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Influence of Genetic Polymorphisms in CYP3A5, CYP3A4, and MDR1 on Tacrolimus Metabolism after kidney transplantation

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Abstract

Kidney transplantation stands as the ultimate recourse for restoring vital organ functions, particularly in cases of end-stage kidney disease where alternative treatments, such as dialysis, prove less effective. With over 102,000 kidney transplants conducted globally in 2022, the demand for organ transplantation is ever-increasing, fueled by a rising incidence of end-stage renal disease attributed to causes like diabetes and hypertension.

Despite significant advancements in kidney transplantation, immunosuppressive therapy remains crucial to preventing graft rejection. Tacrolimus (TAC), a calcineurin inhibitor, plays a pivotal role in this regard. Discovered in 1984, TAC inhibits T-lymphocyte activation, preventing acute rejection by disrupting the transcription of crucial genes involved in early T-cell activation. However, the use of TAC is not without challenges. The drug exhibits serious side effects, a narrow therapeutic index, and unpredictable pharmacokinetics. Therapeutic drug monitoring (TDM) becomes imperative in daily practice to maintain TAC blood concentrations within the therapeutic range. This literature review delves into the genetic aspects influencing TAC metabolism, focusing on key polymorphisms in CYP3A5, CYP3A4, and ABCB1 genes. Genetic variations in CYP3A5, a major enzyme in TAC metabolism, impact enzyme activity, necessitating personalized dosing strategies. CYP3A4 polymorphisms, especially CYP3A4*22, demonstrate associations with altered TAC clearance and dose requirements. The ABCB1 gene, encoding P-glycoprotein, another player in TAC pharmacokinetics, also exhibits polymorphisms influencing drug absorption and distribution. The ABCB1 3435C>T variant, in particular, shows potential implications on Tacrolimus bioavailability. Understanding these genetic variations aids in the development of personalized dosing regimens. Studies suggest that tailoring TAC doses based on CYP3A5 genotypes significantly improves the proportion of patients achieving therapeutic concentrations. Additionally, incorporating genetic information, particularly CYP3A4*22, into dosing strategies enhances the precision of TAC therapy, reducing the risk of adverse effects. .

Keywords: kidney transplantation, tacrolimus, immunosuppressive therapy, genetic polymorphisms, pharmacogenetics, pharmacokinetics.

Introduction

Transplantation is the last resort to restore vital organ functions when there are no other options that offer similar effectiveness. Hence, kidney transplantation stands as the sole remedy for end-stage kidney disease. An effective kidney transplant enhances life quality and diminishes the mortality hazard for the majority of patients in contrast to ongoing dialysis treatment [1].

The inaugural kidney transplant took place in a canine at the Vienna Medical School in Austria. In 1954, a significant breakthrough occurred when Joseph Murray achieved the first long-term successful human kidney transplantation; the procedure involved monozygotic twins, and remarkably, the transplanted organ endured for 8 years [2].

Nowadays, the kidney is the most transplanted organ worldwide. In 2022, a total of 102,090 kidneys were transplanted in Americas, Europe, the Western Pacific, Southeast Asia, the Eastern Mediterranean, and Africa [3].

The prevalence of end stage renal disease is experiencing a swift increase. Diabetes and hypertension stand as the leading causes of renal failure. Other factors contributing to chronic kidney disease or end stage renal disease are categorized into prerenal causes (chronic or acute ischemia), intrinsic renal causes (such as glomerulonephritis and focal-segmental glomerulosclerosis), or postrenal causes (including reflux nephropathy and obstruction) [4].

Despite the huge growth in the field of kidney transplantation, which is reflected in a fairly large number of successful long-term outcomes, kidney transplantation from a donor who is not an exact match, without the introduction of immunosuppressants, invariably leads to rejection and loss of the allograft. Thus, almost all the patients with renal allograft require ongoing immunosuppressive treatment.

The optimal ongoing immunosuppressive treatment for kidney transplantation remains uncertain. Various combinations of significant immunosuppressive agents accessible [1]. Treatment plans typically involve combinations of these immunosuppressive agents. A carefully selected regimen aims to minimize the morbidity and mortality correlated with each class of agent, all the while striving to enhance overall efficacy.

The choice of regimen depends not only on the knowledge and on experience of the attending physician, but also on many other factors such as age, weight, ethnicity, as well as the organs function responsible for drugs metabolism. That is why pharmacogenetics has gained special importance in recent decades, playing a critical role in interindividual variability in drug disposition and effects.

In this work, a literature review will be conducted regarding Tacrolimus (TAC), as the main immunosuppressive drug after kidney transplantation, from the point of view of the genetic characteristics of its metabolism.

Aim of the review: The purpose of the review is to study the genetic aspects affecting the metabolism of TAC as the main immunosuppressive drug in patients undergoing kidney transplantation. Special attention is paid to key genetic polymorphisms such as CYP3A5, CYP3A4 and ABCB1, which are considered crucial in the metabolism and pharmacokinetics of TAC. The review highlights the effect of genetic variations on the activity of enzymes encoded by the named above genes. The review presents data that can be used to develop personalized dosage regimens for TAC. As a result, it can increase the accuracy of TAC therapy, optimize the timing of achieving therapeutic concentrations, and reduce the manifestation of side effects for each individual patient.

Tacrolimus (TAC) in Kidney Transplantation

TAC serves as a pivotal immunosuppressive agent, crucial in preventing organ transplant rejection. This calcineurin inhibitor was identified in 1984 through the fermented solution derived from a soil sample obtained in Japan, containing the bacterium Streptomyces tsukubaensis [5].

Research has shown that TAC hinders T-lymphocyte activation by initially binding to an intracellular protein called FKBP-12. This binding forms a complex comprising tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin, which subsequently inhibits the phosphatase activity of calcineurin. Consequently, this inhibition prevents the dephosphorylation and translocation of the nuclear factor of activated T-cells (NF-AT), a nuclear component believed to trigger gene transcription necessary for lymphokine formation. Additionally, TAC suppresses the transcription of genes encoding IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which play roles in the initial stages of T-cell activation and, consequently, in the development of acute rejection [5].

Despite the enormous benefits that TAC brings to patients with kidney allograft, it is still a medical drug with a number of quite serious adverse effects, a limited therapeutic range, and pharmacokinetics that are variable and difficult to predict. Therefore, Therapeutic Drug Monitoring (TDM) is essential in routine clinical practice. Patients who have undergone renal transplantation typically start with a standard weight-dependent dosage of TAC, which is then corrected according to TDM to keep TAC blood levels within the desired therapeutic range [6]. Nonetheless, owing to variances in individual first-pass effects, attaining the target TAC concentration might be subject to a relative delay. Furthermore, reaching the desired concentration does not guarantee the intended therapeutic outcome or prevent adverse reactions [7].

CYP3A5, CYP3A4 and ABCB1 polymorphisms characteristic

The CYP3A subfamily responsible for the phase I metabolism of more than half of the drugs administered, is primarily found in hepatocytes, biliary epithelial cells of the liver, and the villous columnar epithelial cells of the jejunum [8]. CYP3A5 and CYP3A4, constituting around 30% of hepatic cytochrome P450, are crucial in metabolizing TAC [8-10]. Genetic polymorphisms in CYP3A5 and CYP3A4 genes contribute to variations in drug metabolism, including TAC [11].

The CYP3A5*1 allele encodes the functional form of CYP3A5, which is associated with elevated enzyme expression, whereas the nonfunctional *3 allele leads to the lack of gene expression [9, 12]. The prevalence of these alleles varies across populations, with CYP3A5*3/*3 genotype being prevalent in Caucasians and African Americans, influencing enzyme expression levels [13-16].

The CYP3A4*22 allele, characterized by the C>T substitution (rs35599367) in intron 6 of the CYP3A4 gene, correlates with reduced mRNA levels and enzyme activity within the liver, this allele could account for differences in individual reactions to drugs metabolized by CYP3A4 [17, 18].

The ABCB1 gene is responsible for encoding P-glycoprotein, which plays a role in multidrug resistance by expelling drugs from cells, variations in the ABCB1 gene, notably in exon 26 (C/T at position 3435), impact the expression levels of P-glycoprotein [19]. Carriers of the T-allele exhibit lower levels of P-glycoprotein compared to C/C homozygotes.

These genetic variations play a crucial role in individual responses to drugs, emphasizing the importance of pharmacogenomics in personalized medicine. In the Table 1 a summary overview of the alleles, associated reference single nucleotide polymorphisms (SNPs), and the functions of the SNPs in the specified genes (CYP3A5, CYP3A4, and ABCB1) is provided.

Table 1 Genotype variants and SNP effect of alleles [9, 17]

Allele	Reference SNP (dbSNP)	Function of SNP
CYP3A5*1	Wild type	Normal function
CYP3A5*2	rs28365083	missense
CYP3A5*3	rs776746	cryptic splice site
CYP3A4*1	Wild type	Normal function
CYP3A4*22	rs35599367	changes the folding of sin-gle-stranded DNA and RNA
ABCB1:c.1236T>C	rs1128503	Exon skipping

The CYP3A5 polymorphisms influence on TAC metabolism

Review, that studied several published data on CYP3A5 influence on TAC metabolism in kidney transplant recipients, performed an information on two meta analyses which included 56 studies in summary [15, 21, 22]. Individuals with the *3/*3 genotype consistently displayed considerably elevated trough concentrations adjusted for dosage, with a mean difference adjusted by weight of 63.57 ng/mL per mg/kg (95% confidence interval [CI]: 50.85–76.30) [21]. This difference was observed when compared to a combined group of *1/*3 and *1/*1 patients. The effect was consistent across diverse ethnic groups (Caucasian and Asian) and different time intervals following transplantation (≤1 month, 3–6 months, 12–24 months) [20]. Similar findings were reported, reinforcing the outcomes. TAC dose-adjusted trough concentrations were significantly lower in individuals expressing CYP3A5 [22].

In a retrospective study, a weight-based initial dose of 0.1 mg/kg targeted a therapeutic range of 4–8 mcg/mL, revealing that while 50% of individuals with the CYP3A5 non-expressor genotype reached the target concentration within three days, only 35.3% of expressors achieved the same, with TDM aiding in dose adjustments, leading to 64.2% of expressors and 55.4% of non-expressors attaining therapeutic trough concentrations by the 7th day, suggesting potential benefits of CYP3A5 genotyping prior to kidney transplantation [23]. These results imply that performing CYP3A5 genotyping before kidney transplantation may offer benefits [15].

In a prospective randomized controlled trial, that compared the standard and genotype-based dosage of TAC, the majority of patients (78.8%) had the CYP3A5 *3/*3 genotype (as Caucasian population was predominant 89,9%), with 16.9% being *1/*3 heterozygotes and 4.2% *1/*1 homozygotes [24]. There was no disparity in allele frequency between standard and genotype-based dosing groups. By day 3, the genotype-based dosing group exhibited a significantly higher proportion of patients who achied therapeutic TAC concentrations compared to the standard dosing group ($p<0.05$) [24]. The results of the study are presented in Table 2.

Table 2 Results of genotype-based dosing and standard dosing [24]

	CYP3A5*1/*1	CYP3A5*1/*3	CYP3A5*3/*3
Standard dosing (mg/kg/d)	0.200	0.200	0.200
Tacrolimus concentrations within the therapeutic range (percentage)	29.1		
Genotype-based dosing (mg/kg/d)	0.3	0.3	0.15
Tacrolimus concentrations within the therapeutic range (percentage)	43.20		

In a retrospective study on a Kazakh population comprising 80 kidney transplant recipients, participants were divided into homozygous (*3/*3) and heterozygous (*1/*3) groups, all administered TAC at an initial dose of 1 mg/kg body weight; TAC concentrations were measured at various intervals up to the 14th day, revealing higher concentrations in *3/*3 heterozygous carriers with significant differences observed on the 2nd, 5th, 7th, and 10th days in both groups ($p = 0.02$, 0.01, 0.12, and 0.016, respectively), while no statistically significant differences were noted on the 14th day post-surgery and at discharge ($p = 0.085$ and 0.171, respectively), with TAC nearing the target level in both groups by the end of the second week [16].

The Clinical Pharmacogenetics Implementation Consortium issued guidelines in 2015, providing recommendations for the genotype-based dosing of TAC with respect to CYP3A5 [25]. According to the recommendations, recipients after kidney transplantation with the CYP3A5*1/*1 or CYP3A5*1/*3 genotype experience notably lower dose-adjusted trough concentrations of TAC compared to those with the CYP3A5*3/*3 genotype. Carriers of the *1 alleles typically require 1.5–2 times higher dosage to achieve similar blood concentrations as *3 carriers, as shown in the Figure 1 (see the next page).

The CYP3A4 polymorphisms influence on TAC metabolism

The impact of the CYP3A4*22 genetic polymorphism on C0/D was assessed through a meta-analysis that involved eight cohort studies with data of 2,624 patients [26-33]. This analysis included a comparison of C0/D in 6 time periods during the first year after transplantation. Combining data across all study periods revealed that CYP3A4*22 carriers exhibited a significantly higher C0/D than CYP3A4*1/*1 recipients, with considerable differences observed in C0/D, except during the first 2 weeks post-transplantation. Despite substantial heterogeneity ($I2 = 76\%$, $p < 0.00001$), no subgroup differences were reported across time periods [34].

Among this meta-analysis six studies assessed the impact of the CYP3A4*22 variant on the daily TAC dose [26, 27, 29, 30, 32, 33]. The combined data indicated that CYP3A4*22 carriers required a 2.02 mg/day lower dose to achieve the optimal trough level compared to non-carriers ($p < 0.00001$), except for 1-year post-transplantation. Substantial heterogeneity was present

CYP3A5 phenotype	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations	Classification of recommendations
Extensive metabolizer (CYP3A5*1/*1 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.d Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5*1/*3 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.a Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5*3/*3 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Figure 1 – Consortium dosing recommendations for TAC based on CYP3A5 phenotype [25]

(I2 = 75%, p < 0.00001), with no significant subgroup differences. Sensitivity analyses were conducted, revealing reduced heterogeneity when excluding data from the first week and 1 year after transplantation.

To evaluate the individual influence of CYP3A422 while accounting for CYP3A53, the effect of CYP3A4*22 in individuals lacking CYP3A5 expression was examined in four studies conducted within 3 to 6 months post-kidney transplantation [26, 29, 35, 36]. After adjusting for CYP3A5*3, CYP3A4*22 carriers showed a 0.67 ng/mL/mg higher C0/D (p < 0.00001) and a 1.83 mg/day lower dose requirement (p < 0.00001) compared to CYP3A4*1/*1 carriers, indicating a significant effect of CYP3A4*22 on TAC pharmacokinetics and dose requirement even after adjusting for CYP3A5*3, what is shown in the Table 3.

discernible impact on TAC dosage within subgroups categorized by various initial doses.

The findings revealed no significant difference in dosage between ABCB1 3435CC and ABCB1 3435CT, however, ABCB1 3435TT exhibited a notably lower dosage than ABCB1 3435CC [37].

This review of fifteen studies examined the association between the genetic variant ABCB1 3435C>T and the C0/D ratio at different time points post-transplantation. The results revealed a significantly higher C0/D ratio in ABCB1 3435T carriers compared to ABCB1 3435CC carriers at 1 and 6 months post-transplantation, with a trend towards higher ratios observed at 7 days, 3 months, and 1 year post-transplantation. Subgroup analysis based on initial TAC dosage showed that ABCB1 3435T carriers had a higher C0/D ratio than ABCB1 3435CC carriers

Table 3 Comparative Analysis of CYP3A4*22 and CYP3A4*1/*1 in Tacrolimus Pharmacokinetics and Dosing [26-36]

Analysis	Comparison	Outcome	Result (95% CI)	p-value	Heterogeneity (I2, p)
CYP3A4*22 vs. CYP3A4*1/*1 [26-33]	C0/D in Various Post-Transplant Periods	Higher C0/D in CYP3A4*22 carriers	0.57 ng/mL/mg (0.28 to 0.86)	0.0001	I2 = 76%, p < 0.00001
CYP3A4*22 vs. CYP3A4*1/*1 [26,27,29,30,32,33]	Daily Dose Re-quirement	Lower dose requirement in CYP3A4*22 carriers	-2.02 mg/day (-2.55 to -1.50)	< 0.00001	I2 = 75%, p < 0.00001
CYP3A4*22 vs. CYP3A4*1/*1 (Adjusted for CYP3A5*3) [26,29,35,36]	C0/D and Dose Requirement in CYP3A5 Non-Expressers	Higher C0/D and Lower Dose Re-quirement in CYP3A4*22 carriers	C0/D: 0.67 ng/mL/mg (0.44 to 0.89), Dose: -1.83 mg/day (-2.59 to -1.06)	< 0.00001	Not specified

ABCB1 polymorphisms influence on TAC metabolism

Based on a review encompassing 16 studies focusing on the influence of ABCB1 polymorphisms on TAC dose and concentration (C0/D), recipients were categorized into two groups: ABCB1 3435CC and ABCB1 3435T (comprising CT and TT variants), with their dose and C0/Dose ratio compared across various post-transplantation timeframes, ethnicities, and initial TAC doses [37].

The findings indicated that ABCB1 3435CC carriers required a dosage increase compared to 3435CT variant carriers, however, there were no notable variances observed in the remaining subgroups. The 3435CT variant did not have a

in both the 0.08-0.14 mg/kg per day and 0.15-0.2 mg/kg per day subgroups [37].

The meta-analysis revealed that the genetic variant ABCB1 3435C>T influences the pharmacokinetics of TAC in adult renal transplant recipients during the first year post-transplantation. Patients with the ABCB1 3435T variant showed a higher dosage ratio compared to those with the ABCB1 3435CC genotype. Notably, individuals homozygous for ABCB1 3435TT demonstrated significantly higher TAC dosage and a lower dosage ratio compared to those with ABCB1 3435CC.

Genotype tests cost-effectiveness

A study examining TAC administration, TDM, and hospitalization costs for kidney transplantation across CYP3A5*1/*1, *1/*3, and *3/3 genotypes found that CYP3A51/1 patients had the highest median combined costs for TAC and TDM ($1062) and hospitalization ($9097), followed by CYP3A51/3 patients with costs of $859 for TAC and TDM and $6467 for hospitalization, while CYP3A53/3 patients incurred the lowest costs, with $761 for TAC and TDM and $5604 for hospitalization, moreover the analysis revealed that CYP3A51/1 patients had significantly higher hospitalization costs compared to CYP3A51/3 patients (by $2787), though this difference had marginal significance, and they also incurred significantly higher costs for TAC and TDM (by $309) and hospitalization (by $3275) compared to CYP3A53/*3 patients.

Other studies on the cost-effectiveness of genotyping have indicated that conducting genotyping for all transplant recipients is currently financially prohibitive in numerous countries due to the elevated expenses associated with pharmacogenetic tests. Nevertheless, there is optimism regarding potential changes in the future, driven by the generation of valuable data from pharmacogenetic studies and advancements in genotyping analyses leading to cost reductions [39-42].

For example, genetic tests for determining CYP2D6 and CYP2C19 polymorphisms, crucial for drug metabolism, cost around $350 to $400. Although most genetic tests are priced in a few hundred dollars, they are expected to become less expensive in the future [38]. However, to justify these costs, genotypic analyses must demonstrate a significant improvement in transplant patient outcomes and cost savings [38].

The scenario regarding the expenses and insurance provisions for pharmacogenetic testing varies greatly. Multigene panel-based tests are typically not covered by insurance, with patients facing a median cost of approximately $700. Single-gene tests may receive coverage for specific genes like CYP2C19, CYP2D6, and HLA-B, depending on the indication. The highest mean cost billed to a patient for a single-gene pharmacogenetic test exceeded $1200, with an average insurance coverage of $160. Coverage for CYP3A5 testing for TAC dosing is infrequent, resulting in a median patient cost of approximately $300 [38].

The cost-effectiveness of genotype testing for kidney transplant recipients hinges on the ability of genotypic analyses to significantly enhance patient outcomes and demonstrate cost savings, while the current costs and insurance coverage for pharmacogenetic testing remain variable and may evolve in the future.

Conclusion

In conclusion, the integration of pharmacogenetics into clinical practice holds promise for refining TAC therapy in kidney transplantation, optimizing dosing regimens, and ultimately improving patient outcomes. As research in this field progresses, the vision of personalized medicine in transplant care may move closer to realization, offering tailored approaches that enhance efficacy while minimizing adverse effects.

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