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Review article

Calcineurin Inhibitor - A Necessary Evil: Pharmacogenetical Approach to a Promising Future

Lexi Zhang[1], Chenli Gu[2], Shang Huang[1], Ruiming Rong[1]* and Tongyu Zhu[1]*

[1]*Department of Urology, Fudan University, China*
[2]*Shanghai Key Laboratory of Organ Transplantation, China*

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***Corresponding author**

Ruiming Rong and Tongyu Zhu, Department of Urology, Zhongshan Hospital, Fudan University, Shanghai Key Laboratory of Organ Transplantation, #180 Fenglin Road, Shanghai, 200032, China, Email: guchenli89@126.com

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Abstract

The backbone of modern immunosuppressant regimens after kidney transplantation is Calcineurin Channel Inhibitor (CNI) drugs including tacrolimus and cyclosporine A. Its mechanism is binding to immunophilins, forming complexes, binding to calcineurin, and leading to inhibition of T cell activation. Since CNI drugs are eliminated by cytochrome P450 system, especially the CYP3A subfamily, exploring their interaction exhibits great importance. It is known that CYP3A4 and CYP3A5 are involved in tacrolimus metabolism while CYP3A5 alone plays a major role in cyclosporine A metabolism. The polymorphism of CYP3A4 and CYP3A5 genes results in different CNI drugs dose requirements in transplant recipients. Pharmacogenetic approaches to figure out donors' and recipients' CYP3A4 and CYP3A5 genotypes may give us better understanding of pharmacodynamics of CNI drugs. Additionally, monitoring CNI blood concentration can reflect its pharmacokinetics. Combination of pharmacodynamics and pharmacokinetics may be used as a guide in clinical practice to administer CNI drugs in optimal dose, to avoid acute rejection or adverse effects of CNI drugs such as nephrotoxicity.

Introduction

Solid organ transplantation is a promising treatment for patients with end-stage renal failure, and the use of immunosuppressive agents, such as cyclosporine and tacrolimus, has decreased the acute rejection rate and increased graft survival. However, the long-term graft and patient survival rates have remained unchanged. This finding is mainly correlated with the imbalance caused by the chronic use of immunosuppressant, which can corrode the graft and hinder normal physiology. Individualized therapy that provides adequate immunosuppressant and limits adverse drug effects is crucial for graft survival. TDM (Therapeutic Drug Monitoring) is a universally accepted method that is used to approximate individualized drug therapy in the transplant patient. Efforts to design more appropriate methods that enhance this current practice are in progress. There has been success in identifying target genes that impact the pharmacokinetics of CNI (Calcineurin Channel Inhibitor) and other commonly used immunosuppressant's. We hope that in the near future, the information obtained through the genetic analysis of a patient will aid in the selection of the drugs and therapeutic doses that are necessary to show efficacy but limit toxicity.

Transplantation and Evolution of CNI

The first Successful kidney transplantation, which was performed between identical twins in 1954, opened a new era in modern medicine and proved to be an effective therapy for end-stage renal disease. Since then, the field of kidney transplantation has advanced with improved graft outcomes, reduced rates of Acute Rejection (AR) and increased patient survival [1]. The reason for this success can be attributed to the use of drugs that inhibit the immune response and prevent rejection. Combined immunosuppressive therapy, which consists of a CNI such as Cyclosporine A (CsA) or Tacrolimus (Tac), an anti-proliferative agent (i.e., mycophenolate) and glucocorticoids, is the predominant post-transplant therapeutic regimen in current practice.

The introduction of cyclosporine in the early 1980s and tacrolimus in the mid-1980s was a breakthrough in modern medicine, especially in transplant medicine. Cyclosporine and tacrolimus share the same pharmacodynamic property, which is the suppression of activated T cells by inhibiting the protein calcineurin. The addition of CNIs to the list of immunosuppressive drugs led to a dramatic improvement in graft outcomes in organ transplant recipients [2,3]. Cyclosporine was widely used because of its weak myelotoxicity compared to other available immunosuppressants and cytostatic drugs in that era (Figure 1) [4].

Structure and The Mechanism of Action of CNIs

Cyclosporine is a cyclic endecapeptide (molecular mass of 1203kDa) that includes N-methylated amino acids that make the molecule resistant to inactivation by the gastrointestinal tract; it can therefore be used as an oral immunosuppressive drug [4]. Tacrolimus is a macrolide antibiotic

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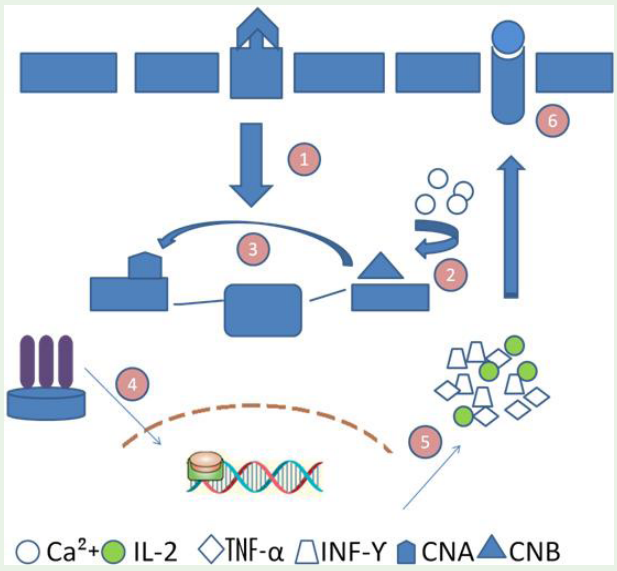

Figure 1: The role of calcineurin in T-cell activation. TCR stimulation by an alloantigen (step 1) leads to an increase in intracellular calcium concentration (step 2), which activates CnB (step 3). Once activated, CnB unleashes the phosphatase activity of CnA. Activated CnA dephosphorylates cytoplasmic NFATc, a transcription factor, thereby allowing for its translocation, along with activated calcineurin, into the nucleus (step 4), where it upregulates the expression of multiple cytokines and costimulatory molecules necessary for full T-cell activation (step 5). The cytokine IL-2 binds to IL-2 receptors and induces cell activation and proliferation (step 6).

(molecular mass of 804kDa). Although it is more soluble in water than is cyclosporine, it is also highly soluble in lipids and other organic solvents. Immunophilins are the intracellular proteins to which CNIs bind. These include the cyclophilins, which CsA binds, and the FK-binding proteins, which tacrolimus (also known as FK506) binds. These complexes then bind to an intracellular molecule called calcineurin, leading to an inhibition of its activity and thus inhibiting T-cell activation [5]. Calcineurin consists of two subunits: A, a Catalytic Subunit (CnA) that is responsible for the phosphatase activity of calcineurin, and B, a Regulatory Subunit (CnB) that is particularly responsive to intracellular calcium and regulates CnA activation [6-9]. TCR or T cell receptor, which binds to antigen-major histocompatibility complex molecules, is responsible for antigen recognizing. The intracellular calcium concentration increases when T cells are activated following TCR stimulation. This calcium increase activates CnB, which unleashes the phosphatase activity of CnA. The activated CnA then dephosphorylates cytoplasmic NFATc, (Nuclear factor of activated T-cells) causing it to translocate, along with the activated calcineurin, into the nucleus. Finally, the T cell is activated and expresses multiple cytokines and other costimulatory molecules. In particular, the production of the cytokine IL-2 stimulates the growth and differentiation of T cells [10]. The cyclophilin/CsA and FK-binding protein/FK complexes directly bind to CnA and inhibit its phosphatase activity.

Genomics in Metabolism of CNI

Cyclosporine

Phase-I metabolism by the Cytochrome P450 (CYP450) system, specifically the CYP3A subfamily [11], is the main mechanism for CsA elimination. Functional activity of CYP3A is determined through three isoenzymes: CYP3A4, CYP3A5, and CYP3A7. CsA is primarily metabolised by CYP3A4 with a limited role of CYP3A5 [12]. Both CYP3A4 and CYP3A5 are characterized by large variations in their activity and expression, which are caused by genetics or through interactions with other substances. For CYP3A5, the CYP3A5*3 allele is fully characterized. CYP3A5*3 is considered a candidate gene that is responsible for the genetic differences observed in CsA metabolism because of the functional defect associated with this allele. Different studies evaluating the CYP3A4 gene have been performed in renal transplant recipients to specifically identify the impact of CYP3A4*1B on CsA metabolism. In the work by Min DI and Ellingrod VL., the presence of a CYP3A4*1B 5'-flanking region polymorphism was found to affect cyclosporine pharmacokinetics in 14 healthy volunteers. CYP3A4*1/*1 homozygous individuals showed a higher dose-adjusted area-under the CsA concentration versus time-curve (AUC) and a lower oral clearance (CL/F) after a single drug administration compared with individuals who were homozygous for the variant allele [13]. This finding is in agreement with the increased expression associated with this Single-Nucleotide Polymorphism (SNP) [14]. Recent published work has associated a higher CsA dose requirement in CYP3A4*1B carriers compared to non-carriers [15]. These inconsistencies observed for the association between CsA PK and the CYP3A4*1B variant allele may be due to the Linkage Disequilibrium (LD) observed with the CYP3A5*1-expressing allele. In a study by Hu et al., which evaluated the effect of CYP3A5*3 on CsA PK during the first week after transplantation in 106 Chinese patients [16], and in a similar study in 224 north Indian transplant recipients, CYP3A5 expressers demonstrated a higher dose requirement at months one and three after transplantation than did the non-expressers [17].

Chinese population study by Zheng et al., observed that the mean oral CsA CL/F (Cl/F = Dose / AUC0-∞) was similar between CYP3A5 expressers and non-expressers but that the average AUC (area under concentration-time curve) for the CsA metabolites were 51.3% higher in CYP3A5 expressers, corresponding to 30% higher metabolite ratios in these individuals [18]. It is well established that CYP3A5 is expressed in the kidney [19]. Based on the work of Haehner BD and his colleagues, who demonstrated a mean apparent urinary clearance that was lower among CYP3A5 expressers compared with non-expressers, it can be speculated that the intra-renal accumulation of CsA and its metabolite might depend on CYP3A5 expression. This observation therefore indicates that a CYP3A5 genotype is important to consider for its impact on CsA-related nephrotoxicity. In studies conducted on Caucasian patients, Hesselink et al. demonstrated a significant influence of a CYP3A5 genotype on CsA dose requirement at month 12 after transplantation, and this result was confirmed by Haufroid et al., who demonstrated that 23 CYP3A5*1 carriers had a somewhat lower CsA dose-adjusted trough concentration (C0) compared with CYP3A5*3/*3 patients [20]. A recent study suggests increased CsA clearance occurs in healthy Asian individuals carrying the CYP3A4*18B allele [16,21,22]. This effect of the CYP3A4*18B allele on CsA metabolism has been successfully repeated in Chinese renal transplant recipients, but only when CsA dose-adjusted peak concentration (C2), not dose-adjusted C0, was considered. Larger clinical studies to validate the importance of the CYP3A4*18B allele in Asian kidney transplant recipients treated with CsA should not be denied.

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Tacrolimus

Both CYP3A4 and CYP3A5 are involved in the oxidative metabolism of Tacrolimus; however, CYP3A5 is a more potent catalyst compared to CYP3A4. Kamdem LK et al. reported that CYP3A5 has a 1.6-fold higher *in vitro* catalytic activity towards Tac than does CYP3A4 [23]. Earlier studies have confirmed that CYP3A5 expressers require a two-fold higher Tac dose to reach the same steady state C0 as CYP3A5 non-expressers, indicating that Tac CYP3A5-mediated metabolism is higher in CYP3A5-expressing individuals [24-36]. It has also been shown that there is a delay in achieving the target Tac C0 in the blood of CYP3A5 expressers compared with that of non-expressers, despite the use of the same TDM scheme [37]. This observation allows us to rapidly achieve target concentrations and can be used as a guideline in clinical practice to acquire optimal drug doses and avoid Acute Rejection (AR) in the early stages of transplantation [38,39]. The variety of metabolic defects caused by the CYP3A5*3/*3 allele is not only independent of influencing factors such as the transplant population or the PK parameter analyzed (AUC, CL/F, C0), but it is also independent of the age, ethnicity and gender of the patients and the time after transplantation. Birdwell et al. reported that among a panel of more than 2000 SNPs involved in the Absorption, Distribution, Metabolism and Excretion (ADME) pathway (which did not include the CYP3A4*22 allele), no variants other than CYP3A5*3 were significantly correlated with the dose-adjusted Tac C0 [40]. Likewise Elens et al. concluded in two independent studies that the required Tac dose was significantly lower for CYP3A4*22 carriers compared to individuals homozygous for CYP3A4*1/*1 [41]. This observation is in accordance with the reduced activity related to this SNP [42].

CNI-based immunosuppressive therapy seems to be a double-edged sword: CNIs not only improve patient and graft survival but may also cause chronic side effects with its long-term use. Physicians are under pressure to manage the precise dose of these drugs for the following reason:

Low levels of immunosuppression in the acute post-transplant period increases the risk of rejection [39,43], whereas increased exposure to calcineurin inhibitors and corticosteroids increases the risk for adverse effects [44,45]. These adverse effects include nephrotoxicity and malignancy, and new-onset diabetes mellitus after transplantation is particularly associated with tacrolimus use.

Nephrotoxicity of CNIs

The nephrotoxicity associated with the use of cyclosporine that was reported in early human studies remains a major concern of experts in transplant medicine [46]. Tremendous work has been performed to explain the pathophysiology of cyclosporine's nephrotoxicity. Functional abnormalities involving the pathology of renal vasculature or renal tubules may be due to an imbalance between vasoconstrictive and vasodilatory mediators, an activation of the renin-angiotensin-aldosterone system [47], an increase in the release of endothelin [48] or free radicals [4], and sympathetic nerve activation in the native kidneys through synapsin effects [49]. Abnormalities also involve different anatomical structures of the kidney. Irreversible arterial hyalinosis results from the prolonged vasoconstriction or regulation of NFAT and smooth muscle [50]. Tubulointerstitial injuries (stripped fibrosis) and tubular atrophy are multifactorial in origin, resulting from an increase in free radicals [51], an upregulation of TGF-β [52] and subsequent epithelial to mesenchymal transition [53], or an activation of the renin angiotensin-aldosterone system with an increase in aldosterone [54]. The main glomerular lesions include global glomerulosclerosis due to secondary ischemia [55] and focal segmental glomerulosclerosis secondary to hyperfiltration injury [3]. Aldosterone, whose antagonists may prevent the functional or structural renal lesions, has been described to play a major role in CNI toxicity [3]. Many parameters contribute to CNI nephrotoxicity, including the serum concentration of the drug [56]. However, there is also an individual susceptibility to chronic nephrotoxicity because chronic histological changes have been observed at low-dose levels [57] and because significant graft dysfunction has not developed in some patients exposed to high-dose levels [47]. Neurotoxicity, adverse effects on the central and peripheral nervous systems, is another major side effect observed with cyclosporine use. Peripheral tremors are common, and headaches may be severe and recurrent. Additional severe symptoms may occur shortly after starting cyclosporine and include seizures, encephalopathy, extrapyramidal syndrome or posterior leukoencephalopathy [58]. The notable adverse effects associated with tacrolimus include an increased risk for New-Onset Diabetes after Transplant (NODAT), neurological toxicities and electrolyte disturbances.

Finally, the role of exposure to CNI metabolites and their widespread adverse late effects on the graft and the patient remains the core focus of future studies.

Current Approaches in the Measurement of CNI

Therapeutic Drug Monitoring (TDM), which is the most clinically applicable method for immunosuppressant titration, with subsequent dose adaptation is an indispensable tool for maintaining the CNI doses within their therapeutic window and is universally accepted. TDM only provides pharmacokinetic information, and the correlation between pharmacokinetics and pharmacodynamics remains controversial [59]. Moreover, the narrow therapeutic index of these medications is further affected by inter-individual variability in pharmacokinetic and pharmacodynamic responses and is subject to drug–drug and drug–disease interactions [60]. The limitations of TDM include a delayed ability to achieve adequate levels of immunosuppression early post-transplant [61] and a failure to consistently predict episodes of rejection or toxicity. Blood concentrations of the calcineurin inhibitors (cyclosporine and tacrolimus) are routinely evaluated by measuring the Calcineurin (CN) phosphatase activity, which is a complementary pharmacodynamic approach to optimize CNI dosage at the patient's molecular target. Due to the lack of a simple and high-throughput assay, only a few studies have been conducted to monitor this enzymatic activity. CN activity was measured in the different blood cellular fractions from five healthy volunteers in a study by Blanchet et al. [62]. Peripheral Blood Mononuclear Cells (PBMCs) proved to be a suitable matrix for measuring CN activity. An activity of 228.8 (27.4) pmol peptide/min/106 PBMCs was reported, and *in vitro* addition of tacrolimus inhibited this activity by 50%. CN activity was also significantly reduced in PBMCs collected from patients with alcoholic cirrhosis or hepatocellular carcinoma, and who are candidates for liver transplantation, compared to healthy volunteers [63,64]. A study carried out by Sanquer et al. [65] used a spectrophotometric CN activity assay to measure calcineurin activity in PBMCs from 107 patients two years after lung transplantation and showed no correlation between the blood CsA concentration and CN

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activity. Interestingly, the risk of acute rejection was higher when the enzyme activity was above the upper threshold of 102pmol/mg/min or below the lower threshold of 12pmol/mg/min. Moreover, the risk of malignancy and viral infection was higher in patients with low CN activity [12]. To address the high variability in results obtained using PBMCs, Caruso et al. [66] explored calcineurin activity in whole blood, and the reported CVs (Coefficient of Variation) for measurement of CN activity in whole-blood extracts were lower than those for PBMC extracts from the same individuals. However, the CsA trough concentrations from kidney transplant patients (n=15) failed to predict CN activity. Due to the lack of a solid correlation between CNI concentrations and calcineurin activity in long-term users of CNIs, Pena et al. [67] investigated the quantitative expression of the different isoforms of Calcineurin Catalytic Subunits (CNA) using isoform-specific antibodies. Interestingly, the CNA β isoform was found in lower quantities in transplant patients, particularly those with no acute rejection, compared with healthy controls. Unfortunately, no isoform-specific calcineurin substrate has been discovered [67]. Using Liquid Chromatography-Multiple Reaction Monitoring Mass Spectrometry (LC-MRMMS) Carr et al. [68] quantified CN activity by measuring the dephosphorylation of a synthetic phosphopeptide substrate. The assay was used to determine CN activity in Peripheral Blood Mononuclear Cells (PBMCs) isolated from 20 CNI-treated kidney transplant patients and nine healthy volunteers. Linearity was observed from 0.16 to 2.5mol/L of product peptide with accuracy in the 15% tolerance range. Although a spread of activities was also observed in tacrolimus-treated patients, the activities of CsA-treated patients were more homogeneous.

Clinical Relation between CYP3A5 and CNI

Studies have shown significant relation between CYP3A5 polymorphism and CNI, especially tacrolimus. CYP3A5 could affect early dose of tacrolimus greatly. In a clinical study conducted by Bruckmueller et al. [69], CYP3A4, CYP3A5 and age explained 18.3% of the inter individual variability of tacrolimus trough concentration/dose ratios. The authors found genotyping of CYP3A5 and CYP3A4 could facilitate rapid dose finding to adapt the appropriate immunosuppressant dose, whereas other genetic factors had only little or no effects. By using therapeutic drug monitoring, Niioka et al. [70] showed the influence of the CYP3A5polymorphism on the tacrolimus maintenance dosage became evident after Day 14 post-transplantation, although the tacrolimus dosage was determined based only on patient body weight the first three days after surgery. These results suggested measurement of CYP3A5 polymorphism in clinical settings to determine the early dose of CNIs. However the studies on CYP3A5 and precise initial tacrolimus dose to achieve optimal trough concentration still lack. On the other side, CYP3A5 polymorphism is not associated to graft survival, cancer occurrence, or delayed graft function according to Traynor et al. [71], which lowered the importance of genotyping. The assessment of pharmacogenomic factors, in addition to TDM, may help overcome some of these challenges by providing a method to better predict an initial immunosuppressant dose, identifying patients at a higher risk of certain adverse effects, and predicting patients who are more likely to experience AR due to a lack of drug response. It is noteworthy that implementation of CYP3A5 polymorphism measurement should be comprehensively evaluated due to its impact on CNI doses, prognosis of patient and graft, cost and other aspects since some studies have shown controversies.

Conclusion

Because thousands of transplant recipients worldwide still rely on CNIs, continuous efforts have been made to develop new drugs with a low nephrotoxic profile or new methods that minimize or eliminate CNI treatment during the post-transplant period. These developments would reduce toxicity and maintain the required concentration of drug in the blood. However, CNI-based regimens remain the backbone of modern therapy for transplantation. Thus, the best option would be to formulate a safer and more effective individualized approach to monitor the CNI therapeutic window. This would provide a better way to evaluate these agents and help minimize immunosuppression while preserving graft function and increasing survival. A pharmacogenetic approach seems to be a very optimistic way to rationally achieve the goal.

As discussed above, there is a strong correlation between different genetic polymorphisms and CNI metabolism. Therefore, developing genetic monitoring of the drugs should be a focus of future research. Both CYP3A4 and CYP3A5 are involved in Tac oxidative metabolism. In contrast to CsA, CYP3A5 is a more competent catalyst than CYP3A4 for Tac. CYP3A5 shows an *in vitro* catalytic activity towards Tac, which is 1.6-fold higher than CYP3A4 [23].

The kidney transplantation is unique because there is a greater chance the CYP3A genotype of the donor kidney might differ from the genotype of the recipient. As local drug concentrations within the targeted organ are important to explain individual susceptibility to (adverse drug reactions) ADRs, the CYP3A5 donor genotype (i.e., that of the transplanted kidney) may influence a kidney transplant patient's susceptibility to the nephrotoxic effects of CNIs more than the recipient CYP3A5 genotype. Current research is limited on donor genotype, and very few data exist regarding the impact of the donor CYP3A5 genotype on CsA-related nephrotoxicity

The fact that CYP3A5 expressers require a two-fold higher Tac dose to reach the same steady state C0 as CYP3A5 non-expressers indicates a higher CYP3A5-mediated metabolism of Tac in CYP3A5-expressing individuals, and this observation has been repeated in other studies [24-36]. Despite the assessment of drug concentration through TDM, a delay in achieving target blood Tac C0 for CYP3A5 expressers was observed when compared to non-expressers [37]. This observation advocates the benefits of a pharmacogenetic dosing strategy, which in this case would adjust the initial Tac dose administered to CYP3A5 expressers to be two-fold higher, such that the targeted concentration is achieved more rapidly. This is a promising strategy, particularly for minimizing AR occurrence by achieving optimal drug exposure during the early days after transplantation [38,39].

Thervet et al. conducted a Randomised Clinical Trial (RCT) to evaluate whether new dosing guidelines based on the CYP3A5 genotype would allow target blood concentrations, as defined by a therapeutic window ranging from 10 to 15ng/ml, to be achieved earlier and result in an amelioration of the overall clinical response [32]. The study concluded that using a priori CYP3A5 genotyping to adapt the Tac starting dose is beneficial it resulted in a more rapid achievement of the target Tac C0 and required fewer dose adjustments than needed with the universal starting dose of 0.1mg/kg twice daily. This study failed to give any clinical significance assessed by the incidence of AR and Delay Graft Function (DGF). This observation

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suggests that factors other than the CYP3A5 genotype may explain the between-patient variability observed in Tac pharmacokinetics which might allow a dosing algorithm with high predictive performance to be established. In a meta-analysis, Tang HL et al. concluded that the increased risk for the early episodes of AR (<3 months after transplantation) observed in CYP3A5 expressers was due to the longer time needed to achieve the optimal Tac levels during the first week of therapy compared with CYP3A5 non-expressers.

In reference to the published literature to date for CNIs, especially tacrolimus, there is evidence to support a potential benefit of pharmacogenetic testing before starting a CNI-based immunosuppressive treatment following kidney transplantation. For Tac therapy, there is a greater potential the recipient's CYP3A5*3 allele will be screened in every patient. It should be noted that TDM clearly moderates the potential benefit of a genotype-based adjustment, as the routine use of TDM allows the clinician to bring the majority of patients within the targeted C0 window rapidly after the first Tac administration (i.e., within 10 days). We carried out a similar study in our centre to evaluate the effects of CYP2D on Cyclosporine in sixty-nine kidney transplant patient. The results (to be published) CYP2D6 100C > T polymorphism was correlated with CsA dosing, wild-type genotype carriers required higher doses of CsA. We also noticed that CYP2D6 100C> T polymorphism is not a complete predicator for the necessity of personalized CsA treatment. Pharmacogenetic analysis of the recipient genotype seems of limited value in CsA therapy. The pharmacogenetic approach is still in its primary stages so it may only aid in identifying patients at risk for intra-renal accumulation of the CsA or Tac drug. This approach may also rule out the possibility of identifying patients at risk for CNI-related nephrotoxicity and adjust or change the immunosuppressive regimen. In view of the reported data, pharmacogenetic screening may help the clinician define a better dosage plan for Tac compared with the universal dosage that is currently prescribed.

Future Prospects

Although the introduction of CNI therapy was a great achievement, the transplantation community still needs extensive efforts to make transplantation free of immunosuppressive agents. During this transition period, choosing the suitable immunosuppressive therapy will remain a complex process. Evaluating the safety of immunosuppressive drugs is a major challenge because kidney transplantation requires the simultaneous use of multiple classes of drugs at varying doses.

Thus, precise and accurate modes of drug evaluation should be developed to assist TDM. A pharmacogenetic approach to therapy is promising because it helps explain the inter-individual variations observed in the pharmacokinetics and pharmacodynamics of CNIs, and it would identify high-risk patients who may benefit from alternative dosage or drug regimens before therapy begins. Therefore, pharmacogenetics may be used complementarily with TDM to optimize immunosuppressive treatment, improve effectiveness and reduce adverse drug reactions.

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