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# Pharmacogenetics and Renal Transplantation

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## 1. Introduction

Different patients receiving the same dose of a drug can exhibit a wide range of blood concentrations. This is a main concern regarding the immunosuppressive drugs because of their narrow therapeutic indices. Subtherapeutic blood concentrations are associated with an increased risk of acute rejection while overdosing may increase the risk of over-immunosuppression, with subsequent increased risk of infection and malignancies. Moreover, there are also numerous drug-specific adverse effects. At present, therapeutic drug monitoring (TDM) is used to address the issue of inter-individual variation in pharmacokinetics of immunosuppressive agents. However, TDM cannot influence drug exposure during the first 2-3 days after transplantation. Thus many patients experience a significant delay in achieving target blood concentrations, significantly increasing the risk of acute graft rejection (Clase et al., 2002; Undre et al., 1999). The narrow therapeutic index of these agents prevents use of a strategy based on a higher initial dose for all patients. As a result, there is a clear need for a strategy to allow individualized immunosuppressive drug dosing in the immediate post-transplant period.

After administration, the drug is absorbed and distributed to its site of action, where it interacts with targets such as receptors and enzymes, undergoes metabolism, and is then excreted. Each of these processes might involve clinically significant genetic variations. In the general population, it is estimated that genetics accounts for 20% to 95% of the variability in drug disposition and effects (Kalow et al., 1998). Other non-genetic factors, such as hepatic or renal function, drug interactions, and nature of diseases will also influence the effects of medication. With the introduction of tools for genomic analysis, the DNA variants responsible for the differences in drug-metabolizing capacities were discovered. Subsequently, individuals can be characterized as efficient or poor metabolizers for a particular drug based on their gene polymorphisms encoding protein variants that metabolize the drug. The genetic polymorphisms in drug-metabolizing enzymes together with drug transporters and drug receptors led to the hypothesis that genetic factors may be implicated in the inter-individual variability of the pharmacokinetic or pharmacodynamic characteristics of immunosuppressive drugs, major side effects, and immunologic risks.

By definition, pharmacogenetics is the study of genetic variation that gives rise to differing responses to drugs, whereas pharmacogenomics is the application of genomic technologies to drug discovery (Goldstein et al., 2003; Phillips & Van Bebber, 2005; Stoughton & Friend, 2005). Nowadays, the two terms are often used interchangeably. The promising role of pharmacogenetics and pharmacogenomics illustrates the concept of personalized medicine,

in which the characterization of the patients' genotype may help to identify the right drug and dose for each patient. The wider use of pharmacogenetic testing is also currently viewed as an important tool to improve drug safety and efficacy (Hesselink et al., 2005a; Shastry, 2005).

## 2. Pharmacokinetics and pharmacogenetics

The relationship between genetic variation and drug response was first observed in the 1950s for drugs metabolized by N-acetyltransferase. Based on the blood concentrations of drugs metabolized by this enzyme, patients were classified into "fast and slow acetylators". However, the molecular genetic basis for such inherited traits began to be elucidated only in the late 1980s, with the initial cloning and characterization of polymorphic human genes encoding for drug metabolizing enzymes.

Whether pharmacogenetics can be applied successfully in daily clinical practice depends on our understanding of the enzymes which metabolize the drugs. When a drug is administered, it is first absorbed in the intestine, and different proteins in the intestinal wall can determine the amount that finally passes into the blood. The calcineurin inhibitors (CNIs), the mammalian target of rapamycin (mTOR) inhibitors and corticosteroids are all metabolized by the oxidative enzymes in the cytochrome (CYP) 3A family (Dai et al., 2004, 2006; Kamdem et al., 2005) and are substrates for the P-glycoprotein (P-gp) (Miller et al., 1997; Saeki et al., 1993). They work together to form an active barrier to drug absorption, limiting the oral bioavailability of the CNIs and mTOR inhibitors (Zhang & Benet, 2001). Some drugs require binding proteins before their delivery to the targets, such as CNIs that bind to immunophilins as part of their mechanism of action. As a result, only a proportion of an administered drug can reach the target. In order to define the association between the genotypes and the pharmacokinetics of a drug, a group of individuals are given the same dose of a drug, and the blood concentrations will then be measured at different intervals (Dunn et al., 2001; Schiff et al., 2007). These individuals are genotyped for polymorphisms at certain candidate genes, and the association between the genotypes and the pharmacokinetics is subsequently statistically analyzed. The ultimate goal is to find out the gene variants that can help in predicting the pharmacokinetics of a drug, and identifying patients who need a higher dose to reach the desired blood concentration (Evans & McLeod, 2003; McLeod & Evans, 2001). The combined analysis of gene variants encoding the different proteins that mediate the drug action may help to determine the final dose necessary to obtain a pharmacological effect (Kruger et al., 2008). This complicated picture shows that a successful pharmacogenetics approach would require the genotyping of several genes in each patient.

## 3. P-glycoprotein

Many drugs, including some immunosuppressive agents, are pumped out of the endothelial cells by P-gp, encoded by adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) gene (formerly called multidrug resistance-1 [MDR1] gene) (Benet et al., 1999; Lown et al., 1997). One of the main functions of P-gp is to ensure the energy-dependent cellular efflux of substrates. The P-gp expression in the intestinal wall and in the proximal tubular cells of the kidneys suggests that it may have a role in the absorption and excretion of xenobiotics. In the gut, alteration in its expression, function, or both raises the absorption

of its substrates (Ambudkar et al., 1999). Individuals with a genotype with high intrinsic P-gp activity have a lower proportion of the drug that reaches the blood stream compared with a genotype with less P-gp activity (Choudhuri & Klaassen, 2006). Various single nucleotide polymorphisms (SNPs) have been identified within the *ABCB1* gene over the recent few years (Kim, 2002). An SNP, located in exon 26 (exon 26 3435C>T), was associated with variations in the intestinal expression and function of P-gp. However, this SNP is a silent polymorphism that does not result in any amino acid changes. It was suggested that it may be in linkage disequilibrium with other functional polymorphisms within the *ABCB1* gene. A co-segregation of exon 26 3435T with the T allele of the non-synonymous exon 21 SNP (exon 21 2677G>T), resulting in an A893S amino acid change, and also with the T allele of the synonymous exon 12 SNP (exon 12 1236C>T) was reported. This disequilibrium led to haplotype analysis of the ABCB1 gene and identification of the links between the genomic variations represented by each haplotype on ABCB1 function. This approach takes into account the combination of SNPs present in an allele (Kim, 2002) and might be more predictive of changes in response to drugs than SNP-based approaches.

## 4. CYP3A

CYP3A proteins can be classified into families and subfamilies on the basis of amino acid sequence similarities. Members of the CYP3A subfamily are implicated in the metabolism of structurally diverse endobiotics, drugs, and protoxic or procarcinogenic molecules. Substantial inter-individual differences in CYP3A expression contribute greatly to variations in the oral bioavailability and systemic clearance of CYP3A substrates (Nebert & Russell, 2002). Human CYP3A activities reflect the heterogeneous expression of at least three CYP3A members, CYP3A4, CYP3A5, and CYP3A7, which are adjacent to each other on chromosome band 7q21. CYP3A7 is normally only expressed in fetal liver. CYP3A4 and CYP3A5 have been identified as the major enzymes responsible for the disposition of drugs (Sattler et al., 1992). In enterocytes, CYP3A4 and CYP3A5 are involved in intestinal metabolism, preventing systemic uptake of immunosuppressive agents; while in the liver, they provide a further layer contributing to first-pass metabolism, thus affecting the drug clearance. For example, CYP3A5 variants alter the dose requirement of tacrolimus (Tac). Since CYP3A5 is involved in Tac deactivation, patients with a genotype that encodes for lower enzyme activity would have an increase drug exposure. Thus a lower dose will be required to be within the target blood concentration. The normal (wild-type) sequences of CYP3A4 and CYP3A5 are designated as CYP3A4*1 and CYP3A5*1. The most frequent CYP3A4 SNP linked to different enzymatic activities is -392 A>G in the gene promoter. The -392 G allele (also called CYP3A4*1B) increased CYP3A4 expression in vitro (Rebbeck et al., 1998; Westlind et al., 1999). This SNP is common in individuals of African descent (30%–70%) but rare among whites (1%–10%) (Makeeva et al., 2008; Quaranta et al., 2006). On the other hand, the most important SNP of the CYP3A5 gene leading to the alteration of gene expression and enzymatic activity is the SNP 6986 A>G in intron 3. Analysis revealed that only individuals with at least one CYP3A5*1 allele (A at position 6986) produce high levels of full-length CYP3A5 mRNA and express CYP3A5, which then accounts for at least 50% of the total CYP3A content. Those with the CYP3A5*3 allele (G at position 6986) display sequence variability in intron 3 that creates a cryptic splice site and encodes an aberrantly spliced mRNA with a premature stop codon, leading to the absence of protein expression (Kuehl et al., 2001).

## 5. Tacrolimus

Among the factors which have been investigated for the possible influence on CNIs pharmacokinetics, polymorphisms in genes coding for CYP3A (3A4 and 3A5) and P-gp received much attention. The impact of CYP3A4, CYP3A5, and MDR1 SNPs on Tac pharmacokinetics has been analyzed extensively in recent years. CYP3A5 expressers, who are carriers of at least one CYP3A5*1 allele, would have higher Tac clearance and lower dose-normalized $C_0$ at different times after renal transplantation compared with CYP3A5*3 homozygotes (Haufroid et al., 2004; Haufroid et al., 2006; Hesselink et al., 2003; Macphee et al., 2005; Mourad et al., 2006; Roy et al., 2006; Tada et al., 2005; Thervet et al., 2003; Tsuchiya et al., 2004; Zhang et al., 2005; Zhao et al., 2005). A study of 118 kidney recipients examined the relationship between CYP3A5*1/*3 and Tac dose-normalized concentrations at 1 week, 1 month, and 3 months post-transplantation. At 1 week, the mean dose-normalized blood concentration was significantly lower in CYP3A5*1 carriers (33 ng/mL per mg/kg/day) compared with CYP3A5*3 homozygotes (102 ng/mL per mg/kg/day). This difference remained significant at 1 month and 3 months post-transplant (Zhang et al., 2005). A temporal change in Tac oral bioavailability has been reported by Kuypers et al. The dose-normalized exposure to Tac increased progressively over a 5-year period in individuals predicted to be CYP3A5 non-expressers but not in CYP3A5 expressers (Kuypers et al., 2007). The frequency of these alleles depends on the population studies: the CYP3A5*1 allele is present in 15 % of the Caucasian, 45% of the African-American (Kuehl et al., 2001), and 25% of the Chinese population (Balram et al., 2003). Since many genetic differences exist between races, it is also important to examine whether the described polymorphisms are related to differences in pharmacokinetic and dosing of Tac in different population. In a study of 103 stable Chinese renal transplant recipients (Cheung et al., 2006), a strong significant genetic effect between CYP3A5*3 polymorphism and both the dose-normalized $AUC_{0-12}$ and the daily Tac dose has been demonstrated. In fact, the CYP3A5*3 polymorphism may explain 35.3% of the variation in the daily Tac dose observed in the renal transplant recipients. In another study involving Caucasian population (Op den Buijsch et al., 2007), significantly higher dose-normalized $C_0$, dose-normalized $AUC_{0-12}$ and dose-normalized peak concentrations ($C_{max}$) is demonstrated in carriers of the CYP3A5*3 allele in both early and late post renal transplant recipient groups than in patients homozygous for CYP3A5*1. In their centre, a complete Tac pharmacokinetic profile was usually requested early for patients who failed to achieve the target Tac concentration shortly after transplantation. Since the CYP3A5*1 allele was over-represented in this early phase group in their study, the authors concluded that renal transplant recipients carrying this allele have more difficulties in achieving and maintaining Tac concentrations compared to homozygous carriers of the CYP3A5*3 variant. This might be of importance for the Chinese population in which the CYP3A5*1 allele has a much higher prevalence than in the Caucasian population.

CYP3A5 is closely linked to the CYP3AP1 pseudogene, and the CYP3AP1*1 allele (-44 G) was in strong linkage disequilibrium with the low-expression CYP3A5*3 allele. In fact, the CYP3AP1 genotype resembles the CYP3A5 genotype (Kuehl et al., 2001). A significant association was found between the CYP3AP1 polymorphism and three parameters, namely, drug concentrations during the first week post-transplant, time to reach the target blood concentrations, and the risk of early allograft rejection (MacPhee et al., 2002, 2004).

On the other hand, the impact of the CYP3A4 and ABCB1 polymorphisms in Tac pharmacokinetics is not clear. Most studies failed to show any association between

CYP3A4 gene polymorphisms and Tac pharmacokinetics although at least one group has reported lower $C_0$ concentrations at 3 and 12 months post-transplantation in carriers of the CYP3A4*1B allele than in the CYP3A4*1 homozygotes (Hesselink et al., 2003). Similarly, there has been conflicting pubished data about the influence of the polymorphisms of the ABCB1 system on the pharmacokinetics of Tac. A number of studies have reported that there seems to be no association between the ABCB1 polymorphisms and Tac dose-normalized $C_0$ (Haufroid et al., 2004; Hebert et al., 2003; Hesselink et al., 2003; Mai et al., 2004; Zhang et al., 2005) or the dose-normalized AUC (Tada et al., 2005; Tsuchiya et al., 2004). However, some studies found a correlation between individual ABCB1 polymorphisms and a higher Tac dose (MacPhee et al., 2002; Zheng et al., 2003; Zheng et al., 2004). Carriers of the 2677T or the 3435T MDR1 alleles showed higher dose-normalized Tac $C_0$ concentrations compared with 2677 G-homozygous (GG) and 3435 C-homozygous (CC) patients (Akbas et al., 2006; Anglicheau et al., 2003; Li et al., 2006). Because of differences in design and study populations it might be that a polymorphism, that has a minor influence on the Tac blood concentrations, demonstrates contrasting results among these studies. Moreover, there are several SNPs that may occur together, resulting in different haplotypes. The correlation of these haplotypes with the pharmacokinetics of Tac has not yet been described extensively. In one study, a correlation between the ABCB1 1236C-2677G-3435C haplotype and a higher Tac dose was found (Anglicheau et al., 2003). However, in another study of 63 Caucasian renal transplant recipients with a complete 9-point 12-hour AUC of Tac, 3 SNPs in the ABCB1 system were genotyped. Neither the individual ABCB1 polymorphisms nor the ABCB1 haplotypes were associated with any pharmacokinetic parameter (Op den Buijsch et al., 2007). On the other hand, in a study of Chinese renal transplant recipients (Cheung et al., 2006), individuals carrying the 2677TT or 3435TT genotype has a significantly lower dose-normalized $AUC_{0-12}$, but no correlation was found between ABCB1 system haplotype and dose-normalized $AUC_{0-12}$. In multiple regression analysis the 2677TT and 3435TT genotype was not shown to be significant if the CYP3A polymorphism was included. Therefore, the published correlation of SNPs of the ABCB1 system with dose-normalized AUC of Tac might be related to genetic linkage of the ABCB1 system with other polymorphisms, such as the CYP3A system. Individuals with the mutant genotype appear to be over-represented in the CYP3A5 expresser population and under-represented in the CYP3A5 non-expresser population. Thus the interaction between P-gp and CYP3A5 further complicates the analysis of interaction between ABCB1 genotype and Tac pharmacokinetics.

Despite the fact that expression of CYP3A5 results in higher Tac dose requirements and significant delay in achieving target blood concentrations early after transplantation, most of the previous studies failed to identify the association of the genetic polymorphisms with increased incidence of acute rejection (Hesselink et al., 2008; Macphee et al., 2004). However, in a recent prospective study of 62 patients who underwent 10-day scheduled renal graft biopsy, significantly higher overall incidences of early T-cell-mediated rejection of at least Banff grade 1 in severity were detected in CYP3A5 expressers. The severity was also associated with the CYP3A5 genotypes. Moreover, the estimated glomerular filtration rate in CYP3A5 expressers was lower than that of the non-expressers until one month after transplantation (Min et al., 2010). However, further large-scale long-term outcome studies are necessary to confirm the clinical relevance of the findings.

## 6. Cyclosporine

Healthy volunteers who are CYP3A5*1 carriers had a lower cyclosporine (CsA) AUC when compared with individuals with homozygous for CYP3A5*3 (Min et al., 2004). Moreover, renal transplant recipients who carry CYP3A5*1 were also found to exhibit lower dose-normalized CsA $C_0$ (Haufroid, et al., 2004). However, this association has not been confirmed by most authors (Anglicheau et al., 2004; Hesselink et al., 2003, 2004; Kreutz et al., 2004). This is strange because the clear influence of CYP3A5 genotype on Tac absorption could not be shown similarly in CsA (as both are CNIs). A possible explanation is that the molar dose of CsA administered is approximately 30-fold higher than that for Tac and it blocks a saturable barrier to drug absorption more effectively than for Tac (Higgins et al., 1999). The association between CYP3A4 SNPs and CsA pharmacokinetics is also controversial. The CYP3A4*1B allele has been linked to significantly higher CsA clearance compared with wild-type homozygotes (Hesselink et al., 2004; Min & Ellingrod, 2003). However, this association was not confirmed in other studies (Rivory et al., 2000; von Ahsen et al., 2001). In whites, the 3A4*1B occurs at a low frequency (Coto & Tavira, 2009), and recruitment of the minimum number of carriers to reach statistical significance is difficult.

The association between ABCB1 SNPs and CsA pharmacokinetics is also controversial. In a study involving 106 renal transplant recipients, carriers of the ABCB1 1236 wild-type allele had a lower dose-normalized $C_{max}$ and lower increased AUC when compared with the 1236 T allele homozygotes (Anglicheau et al., 2004). In another study with 69 renal transplant recipients, a significantly lower AUC and $C_2$ in carriers of the ABCB1 3435 T allele was shown at day 3 post-transplant but the difference did not remain significant at 1 month (Foote et al., 2007). However, most of the large studies did not find an association between any of the ABCB1 polymorphisms and CsA pharmacokinetics (Haufroid et al., 2004; Kuzuya et al., 2003; Mai et al., 2003). On the other hand, the influence of ABCB1 genotype on pharmacodynamics seems more compelling. The incidence of CsA nephrotoxicity was significantly higher when the donor had the ABCB1 3435TT genotype (Hauser et al., 2005). This is consistent with the hypothesis that local levels of P-gp expression in renal tubular epithelial cells can explain the susceptibility to CNI nephrotoxicity. It has been shown that lower levels of P-gp expression were found in renal biopsies in patients with CNI nephrotoxicity (Joy et al., 2005). CsA nephrotoxicity is also exacerbated by concomitant use of sirolimus, which can be explained by the inhibitory effect of sirolimus on P-gp-mediated efflux and subsequent increased cellular concentration of CsA (Anglicheau et al., 2006). Moreover, another study also found that ABCB1 polymorphisms in donors influence long-term graft outcome. The donor ABCB1 haplotype 1236T/2677T/3435T was significantly associated with increase graft loss, acute rejection episodes and greater decrease in renal function (Woillard et al., 2010).

In addition to CYP and ABCB1 genes, other gene variants can also affect CNIs pharmacokinetics and clinical outcomes. In a study of subpopulation of patients participating in the CAESAR study, 4 gene polymorphisms including ABCB1 G2677T/A, IMPDH2 T3757C, IL-10 C-592A and TNF-alpha G-308A demonstrated a statistically significant association with biopsy-proven acute rejection at 12 months post-transplant (Grinyo et al., 2008). CsA action is mediated by its binding to the cyclophilins (Cyp). In a study involving 290 kidney-transplanted patients, the effect of two CypA polymorphisms on CsA pharmacokinetics and clinical outcomes was analyzed (Moscoso-Solorzano et al.,

2008). In vitro studies showed that a promoter SNP (-11 G/C) affected gene expression but was not related to differences in $C_0$ and $C_2$ dose-normalized levels. However, an association between the high expression allele and nephrotoxicity was found but these results need further confirmation.

## 7. Azathioprine

Most of the pharmacogenetic traits first identified were discovered by phenotypic analysis detecting a bi- or trimodality of an enzymatic activity (Weinshilboum, 2003). Azathioprine, metabolized in part by S-methylation catalyzed by the enzyme thiopurine methyltransferase (TPMT), is an example. Large inter-individual differences were reported in TPMT activity, which was found to be inherited in an autosomal codominant fashion (Weinshilboum et al., 1999). When individuals with low or undetectable TPMT activity received standard doses of azathioprine, they had high concentrations of the active metabolites 6-thioguanine nucleotides and drug-induced myelosuppression. On the other hand, azathioprine efficacy will be reduced in patients with very high levels of TPMT activity which can be attributed to its rapid metabolization (Chocair et al., 1992; Soria-Royer et al., 1993). TPMT activity correlates with both short- and long-term results after renal transplantation (Thervet et al., 2001). Subsequently, these variations in TPMT activity were shown to be attributed to genetic polymorphisms within the TPMT gene. At present, 20 variant alleles (TPMT*2 - *18) have been identified, which are associated with decreased activity when compared with the TPMT*1 wild type allele. TPMT*3A, the most common variant allele responsible for low TPMT activity in whites, encodes a protein with two single nucleotide polymorphisms (SNP), G460A in exon 7 and A719G in exon 10, leading to modifications in the amino acid sequence. The phenotypic test for TPMT activity determination in red blood cells and, subsequently, DNA-based tests, were among the first pharmacogenetic tests to be used in clinical practice.

## 8. Mycophenolic acid

Mycophenolic acid (MPA) is the active derivative of the prodrug mycophenolate mofetil but MPA itself is also available as enteric coated sodium salt tablet. MPA is metabolized by uridine-glucuronyl-transferase (UGT), primarily UGT1A8 and 1A9, to the inactive metabolite 7-O-glucuronide (MPAG). MPAG is primarily excreted by kidneys, although a proportion is secreted in bile by the drug efflux pump multidrug resistance associated protein 2 (MRP2), now also called ABCC2. Deconjugation by intestinal bacterial flora results in a second peak of absorption at 6 to 8 hours due to enterohepatic recirculation. This second peak accounts for 30-50% of the total AUC. As a result, co-administration with medication that inhibit ABCC2, such as CsA, can result in a significantly reduced MPA exposure (Hesselink et al., 2005b). Several SNPs have been found in the ABCC2 gene (Ito et al., 2001). It has been found that ABCC2 C-24T and C-3972T polymorphisms can protect the renal transplant recipients from a decrease in MPA exposure associated with mild liver dysfunction. Moreover, C-24T SNP was associated with significantly high dose-normalized MPA trough levels at steady state (Naesens et al., 2006).

Polymorphisms have also been identified in both UGT1A9 and 1A8 genes. In vitro studies have shown that polymorphisms in the UGT1A9 gene result in significant alteration of the UGT enzymatic activity. Two polymorphisms in the promoter region of the UGT1A9 gene,

namely C-275T>A and C-2152C>T, result in higher MPA glucuronidation rates (Girard et al., 2004). It has been demonstrated that in renal transplant recipients, carriers of either or both polymorphisms had lower MPA AUC and $C_0$ (Johnson et al, 2008; Kuypers et al., 2005; van Schaik et al., 2009). On the other hand, UGT1A8*3 (P277C>Y) polymorphism results in an approximately 30-fold reduction in MPAG formation (Bernard et al., 2006).

MPA inhibits inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the pathway for purine synthesis.. The two isoforms of IMPDH, IMPHD1 and IMPDH2, have similar enzymatic activity. Individuals with low levels of lymphocyte IMPDH activity are more likely to experience toxicity with MPA and those with high levels are more likely to have rejection (Glander et al., 2004). There were different variants of the IMPDH2 gene and the 263L>F variant resulted in a reduction in enzyme activity to 10% of the wild-type (Wang et al., 2007). Several mutants of IMPDH had decreased affinity for MPA (Farazi et al., 1997). However, there are no clinical associations for this SNP. On the other hand, 2 SNPs in the IMPDH1 gene, namely +125G>A and -106G>A, were found to be associated with increase risk of rejection after kidney transplantation but the underlying mechanism remains uncertain (Wang et al., 2008). Despite of availability of different candidate genes, there are still insufficient data to support the use of pharmacogenetic strategy for mycophenolate.

## 9. Mammalian target of rapamycin inhibitors

There is only limited data concerning the pharmacogenetics of mTOR inhibitors. Usually it takes longer time for sirolimus to achieve desired therapeutic range because of its long half-life (approximately 60 hours). Thus use of pharmacogenetic strategy seems to be an ideal option for sirolimus dosage adjustment. However, the data in literature is controversial. While there were studies showing reduced oral bioavailability of sirolimus in CYP3A5 expressors (Anglicheau et al., 2005; Le Meur et al., 2006), similar association was not found in other studies (Mourad et al., 2005; Renders et al., 2007). Moreover, none of the studies could show the influence of ABCB1 genotype on sirolimus exposure (Anglicheau et al., 2005; Mourad et al., 2005; Renders et al., 2007). As a result, pharmacogenetics is still not suitable for sirolimus dosing.

## 10. Conclusion and future perspective

Currently TDM is the gold standard for monitoring and titration of immunosuppressive drugs in order to ensure adequate immunosuppression but avoid side effects. However, many patients experience significant delay in achieving therapeutic blood concentrations, resulting in a higher risk of acute rejection. As a result, selection of the best drug with an accurate dose is important. Pharmacogenetics have generated considerable enthusiasm in transplantation medicine in recent years and it is widely believed that "personalized medicine" is the ultimate goal of use of immunosuppressive drugs. Although many genetic factors have been shown to influence pharmacokinetics for the immunosuppressive drugs, only CYP3A5 genotyping may help to guide individual tacrolimus dosing in clinical practice. Moreover, the focus of pharmacogenetic studies has recently shifted from pharmacokinetics to transplantation outcomes, such as renal allograft dysfunction. Although there is substantial evidence that intrarenally expressed ABCB1 is implicated in the pathogenesis of CNI nephrotoxicity, there is no direct evidence in human that the association between ABCB1 genotype and CNI nephrotoxicity is indeed caused by higher

intrarenal concentration of CNIs (Hesselink et al., 2010). Further prospective and intervention studies involving genetic profile and transplant outcome are required for recommendation of widespread use of pharmacogenetic testing in routine clinical practice.

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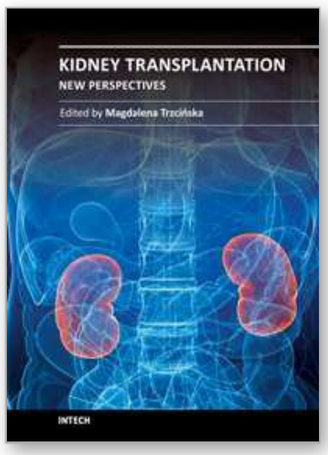


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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and thatâ€™s why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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