' heel of current immunosuppressive regimens.[10] Nephrotoxicity, secondary to CNIs, occurs in 76%–94% of the renal transplant recipients.[11] The acute CNI nephrotoxicity, characterized by the renal vasoconstriction, is generally reversible that may cause diminished renal blood flow and glomerular filtration rate (GFR) and also renal dysfunction. In contrast, long-term exposure to CNIs may result in irreversible damage to the renal structure and function. The chronic nephrotoxic effects of CNIs are linked to irreversible morphological changes in arteriolar hyalinosis, interstitial fibrosis (IF) and tubular atrophy (TA), thickening and fibrosis of the Bowman's capsule, and glomerular sclerosis that lead to disruption of kidney function.[12,13] These changes may be mediated through alteration of nitric oxid synthase, TGF-β, endothelin-1, collagen I and IV, and Bcl-2 expression caused by CsA.[14]

Mechanisms of chronic nephrotoxicity of CsA

A cascade of events have been shown to impose somewhat implications in the development of chronic CsA nephrotoxicity, including (a) stimulation of inflammatory mediators, (b) an elevation in endothelin, thromboxane and angiotensin II, (c) a decrease in prostacyclin and nitric oxid, (d) an upregulation of TGF-β1, (e) enhanced immunogenicity and (f) inappropriate apoptosis.[15] Further, CsA was reported to induce an imbalance in the vasodilator/vasoconstrictor ratio leading to a minimized

generation of vasodilators (prostaglandins and nitric oxide) and maximized liberation of vasoconstrictors (endothelin and thromboxane), which ultimately can enhance the renal vasoconstriction.[16] In addition, CsA leads to the activation of renin–angiotensin system (RAS),[17] whose functionality promotes the renal interstitial fibrosis and the chronic CNI nephrotoxicity directly through (a) stimulation of tubular transport, (b) possible activation of pro-inflammatory phenomena, (c) release of aldosterone, and (d) augmented activity of profibrogenic and growth stimulatory functions. These effects are mediated through angiotensin receptors and also the induction of TGF-β.[18] Further, angiotensin II-induced aldosterone secretion participates in the development of IF/TA through increased renal vasoconstriction, TGF-β expression and apoptosis (Fig. 1). Interstitial fibrosis in CsA nephropathy is also associated with the infiltration of macrophages as well as the expression of osteopontin and TGF-β in the tubulointerstitium,[19] which seem to be caused by angiotensin II-dependent and independent mechanisms.[20] Furthermore, it should be pinpointed that the CNIs may increase the hypoxia in the kidney.[21] Local hypoxia or ischemia of the tubulointerstitial compartment causes the formation of free radicals or reactive oxygen species (ROS) that leads to apoptosis and tubular interstitial fibrosis.[22] The inhibition of calcineurin may directly activate the apoptosis-related genes[23] and/or augment the apoptosis phenomenon in the tubular and interstitial cells, resulting in tubular atrophy to some extend.[24]

An in vitro study identified the protein kinase C-β (PKC-β) that is a potentially key mediator of CsA nephrotoxicity, and possibly responsible for the upregulation of CsA-induced TGF-β1. E2A transcription factors E12/E47 may play a key role in the altered expression profile of CsA-treated cells and cell phenotype. These findings provide some conclusive insights into CsA-induced renal fibrosis and the molecular mechanisms involved in the epithelial-mesenchymal transition (EMT) phenomenon.[25]

In addition to diverse effects of CNIs, they lead to some inadvertent disturbances in the ion homeostasis and have an important effect on the metabolism of Mg^{+}. CsA decreases the reabsorption of Mg^{+} in the Henlé loop due to the reduction of paracellin-1 expression, therefore, causing severe hypomagnesemia. CsA-induced hypomagnesemia appears to facilitate the development of chronic IF through upregulation of fibrogenic molecules, which may activate the expression of tissue inhibitor of matrix metalloproteinase 1 (TIMMP1).[7,26] CsA is also one of the incisive causes of the post-transplant hyperuricemia and gout that is a painful disorder induced through some inflammatory reactions resulting in production of monosodium urate crystals in joint fluid and periarticular tissue. The urinary clearance of uric acid is decreased by CsA, in large part because of its inhibitory impacts on the tubular secretion of uric acid.[28]

Pharmacogenetics of immunosuppressive agents

Polymorphism of CNIs metabolizing enzymes

Growing evidences indicate that the pharmacogenetics parameters may delineate the inter-individual differences in terms of the intestinal absorption and bioavailability of drug, anti-rejection, susceptibility to development

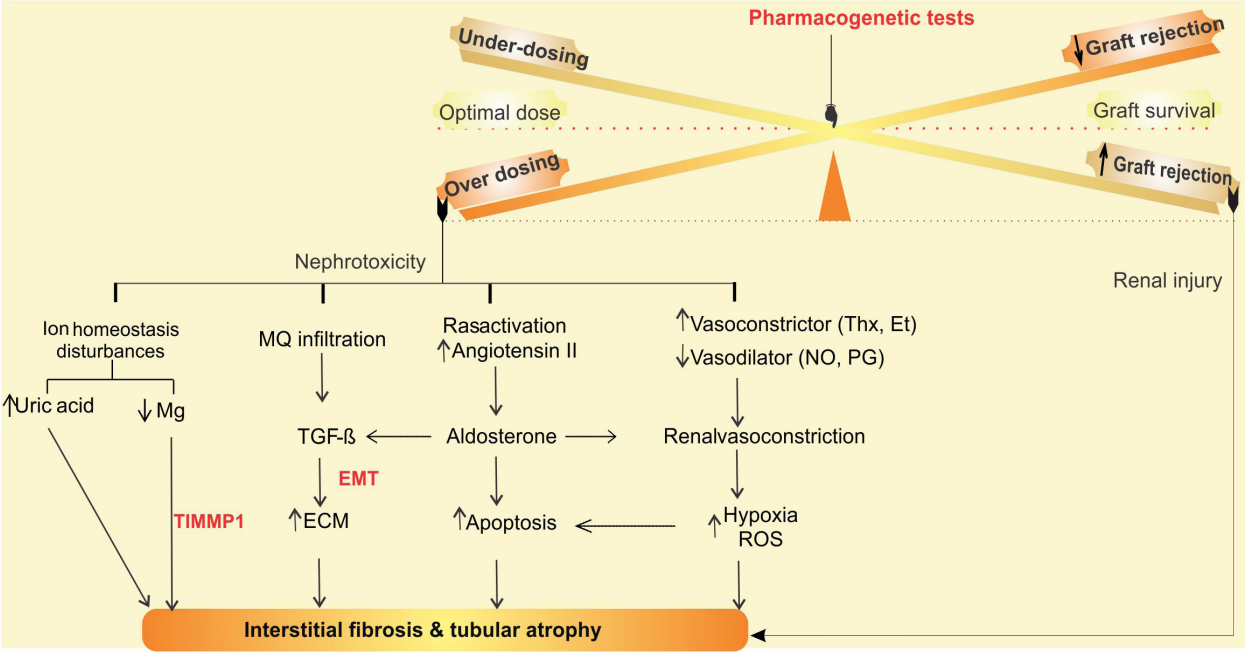

Fig. 1. Impact of CsA on nephrotoxicity and renal IF/TA. CsA is contributed in development of renal IFTA through different pathways. It promotes renal fibrosis through renal vasoconstriction and hypoxia. Moreover, it activates Ras and macrophage infiltration. Angiotensin II-induced aldosterone secretion participates in the development of IF/TA through increased renal vasoconstriction, TGF-β expression and apoptosis. CsA also disturbs Ion homeostasis and leads IFTA. CsA: cyclosporine, PG: prostaglandins, NO: nitric oxide, Thx: thromboxane, Et: endothelin, ROS: reactive oxygen species, RAS: renin–angiotensin system, EMT: epithelial-mesenchymal transition, MQ: macrophage, TIMMP1: tissue inhibitor of matrix metalloproteinase.

of the immunosuppressive-induced nephrotoxicity and fibrosis.[29] Given that the pharmacogenetics is the study of genetic variations which highlights the varying responses to drugs by different individuals, such information can be successfully applied for daily clinical practice and personalized therapies. Such approach not only improves the management of kidney transplantation but also lowers the number of patients with undesired adverse reactions.[30] Genetic polymorphisms of P-gp and CYP3A can influence their expression, activity, metabolism and production of CNIs metabolites and lead to individual differences in pharmacokinetics and pharmacodynamics of CNIs in organ recipients with different ethnic backgrounds. Subsequently, such molecular changes may impose undesired systemic and intra-renal metabolite exposures with some differential risk of nephrotoxicity to some extend depending on the longevity of exposures and the condition of patients. Tables 1 and 2 show detailed information upon genetic variations of cytochromes and ABCB1.

Due to a combination of genetic and non-genetic factors (e.g., hormones and health status) together with the environmental stimuli, the expression and activity of CYP3A appears to be different among individuals.[31] CYP3A4 is deemed to play a more dominant role in the metabolism of CsA and Tac. And, it is expected that environmental factors, rather than patient genotype, involve in variability of CYP3A4 expression.[32] Carriers of the CYP3A4*1B allele have been found to have significantly higher oral CsA clearance as compared to patients homozygous for CYP3A4*1A,[33] nonetheless this findings has yet to be reconfirmed by different studies. The CYP3A4 intron 6 C>T polymorphism (CYP3A4*22) is associated with altered Tac and CsA metabolism.[34,35] The CYP3A4*22 T-variant allele carriers with reduced CYP3A4 mRNA expression need a lower Tac dose requirement than the individuals with the CYP3A4*22 CC genotype, independent of CYP3A5 genotype status.[34] The CYP3A4*22 SNP and Tac dose requirement association was not found by other studies.[36,37] CYP3A4*22 also constitutes to be a risk factor for the delayed graft function and may impose worsened clearance of creatinine in patients under immunosuppressive (CsA) therapy.[38] However, recent studies indicated that CYP3A4*22 does not influence the pharmacokinetics of CsA, everolimus, or Tac to a clinically relevant extent.[37,39]

The functional expression of CYP3A5 in the kidney appears to have a protective impact on the renal dysfunction development, in large part through lowering the exposure of renal cells to CNIs.[7] Homozygous carriers of the CYP3A5*3 allele, possessing SNPs in the intron 3 of the CYP3A5 gene (genomic 6986A>G), may generate inadvertent mRNA splicing and a truncated and non-functional protein of CYP3A5, however high expression of CYP3A5 has been reported among the homozygous and heterozygous carriers of the wild-type CYP3A5*1 allele.[40] As a result, the metabolism and clearance of CNIs may be enhanced within the carriers of the CYP3A5*1 allele.[40,41] These patients may need administration higher doses of CsA to get the desired concentrations of drug in comparison with patients who are CYP3A5*3 variant homozygotes.[42]

It is reported that the carriers of CYP3A4*1/CYP3A5*1 expresser genotype were significantly more susceptible to the development of biopsy-confirmed Tac-mediated nephrotoxicity than non-carriers of the alleles (the CYP3A4*1/CYP3A5*3 genotype).[43] Patients with a poor CYP3A4/5 metabolizer status had the highest risk of being exposed to supratherapeutic Tac concentrations early after the transplantation.[34,35] Nevertheless, it should be pointed out that some CYP3A5 genotype studies in kidney recipients yielded contradictory results. A higher incidence of nephrotoxicity has been reported for the CYP3A5*3/*3 genotype recipients treated with Tac.[44,45] In such cases, it should be stated that, due to a different metabolite pattern over time, CYP3A5 6986A>G SNP may influence long-term survival of patients treated by CsA.[7,32] Song *et al.* determined several covariates that can affect the pharmacokinetics of CsA in renal transplant recipients of living donors. This includes postoperative days, sex, and the CYP3A5 genetic polymorphisms.[46] Recently, it is reported that CYP3A5*3 is only suitable as a predictive marker for Tac clearance and combined CYP3A4 and CYP3A5 genotypes do not improve the predictive performance.[39]

Factors effecting CYP3A4/5

In addition to the genetic polymorphisms, a multitude of epigenetic, environmental, and physiological factors are believed to influence the functional expression of CYP3A4/5 (Fig. 2A). Altered Cyp3A4/5 enzyme activities has been shown to associate with the P450 oxidoreductase (POR*28) allele, which may reasonably delineate the variability observed in CNI pharmacokinetics.[47] Moreover, nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα) variants explain 8–9 % of the variability in hepatic CYP3A activity in humans.[48] In the case of CYP3A5 expressers, POR*28 allele has been shown to associate with an increased in vivo activity of CYP3A5 for Tac, whereas in CYP3A5 non-expressers, POR*28 homozygosity is associated with a significant higher CYP3A4 activity for both Tac and CsA.[49] In a recent study by Lunde *et al.*, potential associations have been reported between the dose-adjusted concentrations of immunosuppressive drugs (i.e., Tac and CsA) and CYP3A5*3, CYP3A4*22, PPARA and POR*28 alleles in the renal transplant patients. The results showed that patients with POR*28 and PPARA variant alleles need respectively lower and higher doses of Tac. Furthermore, CsA was 53% higher among CYP3A4*22 carriers.[50] All these findings confirm that pre-transplantation CYP3A5, POR and PPARA genotyping can improve the initial dosing of Tac to a certain extent.

Drug interactions

Willrich *et al.* found that cholesterolemia status changes,

Table 1. Impacts of CYP3A4/5 polymorphisms on cyclosporine and tacrolimus pharmacodynamics

Gene	SNP	Recipients or donors	CNIs	Population	Results	Ref
CYP3A4	392A>G	-	-	-	Influence of the CYP3A4 392A>G SNP on the pharmacokinetics of either CsA or Tac is limited.	32
		Recipients		Caucasian	No relationship has been reported between recipient CYP3A4–392A>G genotype and the incidence of acute rejection or renal function.	51, 52
		Recipients	Tac	Caucasian, Asian, Black	No association has been shown between the CYP3A4-392A>G genotype and the rate of acute rejection, creatinine clearance, 1-year patient survival or graft loss.	53
	*1B (-290A>G)	Recipients	CsA	Caucasian & North Indian	This SNP has no influence on CsA levels or rejection episodes.	52, 54
		Recipients	Tac	Caucasian, Black, Asian & Korean	No association was seen between CYP3A4*1Bgenotype and Tac dose requirements.	55, 56
	*18B	Recipients	CsA	Chinese	Patients with a CYP3A4*1/*1 genotype were found to have a higher dose-adjusted concentration compared with those with CYP3A4*18B/*18B.	57
	*22 Intron 6,C>T				This allele is linked to a reduction in CYP3A4 mRNA production and enzyme activity in human livers.	
		Recipients	Tac	Caucasians	Patients carrying one or two T alleles required significantly lower Tac doses compared with patients homozygous for the wild-type C allele.	34
		Recipients	Tac	Brazilian	CYP3A4*22 was not associated with changes in tacrolimus dose requirements.	36
CYP3A5	*6986A>G* A>G/*1 (A) A>G/*3 (G)				Carriers of *1 allele have functional enzyme and require higher drug doses to reach target levels. Carriers of *3 allele have nonfunctional allele, the enzyme is not metabolizing the drug, so they need lower doses.	
	6986A>G	Recipients	CsA	Caucasian	No relationship was observed between the recipient CYP3A5 6986A>G genotype and the incidence of acute rejection.	51
		Recipients	CsA	German	No relationship was shown between recipient CYP3A5 6986A>G genotype and patient renal function.	58
		Recipients	CsA	Asian	Patients with *1*1*1*1 CYP3A5- and CYP3AP1-linked genotypes need higher doses of CsA as compared to the patients with *1*3*1*3 and *3*3*3*3 linked genotypes.	59
		Recipients	CsA	German	Patients with at least one CYP3A5*1 allele had a greater survival rate than CYP3A5*3 homozygotes (CYP3A5*3/*3 genotype is associated with decreased patient survival).	60, 58
		Recipients	Tac	Italian	The *3/*3 genotype in recipients is associated with a lowered incidence of acute rejection episodes and hypertension.	61
		Recipients	CsA, Tac	North India	No influence of CYP3A4*1B on CsA/Tac pharmacokinetics was found. CYP3A5 expressers were associated with significantly lower dose-adjusted CsA/Tac concentrations and higher allograft rejection episodes in patients on Tac therapy.	54
		Donors	CsA	German	No relationship was found between donor CYP3A5 6986A>G genotype and the nephrotoxicity.	58
CYP3A4, CYP3A4		Recipients	Tac	Chinese	Carriers of combined genotype of CYP3A4*1/*1-CYP3A5*3/*3 seem to require lower Tac doses to get the target concentration levels.	62
		Recipients	Tac	Caucasian	CYP3A4*1/*1+CYP3A5*1/*3 and CYP3A4*1/*1B+CYP3A5*1/3 genotypes in recipients are associated with a higher incidence of nephrotoxicity.	43

promoted by the administration of atorvastatin, play a key role in regulating the functional expression of CYP3A such as CYP3A4 and CYP3A5.[63] The effects of CNIs relatively are attributed to interactions with other drugs that inhibit or stimulate the functional expression cytochrome enzymes. CYP3A4 and CYP3A5 inhibitors (e.g., erythromycin, nefazodone, clarithromycin, diltiazem, grapefruit juice, itraconazole, ritonavir, ketoconazole, telithromycin, verapamil) and inducers (e.g., phenobarbital, carbamazepine, perforatum, phenobarbital, hypericum phenytoin, rifampin) can affect the pharmacokinetics properties of CNIs.[64] Taken all, any drug interaction possibilities should be taken into account in the renal transplant recipients.

Polymorphism of CNIs transporters

Since CNIs are substrate to functional efflux activity of ABCB1, variation in ABCB1 expression rate is thought to influence the plasma and/or intracellular concentrations of CNIs. Multidrug resistance-associated protein 2 (MRP2 or ABCC2) has a crucial impact on the pharmacokinetics of Tac in a haplotype-specific manner. MRP2 high-

Table 2. Impacts of *ABCB1* polymorphisms on cyclosporine and tacrolimus pharmacodynamics

Gene	SNP	Recipients, donors or both	CNIs	Population	Results	Ref
ABCB1	ABCB1 C>T; 3435 C>T				C: higher transporter activity, less drug absorption; T: lower transporter activity, more drug absorption.	
	3435C>T	Recipients	CsA	Caucasian	Homozygous TT genotype in recipients associated with enhanced incidence of acute rejection.	51
		Donors		German	Homozygous TT genotype in donor kidney associated with enhanced incidence of nephrotoxicity.	58
	1236C>T	Recipients	CsA	Caucasian	Homozygous TT genotype in recipients associated with enhanced incidence of acute rejection.	51
	12677G>T/A	Recipients	CsA	Caucasian	Homozygous TT genotype in recipients associated with enhanced incidence of acute rejection.	51
	12677G>T/A	Recipients/donors	CsA	German	ABCB1 genotype of the donor is a major risk factor for CsA-related nephrotoxicity after renal transplantation.	58
ABCB1	ABCB1 3435C>T; ABCB12677G>T/A	Recipients/donors	CsA	German	Haplotype 2677G-3435C in donor kidney associated with lowered incidence of nephrotoxicity.	58
ABCB1	ABCB13435C>T; ABCB1C1236T; ABCB12677G>T/A	Recipients	CsA/Tac	Czech & Caucasian	Haplotype 1236C-2677G-3435T is prone to an enhanced risk of acute rejection.	51,65

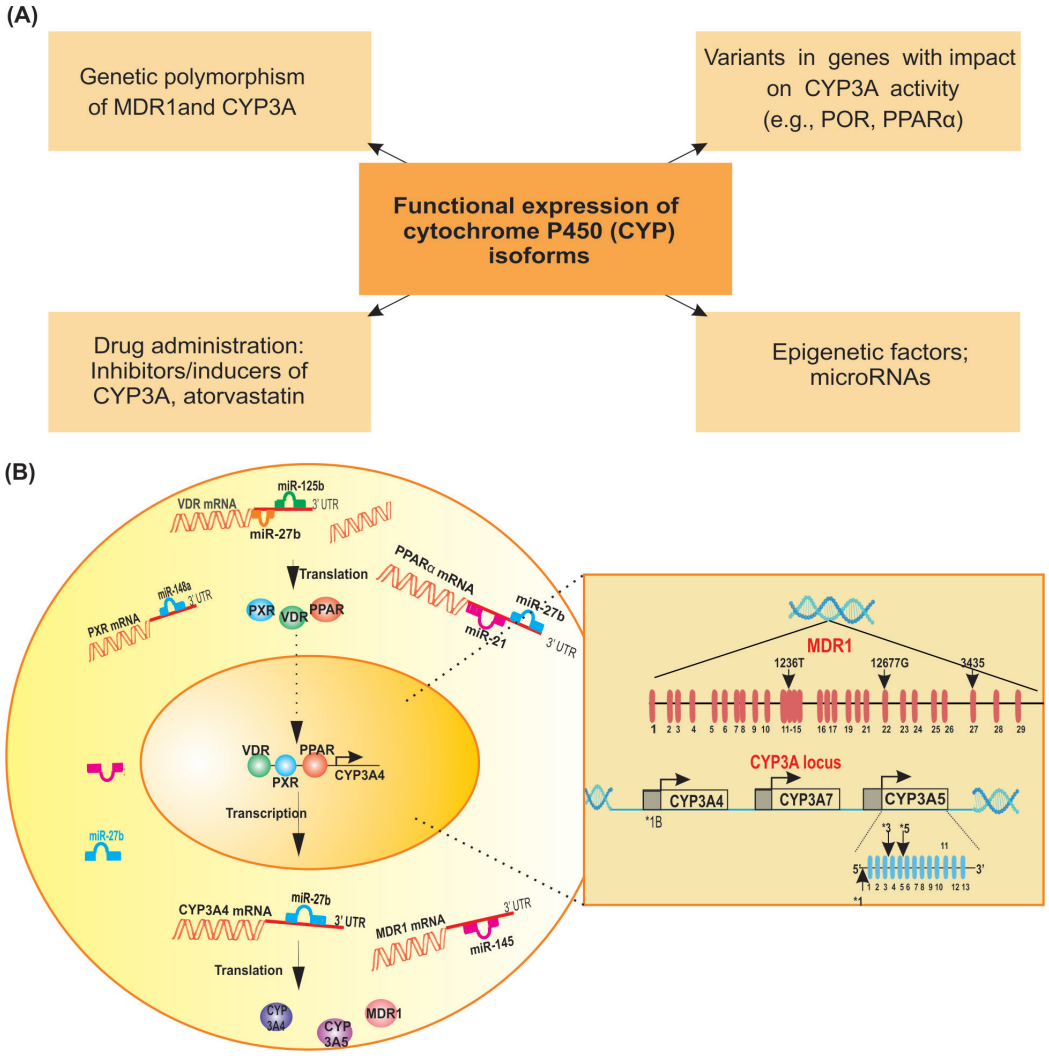

Fig. 2. Factors effecting the expression and activity of CYP3A4/5 and MDR1. A) Genetic polymorphism in MDR-1, CYP3A and in some other genes with indirect impact(s) on CYP3A activity, epigenetic mechanisms especially miRNAs along with other factors such as drug interaction(s) are involved in variable expression of CYPs. These factors cause inter-individual variability between recipients. B) MDR-1 and CYP3A4/5 genes polymorphisms and their mRNA regulation by miRNA are indicated; exons of genes are shown as pink bars. POR, P450 oxidoreductase; PPAR-alpha, nuclear receptor peroxisome proliferator-activated receptor alpha; VDR, vitamin D receptor.

activity recipients (i.e., ABCC2 H2/H2 and H1/H2) showed a significant decrease in Tac dose.[66] It should be evoked that the pharmacokinetics of Tac was found to be best described by a two-compartment model, in which the CYP3A5 expressers and MRP2 high activity groups were found to be the significant covariates for Tac.[66]

Reduced P-gp expression, in comparison with controls, has been shown in specimens with the structural signs of CNIs nephrotoxicity.[67] Naesens *et al.* has reported a significant association between donor and recipient ABCB1 genotype and histological signs of nephrotoxicity, defined by IF/TA.[68] Complementary evidence to these results has been reported by Woillard *et al.*[69] Moreover, Eap *et al.*, reported a "gene– environment" interaction, which may epitomize possible association between the CYP3A5 and ABCB1 genotype and blood pressure, plasma renin activity, plasma aldosterone and blood pressure response to treatment.[70]

The donor kidney genotype, rather than the recipient genotype, appears to play more imperative role in the nephrotoxicity development among the renal transplant patients.[7] The functional expressions of CYP3A5 and P-gp in the donor kidney may regulate the exposure of CNIs to the renal cells.[7] The impacts of CYP3A4, CYP3A5, and ABCB1 SNP on the pharmacokinetics properties of CsA and Tac have previously been well-reviewed in details by Staatz et al.[7,32]

Pharmacoepigenetics and microRNAs

The miRNAs, whose roles are yet to be fully understood, have clearly opened a new horizon in the field of pharmacogenetics and toxicogenomics. In fact, there exists an increasing interest for understanding of the miRNAs contribution to pharmacological outcomes. These biomolecules are a class of small endogenous and noncoding RNAs that are encoded by the genome and expressed in all animal cells. Approximately, 30–80% of human genes are predicted to be influenced by miRNAs.[71] Inter-individual variability in expression of some CYPs may be controlled by miRNAs and epigenetic mechanisms in addition to genetic factors. Thus, any genetic alterations at the mRNA target binding sites or at the miRNA precursor may contribute to a variable CYP expression.[72] It should be pointed out that the P450s and nuclear receptors have been reported to be regulated by miRNAs.[73]

The expression of CYP3A4 is regulated by several transcriptional factors including pregnane X receptor (PXR) and constitutive androstane receptor at the transcriptional level, and it seems to be modulated by miRNA at both the transcriptional/post-transcriptional levels.[74] The miR-27b targets the 3′UTR of CYP3A4 mRNA, and negatively regulates the protein expression CYP3A4.[74] CYP3A4 is also regulated indirectly by miR-148a that post-transcriptionally regulates PXR (Fig. 2B). Using in silico, in vitro and in vivo methods, Wei *et al.* concluded that the human CYP3A4 can be regulated by miR-577, miR-1, miR-532-3p and miR-627 in liver post-transcriptionally.[75] Moreover, the functional expression of P-gp is regulated by miRNA-145 in the intestinal epithelial cells post-transcriptionally.[76] Since the expression of miRNAs is altered by endogenous and exogenous factors (e.g., chemicals, drugs, hormones, stress and diseases), their dysregulation might lead to some inevitable alterations in the drug metabolism potency or pharmacokinetics properties.

Final remarks and conclusion

Genetic polymorphism(s) can influence the metabolism of CNIs (CsA and Tac) and the production of metabolites that cause profound systemic and intra-renal exposure to drug/metabolites, and hence differential risks of nephrotoxicity. As a result, genotyping of the CYP3A isotypes and the carrier-mediated transporters involved in the efflux of the CNIs (e.g., P-gp, MRP) in the kidney-transplant patients can be a putative indicator and potential means for the advancement of pharmacogenetics strategies towards much more personalized pharmacotherapy regimens and TDMs. In fact, pharmacogenetics, toxicogenomics and epigenetics characteristics must be taken into account in order to use the appropriate administration of CNIs in patients with high risks of kidney transplantation. It should be noted that most pharmacological effects are polygenic in nature and several genetic variants and epigenetic factors (age, renal/hepatic function, disease seriousness, co-administrated drug therapies and their interactions, differences in diet, and habits) are often responsible for the intra- and inter-individual variability seen after drug administration. The pharmacogenetics of some other CYP isotypes such as CYP2D6 are also very important in different races, regions and diseases.[77] Taken all, prior to the organ transplantation, the pharmacogenetics examinations upon the functional expression and activity of cytochrome P450 isotypes and efflux transport machineries, respectively responsible for metabolism and efflux of immunosuppressive drugs, appear to be the central factor for an optimized administration of CNIs with maximized efficacy and minimized side effects and ultimately successful treatment of the kidney recipients.

In short, implementation of such strategy in kidney-transplant patients can lead to an efficient personalized administration of CNIs with minimized nephrotoxicity and rejection incidence.

Acknowledgments

This work was fully supported by the Research Center for Pharmaceutical Nanotechnology at Tabriz University of Medical Sciences (Thesis No: 92/4-5/6).

Ethical issues

No ethical issues to be declared.

Competing interests

The authors declare no competing interests.

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Review Highlights

What is current knowledge?

√ Genetic polymorphisms alter the metabolism pattern of immunosuppressive agents such as calcineurin inhibitors.

√ There exist profound systemic and intra-renal exposure to drug/metabolites with differential risks of nephrotoxicity in the kidney-recipient patients.

√ Multidrug resistance protein (MDR1, ABCB1 or P-gp), multidrug resistance-associated protein 2 (MRP2 or ABCC2) and cytochrome P4503A (CYP3A) are responsible for the efflux and metabolism of CNIs.

What is new here?

√ Pharmacogenetics information of CYP3A and ABCB1/ ABCC2 is a putative indicator for the pharmacotherapy regimen and TDM in the kidney-transplant patients.

√ Personalized pharmacotherapy of CNIs is plausible in the kidney-transplant patients.

√ Genotyping of CYP3A and ABCB1/ ABCC2 in the kidney-transplant patients.

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