Insights into Tacrolimus: Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics in Post-Kidney Transplant Care

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Abstract

Tacrolimus is the immunosuppressant of choice post renal transplant to prevent acute rejection. It is a calcineurin inhibitor that forms a complex with the FK506 binding protein and works by inhibiting T-cell proliferation. Tacrolimus is metabolized in the liver and intestinal cells, where CYP3A5, CYP3A4, and ABCB1 are the primary enzymes involved in its metabolism. Patients on tacrolimus experience inter-subject variability in trough levels and toxicity. Factors that contribute to this variability and toxicity could be due to age, comorbidities, and weight. Additionally, genetic factors also play a role. CYP3A5, CYP3A4 and ABCB1 enzymes are known to be polymorphic; hence the function of these enzymes is altered, leading to this variability. This review article discusses the different approaches to pharmacokinetic measuring, and the role of CYP3A5, CYP3A4, ABCB1 and other genetic variants and metabolizing enzymes on variability of Tacrolimus level, toxicity and outcome in post-renal transplant patients. While evidence of *CYP3A5* mainly and other metabolizing enzymes polymorphism is well studied and is available in the Clinical Pharmacogenetics Implementation Consortium (CPIC) and other guidelines, its application and results in different ethnicities are not conclusive. This review has summarized the different published literature on this topic.

Keywords: Kidney Transplant, Tacrolimus, Pharmacokinetics, Pharmacodynamic, Pharmacogenetics, CYP3A5, CYP3A4, ABCB1, Pharmacogenomics

Introduction

Calcineurin inhibitors are the basis of immunosuppressants for renal transplant recipients, as a first-line to prevent organ rejection.[1] Tacrolimus (FK506) specifically is more commonly used as prophylaxis for organ rejection than cyclosporine in post-renal transplant, as it is believed that it has less toxicity and less organ rejection rate.[2,3] According to the Scientific Registry of Transplant Recipients annual report in 2022, Tacrolimus was the immunosuppressant used in more than 90% of all adult kidney transplants.[4] Additionally, the Kidney Disease for Improving Global Outcomes (KDIGO) recommends tacrolimus to be the first line of the calcineurin inhibitors in renal transplant patients.[5]

Tacrolimus is a macrolide antibiotic which functions as an immunosuppressant. Tacrolimus forms a complex with cytosolic immunophilin, FK506 binding protein-12 (FKBP-12) in T cells which inhibits the phosphatase activity of calcineurin, preventing the translocation of nuclear factor of activated T-cells (NFATc) to the nucleus. As a result, the gene transcription of important cytokines including IL-2, IL-3, IL-4, IL-5, IFN-γ, is suppressed. Hence, overall, by inhibiting calcineurin and preventing the production of essential cytokines, tacrolimus acts as an immunosuppressant by downregulating the immune response.[6-8] Figure 1 demonstrates the mechanism of action of tacrolimus.

Tacrolimus is indicated for the prevention of organ rejection in solid organ transplants of kidney, liver and heart as well as for the prevention and treatment of Graft vs Host Disease (GvHD) in post-bone marrow transplant.[1] Tacrolimus can be administered either orally or intravenously, with oral administration being the most common approach post renal transplantation.[1] The weight of the patient determines the starting dose of Tacrolimus and is thereafter adjusted by the results of the Therapeutic Drug Monitoring (TDM).

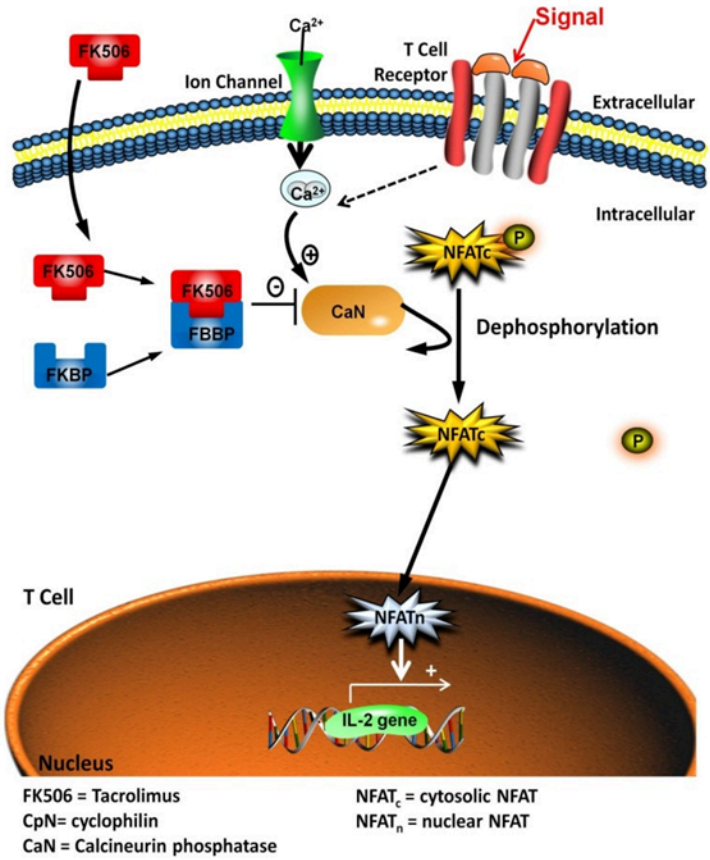

Figure 1: explains the mechanism of action of Tacrolimus (FK506). Adapted from (J Clin Med. 2016 Apr 26;5[5]:50)[8]

Tacrolimus is a narrow therapeutic index medication; hence, it requires rigorous monitoring of drug levels, and close follow-ups for the patient. Furthermore, significant inter-individual variability in its pharmacokinetics poses challenges in monitoring and dosage adjustment.[6,9,10] The achievement of the desired target therapeutic level of tacrolimus is crucial for the patient's post-transplant outcome. Patients with high trough concentrations (C0) may be at higher risk of adverse drug reactions, while patients with low C0 are at an increased risk of acute rejection.[11]

This narrative review aims to highlight the existing literature on tacrolimus and the relationship between pharmacokinetics and pharmacodynamics to pharmacogenetics, and how personalised medicine could lead to better transplant outcomes and reduced toxicity incidence. While previous review, such as the paper by Brunet & Pastor-Anglada (2022),[10] explored the pharmacogenetics of Tacrolimus in different solid organ transplants, this review studies distinct topics to the literature. This review looks at the pharmacogenetics of Tacrolimus in patients post renal transplant specifically, looking into the factors affecting the kidney allograft specifically instead of multi-organ overview. Additionally, the pharmacokinetics measurements explored in the current study, include multiple tools condensed in one paper, such as the C0/D, Rosendaal algorithm, AUC and the traditional trough concentration measurement. This review also explores the conflicting data about the effect of pharmacogenetics in some clinical outcomes, such as acute rejection, delayed graft function, PTDM and others.

1. Pharmacokinetics of Tacrolimus

Tacrolimus has poor bioavailability upon oral administration, in which the mean bioavailability is approximately 25%, but has wide variability ranging from 5% to 93%. Tacrolimus has a high affinity to erythrocytes and plasma proteins. Distribution of Tacrolimus outside the vascular system is in the heart, lungs, kidneys, and pancreas, but not in the cerebrospinal fluid.[12-14]

Tacrolimus is primarily metabolized in the liver by the Cytochrome P450 family enzymes, namely, CYP3A5, CYP3A4, and others, to a lesser extent. Multiple metabolites are formed, with the most predominant being 13-O-demethyl-tacrolimus and 31-O-demethyl-tacrolimus, which exerts an immunosuppressive effect. The metabolites are then mostly eliminated through the biliary route. The activity and expression of the CYP3A5 and CYP3A4 enzymes differ from patient to patient, hence impacting tacrolimus bioavailability and altering its toxicity and immunosuppressive effects.[6,15]

P-glycoprotein, also known as the ATP Binding Cassette subfamily B member 1 (ABCB1), also plays a major role in the metabolism of tacrolimus. This P-glycoprotein acts as a pump at the cellular level, leading to the efflux of the medications outside the cell, hence altering the plasma level of tacrolimus. Figure 2 explains the metabolism of Tacrolimus and the involvement of the CYP3A family enzymes and the ABCB1 gene.[15]

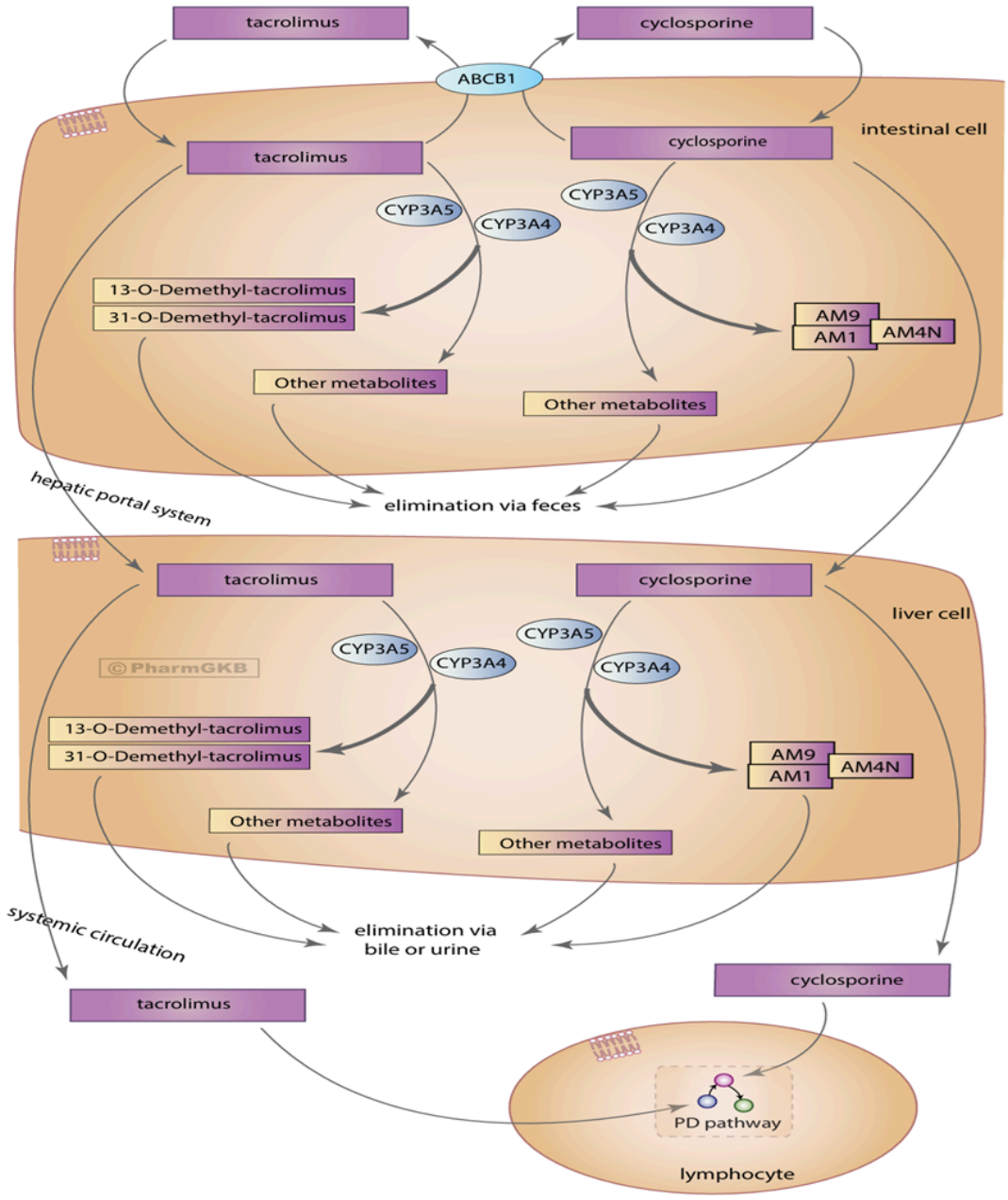

Figure 2: Schematic representation of tacrolimus metabolism (adopted from PharmGKB http://www.pharmgkb.org/pathway/ PA165986114).

The variability in pharmacokinetics and activity of the metabolic enzymes is due to many factors, such as age, food intake, drug adherence, drug-drug interactions, transplant type, albumin and haematocrit concentration, and others. However, the main factor that determines its activity is suggested to be due to polymorphisms and variations in *CYP3A5*, *CYP3A4* and *ABCB1*, which may result in slow or rapid metabolism. Slow Metabolism eventually leads to higher trough concentration levels of tacrolimus or delays in achieving target level, and over immunosuppression and ultimately adverse drug reactions. Conversely, rapid metabolism, which leads to slow activity of immunosuppression and higher incidence of renal rejection.[16-19]

Tacrolimus metabolites excretion is approximately 95% by the bile, while urinary excretion accounts for only approximately 2%, and very minimum of the unbound drug is excreted.[20]

1.1 Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring of Tacrolimus is the measurement of Tacrolimus trough concentration in the blood. It is done regularly once the patient starts on Tacrolimus, to achieve a target trough concentration (C0) of 8-12 ng/ml in the first three months post renal transplant, followed by a trough concentration of 6-10 ng/ml from month 3 onwards post-transplant. Dose for patients post kidney transplant is usually started at 0.1-0.15 mg/kg/day orally and is regularly monitored and adjusted until levels are achieved, to avoid toxicity from overexposure of C0 or rejection from underexposure of C0. Patients attaining different concentrations with a similar dosage range explain the inter-patient variability.[1,10,14,21]

1.1.1 Concentrations adjusted Dose C0/D ratio

Instead of the trough concentration (C0) as a marker for overexposure and underexposure, Thölking *et al*[22] proposed to assess the renal transplant outcome and toxicity by the concentration normalised by the dose (C0/D) ratio, where the concentration obtained at trough (C0) is divided by the dose given to the patient to attain that specific concentration.[18,22] The proposed values of C0/D in the studied population was interpreted as; patients attaining C0/D ratio < 1.05 ng/ml/mg as fast metabolizers, C0/D ratio of 1.05–1.54 ng/ ml/mg as intermediate metabolizers, and C0/D ratio ≥ 1.55 ng/ml/mg as slow metabolizers, additionally patients who attained a C0/D level <1.05 (fast metabolizers) were more at risk of nephrotoxicity, graft loss and mortality than those attaining higher levels. This implies that C0/D has a stronger prognostic factor for toxicity and poor transplant outcome, rather than the genetics and polymorphism of the metabolizing enzymes.[18,22,23]

Thölking *et al* (2019) proposed that fast metabolizers (attaining levels of <1.05 ng/ml/mg) would usually require higher initial dosing as those patients had higher peak concentration at 2 hours post-dose administration compared to slow metabolizers (C2). Thölking *et al* found that. However, current clinical practice does not usually consider concentrations other than C0. There are currently controversies in the correct TDM method for tacrolimus, whether it is C0 or C0/D, or even the Area Under the Concentration-time Curve (AUC).[5,24,25]

1.1.2 AUC

As per the TDM consensus report 2019, the Area Under Concentration-time Curve is one of the best and more accurate parameters to measure pharmacokinetic exposure and relate it to the clinical outcomes.[26] AUC is a measurement of the bioavailability of the drug from multiple plasma concentrations post drug administration.[27]

On the other hand, trough concentration (C0) is a measurement of the overall exposure; hence, it has been poorly correlated to AUC. Patients with the same C0 may not necessarily have similar AUCs. There is evidence to suggest that AUC/C0 ratio is shows minimal inter-patient variability,[28] however, AUC/C0 of tacrolimus is affected by many factors, such as time post-transplant, genetics, conditions affecting gastrointestinal (GI) motility (e.g. bariatric surgery) and drug-drug interactions.[26]

The evidence on the effect of AUC on transplant outcomes, such as rejection, is scarce. Observational studies have shown that the AUC is directly correlated with acute rejection and toxicity post-transplant where the lower the AUC the higher the patient is at risk of rejection, nephrotoxicity and post-transplant diabetes mellitus (PTDM).[29-32] However, these findings are based on earlier studies some of which are limited by their small sample size, and being retrospective in nature. The TDM consensus 2019

recommends measuring AUC/C0 at least once for patients who are early post-transplant, and once when those patients are in the stable period.[26]

1.1.3 Time in Therapeutic range (Rosendaal Method)

The Rosendaal method is an algorithm, first developed for anticoagulation, to calculate the percent of time the patient is in therapeutic range.[33] It considers multiple consecutive measurements and assumes a linear relationship between each value. This method is explored as a tool to optimizes the pharmacologic effect, and improves renal transplant outcomes.[34] Tacrolimus Time in Therapeutic Range (TAC-TTR) in a study by Davis *et al*, 2017, chose a reference range of trough concentration 5-10 ng/ml for the first year post-transplant, and found that patients with less than 60% or 75% of TAC-TTR were at high risk for graft failure.[34] On the other hand, Leino *et al*, 2021observed a reduced risk of acute rejection post-heart transplant in patients attaining TAC-TTR above 30-35%.[35,36] Another study by Song et al, 2019, had a cut-off value of 78%, in which patients attaining TAC-TTR higher than 78% were at increased rejection-free risk compared to the lower percentages, this study compared the TTR values attained and validated it further in a large cohort.[37]

Taken together, observing these TTR values may allow physicians and healthcare providers to identify high-risk patients early on, and avoid the risk of rejection and toxicities.[38]

2. Pharmacogenetics of Tacrolimus Metabolizing Enzymes

2.1 CYP3A5/CYP3A4 Polymorphism:

CYP3A5 polymorphism:

One of the most diverse, multi-functional metabolic pathways is the human CYP3A family. This family of enzymes metabolizes and excretes many drugs commonly used by humans.[39,40] CYP3A5 and CYP3A4 iso-enzymes are part of the Cytochrome P450 enzyme family. They are expressed abundantly in the liver and extrahepatic cells and are involved in the metabolism of almost 90% of currently used medications. Genetic polymorphisms in these iso-enzymes affects pharmacokinetics, therapeutic outcomes, and medication safety of the drugs.[41,42]

The most significant and extensively studied CYP3A5 allele is *CYP3A5*3*, which is associated with a loss-of-function phenotype. Other alleles with loss-of-function include *6 and *7. In contrast, the *1 allele exhibits normal function, while the functions of *8 and *9 remain unknown. Each of these alleles has specific dosing recommendations for tacrolimus (Table 1 below).[43,44]

Table 1: Dosing recommendations for tacrolimus based on CYP3A5 phenotype.[17]

Phenotype	Genotype	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations	Classification of recommendations
Extensive metaboliser (CYP3A5 expresser)	*1/*1	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. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Intermediate metaboliser (CYP3A5 expresser)	*1/*3, *1/*6, *1/*7	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. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metaboliser (CYP3A5 nonexpresser)	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7	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

According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) the frequency of CYP3A5 allele varies significantly in different ethnic groups; for example, the frequency of *CYP3A5*3* is 30% in the African American/Afro-Caribbeans, 75% in East Asians, 92% in Europeans, and 88% in the Middle Eastern population, (Table 2). However, the CPIC does not report the countries included in the Middle Eastern population, and given their genetic heterogeneity, this frequency cannot be generalized to the entire Middle Eastern countries.[17,45,46] While some studies have reported the population frequencies of *CYP3A5*3*, for example 96% in Iran[42] and 74% in Egypt,[47] the frequency remains largely unknown in most of the other Middle Eastern populations. In Oman, the genetic background is different from that of other Middle Eastern countries and is currently not known.

Table 2: CYP3A5*3 allele Frequency in different Ethnicities.[17]

Ethnicity	CYP3A5*3 allele
African American/Afro-Caribbeans	30%
East Asians	75%
Caucasians	92%
Middle Eastern	88%

Because the *CYP3A5*3* allele yields a non-functional CYP3A5 enzyme, individuals carrying the allele tend to be poor drug metabolisers. For example, in an Asian population, Iwamoto *et al* (2015) and has investigated in a prospective study, the effect of *CYP3A5*3*, in which patients who had this variant, patients carrying the *CYP3A5*3* allele had significantly higher Tacrolimus C0/D ratio compared to non-carriers.[48] Niioka *et al* (2015), also observed this effect in another Asian population, where C0/D ratio was 70% higher in patients having *CYP3A5*3*.[49]

In a metanalysis including mixed population of Caucasians, Asians and Africans, the relationship between increased C0/D and *CYP3A5*3* was highly evident, and those patients had a higher risk of acute rejection due to the failure of Tacrolimus level attainment.[50]

In a Caucasian white population (German and Danish), Bruckmueller et al (2015), found that patients who are homozygous carriers of *CYP3A5*3*, required lower doses compared to wild type,[51] which is similar to the Asian population findings. Similarly, in an Iranian population, Ghafari et al (2019), found significant C0/D ratio reduction and increased dose requirement in patients with CYP3A5 expressers compared with non-expressers.[52]

Nonetheless, Contradictory results were found in a Jordanian population, where CYP3A5 expression was found unrelated to dose, C0/D, and transplant outcomes such as graft loss and acute rejection.[53,54]

In the Gulf Arab region, there is scarce research on the effect of *CYP3A5* polymorphism on tacrolimus pharmacokinetics, pharmacodynamics and toxicity. There is though, one case report, in a Saudi patient, where he developed supratherapeutic levels of tacrolimus, and the genotype indicated the patient was a poor expresser of *CYP3A5*.[55] There is, however, one hypothesis by Jithesh *et al* (2022), when conducting the Qatari Genome Project, that fewer Qatari patients would require dosage adjustments compared to other populations. This is because the actionable diplotypes of CYP3A5 have lower frequencies in the Qatari population compared to other populations or ethnicities.[56]

CYP3A4 Polymorphism:

CYP3A4 is the most important CYP enzyme in drug metabolism,[57] and is the most abundant drug metabolizing CYP enzyme in the liver and small intestine. Hence variations in the gene activity affects bioavailability and the exposure of many clinically important drugs.[58] CYP3A4 is the only Cytochrome P450 enzyme that has different frequencies in different genders, where it is more expressed (approximately 1.5-2 times) in females than males.[39] *CYP3A4*1B* (rs2740574) and *CYP3A4*22* (rs35599367) are the two most widely investigated allele polymorphisms in CYP3A4. *CYP3A4*1B* is associated with increased to normal enzyme activity (wild type), while *CYP3A4*22* is linked to decreased enzymatic activity and lower starting dose requirements.[20,58-60]

Although CYP3A4 is also involved in the metabolism of Tacrolimus, and it is abundant in the liver, but according to the literature, it is less susceptible to polymorphism, hence it doesn't get affected by genetic variability and its function remains stable,[57] as shown in the Iranian and Middle Eastern population, the decreased function of CYP3A4 is much less frequent compared to the normal function, unlike CYP3A5 which is the exact opposite.[42,61]

Some researchers hypothesize that *CYP3A4*1B* has a similar sequence similarity with CY3A5, in which when an effect is seen in the tacrolimus pharmacokinetics, the effect is usually due to the CYP3A5, and the exact effect of CYP3A4 on its own is not clear.[20] That's why, the research involving CYP3A4 is inconsistent and controversial.

The frequency of *CYP3A4*1B* is 35-82% in the African and African American population, 2-5% in Caucasians[39,62,63] and some studies show that it is rare or not generally available in the Asian population.[39,63] On the other hand, the frequency of *CYP3A4*22* in the European population ranges from 3.6-9%, while in the Africans and African American is 0.9% and similarly not found in Asians.[58]

In a Meta-analysis by Shi W *et al* (2015), they found in Caucasians, *CYP3A4*1/*1* carriers required lower doses than *CYP3A4*1B* carriers, and that C0/D ratio was significantly higher in *CYP3A4*1/*1* carriers, where in most of the studies included, the allele frequency of *CYP3A4*1/*1* in Caucasians was higher than *CYP3A4*1B*.[64] Similarly, in a Mexican study by Moreno et al (2024), they observed no difference in tacrolimus concentrations in patients carrying *CYP3A4*1B* gene.[65] However, a different study observed that *CYP3A4*1B* gene had lower tacrolimus blood concentrations.[66] Another Meta-analysis done by Li Z *et al* (2024), on approximately 3000 Caucasian patients, found that *CYP3A4*1/*1* required higher Tacrolimus doses compared to patients carrying *CYP3A4*22*.[67] In a North African population (Tunisia), a study by Hannachi *et al* (2020), found that both *CYP3A4*1B* and *CYP3A4*22* affected Tacrolimus clearance at any stage post-transplant.[68]

ABCB1 Polymorphism

ATP binding cassette subfamily B member 1 (ABCB1) is the genetic code for P-glycoprotein (p-gp), also known as multi-drug resistance gene (MDR-1).[69] It is expressed in the liver, pancreas, kidney, T and B lymphocytes, small intestines, colon and the blood brain barrier. Literature indicates that it has a different function in each expression sites where in the intestines it controls xenobiotic absorption, in the kidneys it eliminates waste products, and in the lymphocytes, which is the case for Tacrolimus, its function is to remove the drug outside the cell.[20,70,71] Therefore, it has an important role in Tacrolimus metabolism and transportation intracellularly, as tacrolimus is an ABCB1 substrate. ABCB1 generally acts as an efflux for any biochemically unrelated substrates, such as xenobiotics, pharmaceuticals, dietary compounds, and other compounds outside the cell.[20,70,72]

ABCB1 polymorphism alters the structure and function of p-glycoprotein and alters the drug distribution in the body and medication effectiveness.[73] The most widely studied polymorphisms in ABCB1 are *c.3435C>T*, *c.1236C>T* and *c.2677G>T/A*.[20,72,74] The association of different genotypes with clinical outcomes is inconsistent hence making it questionable.[75]

In a meta-analysis involving cohorts of mixed ethnicities, including white, Asian, African populations, investigating the effect of *ABCB1 c.3435C>T* on Tacrolimus, they observed that *ABCB1 c.3435TT* carriers, required lower doses to reach target level compared to *ABCB1 c.3435CC* carriers, and that the C0/D ratio was higher in carriers of the TT allele as well.[76] Additionally, another meta-analysis found that CC carriers of the gene *ABCB1 c.3435C>T* required higher daily doses compared to T carriers.[77] While contrasting results were found in a Pakistani population, where they found that carriers of the CC variant in the *c.3435C>T* gene had lower C0/D ratio compared to the other variants.[71]

Furthermore, another study found no effect of *ABCB1 c.3435C>T* genotype on tacrolimus concentration or nephrotoxicity.[78] Similarly, in an Indian population, Fernando et al (2019) found no association of *ABCB1 c.3435C>T* polymorphism on rejection incident and nephrotoxicity.[79] Similar results were reported in a Mexican population[65] as well as in a Greek population where there was no significant effect of *ABCB1 c.1236C>T* on C0/D ratio,[80] and in a mixed population where no effect of ABCB1 was found in nephrotoxicity in patients post renal transplant on Tacrolimus.[81]

In the literature, haplotypes of ABCB1 were thought to be more comprehensive, and explained its association to pharmacokinetics more. *ABCB1 c.1236T-2677T-3435T (TTT*) haplotype is known to have a reduced activity in comparison to wildtype.[82]

There are multiple variations in the literature with regards to ABCB1 effect on Tacrolimus pharmacokinetics and toxicity, thus, there are no current guidelines are there to recommend tacrolimus dosing in relation to ABCB1 polymorphism.

Clinical Implications

Several organizations including the FDA, the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG) and the French National Network of Pharmacogenetics (RNPGx) have recently developed dosing guidelines based on CYP3A5 genotypes (Table 1). These guidelines provide specific dose adjustments tailored to individuals with low, intermediate, or normal enzyme activity of CYP3A5. Currently, many institutes utilize this guide for prescribing tacrolimus.[17,83]

Many algorithms were previously developed to calculate the tacrolimus daily dosing required. For example, Passey *et al* (2011), found that tacrolimus levels is influenced by clearance, and hence calculated the clearance using; genetics (CYP3A5), age, time post-transplant, with or without steroid, and

whether the patient was on calcium channel blocker or not,[84] and the algorithm was validated and showed good prediction of Tacrolimus dosing.[85] However, Boughton *et al* (2013) found that the algorithm yielded poor prediction of tacrolimus clearance, when using their cohort's tacrolimus doses and concentrations.[86] Elen's *et al* (2012) later incorporated the loss of function SNP *CYP3A4*22* into the algorithm for its effect on clearance and found that it provided more accurate results.[87] A recent algorithm that was created, also for Caucasians, is one by Francke M *et al* (2021), in a prospective interventional trial, where he found that the algorithm worked on 58% of the patients, and it is an effective method in predicting the tacrolimus starting dose.[88]

Another algorithm was created for the Chinese population, Zou *et al* (2013) incorporated genetics (using CYP3A5 and CYP3A4) with clinical factors, and found that those factors were detrimental for tacrolimus clearance, and had a positive effect on starting dose and maintenance doses of tacrolimus.[89]

These algorithms were designed for specific populations and have not been studied on other groups or ethnicities.

Implementing pharmacogenetics into clinical practise requires properly organized approach. First and foremost, clinicians' awareness is needed for the success of the application, followed by patient education. Choosing the population within the kidney transplant patients that would fit into our algorithm, choosing the variants required and affected by our population, looking at the cost involved, are all crucial aspects prior to the genotype guided dosing implementation.[90]

Pharmacodynamics (PD) of Tacrolimus including Pharmacovigillance (PV):

As mentioned earlier, when therapeutic drug monitoring (TDM) is performed and dosage adjustments are made based on TDM results and pharmacogenetics, patients would achieve levels sooner, and hence, the outcomes of renal transplantation are likely to be favourable with less side-effects.[10] High inter-patient variability (IPV) in Tacrolimus level significantly influences the incidence of side effects and rejection, particularly when tacrolimus levels are either supratherapeutic or subtherapeutic, respectively.[10,91]

Pharmacovigillance is an important pillar of medication and patient safety, close monitoring of real-world patients on medications even well after the controlled-environment of clinical trial phase is completed is important. With the introduction of personalised medicine and pharmacogenetics, it is now feasible to choose the right drug and dose for the patient and have an indication of the toxicity expected by phenotyping patients into different metabolism status (namely, normal, slow or fast metabolisers). For Tacrolimus in specific, the integration of pharmacogenetics and the metabolizing status of the patient with the pharmacokinetics parameters such as therapeutic drug monitoring (TDM) by using trough concentrations, or the C0/D ratio can function as a real-time Pharmacovigillance signal, which should lead to early clinical intervention and hence modulate the pharmacodynamics of the drug and patient in case of over suppression leading to toxicity or under suppression leading to rejection, which ultimately enhance patient safety, optimizes immunosuppressive efficacy, and improve overall survival of the kidney graft.[92,93]

Delayed Graft Function (DGF)

Delayed Graft function (DGF) is a common complication post renal transplant, and is usually diagnosed in the first week post-transplant.[94] It is defined as the inability of the allograft kidney to function immediately post-transplant and during the first week following the transplant. The most common type of DGF is Acute Tubular Necrosis (ATN) which sometimes leads to acute rejection.[95] The occurrence of DGF is usually in relation to the donor characteristics, such as age, live or deceased donor, comorbidities of donor, time of ischemia of the kidneys, and others. DGF could be a prognostic factor for graft loss and can reduce the graft survival by a third.[95,96]

DGF is said to be associated with high blood Tacrolimus levels, but there are limited studies that relate genetics to it.[10] Genvigir *et al* (2020) found that *CYP2C8*3* appears to be a protective factor for DGF in a Brazilian cohort.[97] Another study by Asempa *et al* (2018) on African Americans found that *CYP3A5*1 AA* carriers have an increased risk of DGF.[98]

On the other hand, a case study by Cãlusi *et al* (2025) reported that high tacrolimus levels, in addition to other donor factors, can lead to DGF, but did not include any genetics factor in their study.[99] In an observational study by Kuypers *et al* (2010), patients with DGF on day 4 had higher tacrolimus trough levels among *CYP3A5*3* carriers,[100] but this study does not necessary relate the incidence of DGF to any polymorphism of CYP3A5. In a meta-analysis by Yang *et al* (2021), which included 5 randomized clinical trials and 684 patients, likewise did not find any association between gene polymorphisms and delayed graft function.[101] Finally, several other studies reported similar findings, showing no significant association between genetic polymorphisms and the occurrence of DGF.[52,78,102-104]

Acute Rejection

Acute graft rejection usually occurs between days to weeks post transplantation, when the recipient's immune system attacks the graft organ and recognizes it as a foreign body. Thus, induction therapy and maintenance therapy of immunosuppression is administered to avoid and prevent rejection. It is essential to identify the signs of rejection and treat it early on to avoid graft loss.[105]

Just like DGF, there is conflicting literature on the effect of genetic polymorphism on acute rejection. Multiple studies have shown no association or relation between *CYP3A5* and *ABCB1* variants and acute rejection in different ethnicities[106-113].

On the other hand, in a Tunisian cohort, Abderahmene *et al* (2024), studied the effect of multiple SNPs in *CYP3A5*, *CYP3A4*, *ABCB1* and *POR* genes on renal transplant clinical outcomes, and found only *CYP3A5*1* variant carriers having a significant increase in the incidence of acute rejection.[114] Similar results were found in a different study by Jia *et al* (2024).[115] These results are similar to the CPIC assumptions and recommendations, where they assume that having a *CYP3A5*1* would indicate having low tacrolimus trough levels, hence resulting in acute rejection.[17]

More validation studies are needed to study the correlation between different SNPs and the incidence of acute rejection.

Nephrotoxicity

Calcineurin Inhibitor (CNI) induced nephrotoxicity occurs any time after CNI administration, at any dose and trough level, and is characterized by reduction in renal functions, vasoconstriction, epithelial vacuolization, vascular injury and thrombotic microangiopathy. Acute CNI nephrotoxicity is usually reversible with the reduction of CNI dose or withholding it.[116]Calcineurin Inhibitor (CNI) induced nephrotoxicity occurs any time after CNI administration, and at any trough level, is characterized by reduction in renal functions, vasoconstriction, epithelial vacuolization, vascular injury and thrombotic microangiopathy. It is frequently observed in patients receiving Tacrolimus, though it is more prevalent among those treated with cyclosporine. In Tacrolimus-treated patients, it is generally associated with higher doses, typically exceeding 20 mg per day. Acute CNI nephrotoxicity is usually reversible with the reduction of CNI dose, withholding it and prevention of other concomitant nephrotoxic medications.[116-119]

Over the past few years, there were multiple studies that have shown no relation between *ABCB1* and *CYP3A4/5* polymorphism in the recipient and nephrotoxicity.[50,120,121] On the other hand, Kuypers *et al* (2007) found that recipient patients who are carriers of the combination of *CYP3A4*1/CYP3A5*1* and *CYP3A4*1B/ CYP3A5*1* genotypes were more likely to develop tacrolimus-induced nephrotoxicity.[122]

While another study found that nephrotoxicity occurred more likely in *CYP3A5*3* carriers in donors instead of recipients.[123]

Finally, there is one study on Chinese recipients that observed that the genotype NFATC2 and NFATC1 have a significant impact on tacrolimus-induced nephrotoxicity post-transplant.[124]

The above evidence may suggest that *CYP3A5*1*, *CYP3A4*1* and *CYP3A4*1B* occurrence in recipients might be a risk factor for Tacrolimus-induced nephrotoxicity, but the evidence is still inconclusive and clinical trials and bigger studies need to be conducted.

Neurotoxicity

Neurotoxicity is one of the common side effects post-CNI use that impacts quality of life., It is estimated that up to 50% of tacrolimus users develop fine tremors in the upper extremities initially then can develop to severe tremors.[125,126] Tremors are suggested to occur as a result of the entry and accumulation of tacrolimus in the central nervous system (CNS), which damages the capillaries and affects the efflux transporters at the blood-brain barrier. It was hypothesized that high tacrolimus level in the blood could be associated with a higher incidence of tremors, others associate the high doses to a high incidence. Although a meta-analysis by King *et al* (2024),found no association between trough tacrolimus concentrations and tremors, the incidence was found to be higher in the elderly and the black ethnicity.[126,127] The usual treatment of tremors post-tacrolimus use is dose reduction, and in more severe neurotoxicity, discontinuation of the drug and substituting it to another immunosuppressant instead.

In a paper published by Abderahmene *et al* (2024),[114] they found that *CYP3A5*3* SNP had a protective role towards tremors, but not CYP3A4 and ABCB1, where there was no association with it in regard to tremors.

Post-Transplant Diabetes Mellitus (PTDM)

This new onset diabetes occurrence is a common complication post-tacrolimus use. The incidence of diabetes post-tacrolimus is higher than post-cyclosporine.[20] There are multiple hypotheses regarding the mechanism of action, but one theory suggests that in peripheral cells, tacrolimus lowers insulin sensitivity, leading to hyperglycaemia, and it is usually a dose-dependent effect.[128] The pre-transplant risk factors include age, family history of diabetes, obesity and genetic factors.[129] PTDM was previously known as New Onset of Diabetes After Transplantation (NODAT), but in 2014 it was changed to PTDM by an international consensus.[130]

A number of genes have been implicated in where presence of specific variants within *PPARA, POR, TCF7L2, SLC30A8, HNF-4A, NFATC4, IL-6, IL-28B, IL-2, IL-7R, IL-17R, CCL2, IFN-γ, KCNQ, Angiotensin, and Leptin* is associated with an increased risk of developing PTDM.[20,131] The management of PTDM usually involves close monitoring and starting antidiabetic medications.[117]

There are numerous inconsistent results in the literature. Thus, studying the pharmacogenetics effect on clinical outcome and toxicity of the renal transplant in our population would be of great interest.[10]

Conclusion

In summary, enhanced therapeutic strategies – which effectively integrates pharmacogenetics (e.g. CYP3A5 genotype-guided dosing) with pharmacokinetics monitoring (e.g. trough concentrations, and C0/D ratio with pharmacovigilance signals) – enable clinicians to tailor tacrolimus therapy to each patient's unique clinical profile, thereby facilitating more rapid achievement of levels and optimization of

therapeutic concentrations. This approach can reduce risk factors, ultimately improving long-term graft and patient outcomes, reducing side effects as well as improving overall survival and improving quality of life.

References:

1. Araya AA, Tasnif Y. Tacrolimus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK544318/ PubMed PMID: 31335038.

2. Alghamdi S, Nabi Z, Skolnik E, Alkorbi L, Albaqumi M. Cyclosporine versus tacrolimus maintenance therapy in renal transplant. Exp Clin Transplant 2011 Jun;9(3):170-174.

3. Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, et al; ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007 Dec;357(25):2562-2575.

4. Husain SA, Lentine KL. Policy Strategies to Reduce Financial Risks for Living Donors. Kidney360 2023 Jul;4(7):987-989.

5. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, et al; Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int 2010 Feb;77(4):299-311.

6. Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of calcineurin antagonists. Transplant Proc 2004 Mar;36(2)(Suppl):25S-32S.

7. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. Drugs 2000 Feb;59(2):323-389.

8. Bennett J, Cassidy H, Slattery C, Ryan MP, McMorrow T. Tacrolimus Modulates TGF-β Signaling to Induce Epithelial-Mesenchymal Transition in Human Renal Proximal Tubule Epithelial Cells. J Clin Med 2016 Apr;5(5):50.

9. Yang C, Xi Y, Chen WY, Sang L, Liu DD, Zhang R, et al. Conversion ratio of tacrolimus switching from intravenous infusion to oral administration after lung transplantation. J Thorac Dis 2020 Aug;12(8):4292-4298.

10. Brunet M, Pastor-Anglada M. Insights into the Pharmacogenetics of Tacrolimus Pharmacokinetics and Pharmacodynamics. Pharmaceutics 2022 Aug;14(9):1755.

11. Meziyerh S, van Gelder T, Kers J, van der Helm D, van der Boog PJ, de Fijter JW, et al. Tacrolimus and Mycophenolic Acid Exposure Are Associated with Biopsy-Proven Acute Rejection: A Study to Provide Evidence for Longer-Term Target Ranges. Clin Pharmacol Ther 2023 Jul;114(1):192-200.

12. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet 2004;43(10):623-653.

13. Undre N, Möller A. Pharmacokinetic interpretation of FK 506 levels in blood and in plasma during a European randomised study in primary liver transplant patients. The FK 506 European Study Group. Transpl Int 1994;7(Suppl 1):S15-S21.

14. Venkataramanan R, Jain A, Warty VS, Abu-Elmagd K, Alessiani M, Lever J, et al. Pharmacokinetics of FK 506 in transplant patients. Transplant Proc 1991 Dec;23(6):2736-2740.

15. Barbarino JM, Staatz CE, Venkataramanan R, Klein TE, Altman RB. PharmGKB summary: cyclosporine and tacrolimus pathways. Pharmacogenet Genomics 2013 Oct;23(10):563-585.

16. Coto E, Tavira B, Suárez-Álvarez B, López-Larrea C, Díaz-Corte C, Ortega F, et al. Pharmacogenetics of tacrolimus: ready for clinical translation? Kidney Int Suppl (2011) 2011 Aug;1(2):58-62..

17. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther 2015 Jul;98(1):19-24.

18. van Gelder T, Meziyerh S, Swen JJ, de Vries AP, Moes DJ. The Clinical Impact of the C_0/D Ratio and the CYP3A5 Genotype on Outcome in Tacrolimus Treated Kidney Transplant Recipients. Front Pharmacol 2020 Jul;11:1142.

19. Verona P, Edwards J, Hubert K, Avorio F, Re VL, Di Stefano R, et al. Tacrolimus-Induced Neurotoxicity After Transplant: A Literature Review. Drug Saf 2024 May;47(5):419-438.

20. Yu M, Liu M, Zhang W, Ming Y. Pharmacokinetics, Pharmacodynamics and Pharmacogenetics of Tacrolimus in Kidney Transplantation. Curr Drug Metab 2018;19(6):513-522.

21. Mohamed ME, Schladt DP, Guan W, Wu B, van Setten J, Keating BJ, et al; DeKAF Genomics and GEN03 Investigators. Tacrolimus troughs and genetic determinants of metabolism in kidney transplant recipients: A comparison of four ancestry groups. Am J Transplant 2019 Oct;19(10):2795-2804.

22. Thölking G, Fortmann C, Koch R, Gerth HU, Pabst D, Pavenstädt H, et al. The tacrolimus metabolism rate influences renal function after kidney transplantation. PLoS One 2014 Oct;9(10):e111128.

23. Thölking G, Schmidt C, Koch R, Schuette-Nuetgen K, Pabst D, Wolters H, et al. Influence of tacrolimus metabolism rate on BKV infection after kidney transplantation. Sci Rep 2016 Aug;6(1):32273.

24. Thölking G, Schütte-Nütgen K, Schmitz J, Rovas A, Dahmen M, Bautz J, et al. A Low Tacrolimus Concentration/Dose Ratio Increases the Risk for the Development of Acute Calcineurin Inhibitor-Induced Nephrotoxicity. J Clin Med 2019 Oct;8(10):1586.

25. van Gelder T, Gelinck A, Meziyerh S, de Vries APJ, Moes DJAR. Therapeutic drug monitoring of tacrolimus after kidney transplantation: trough concentration or area under curve-based monitoring? Br J Clin Pharmacol. n/a(n/a).

26. Brunet M, van Gelder T, Åsberg A, Haufroid V, Hesselink DA, Langman L, et al. Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report. Ther Drug Monit 2019 Jun;41(3):261-307.

27. Grogan S, Preuss CV. Pharmacokinetics. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557744/ PubMed PMID: 32491676.

28. Woillard JB, Monchaud C, Saint-Marcoux F, Labriffe M, Marquet P. Can the Area Under the Curve/Trough Level Ratio Be Used to Optimize Tacrolimus Individual Dose Adjustment? Transplantation 2023 Jan;107(1):e27-e35.

29. Undre NA, van Hooff J, Christiaans M, Vanrenterghem Y, Donck J, Heeman U, et al. Low systemic exposure to tacrolimus correlates with acute rejection. Transplant Proc 1999;31(1-2):296-298.

30. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. Clin Pharmacol Ther 2004 May;75(5):434-447.

31. Scholten EM, Cremers SC, Schoemaker RC, Rowshani AT, van Kan EJ, den Hartigh J, et al. AUC-guided dosing of tacrolimus prevents progressive systemic overexposure in renal transplant recipients. Kidney Int 2005 Jun;67(6):2440-2447.

32. Hon YY, Chamberlain CE, Kleiner DE, Ring MS, Hale DA, Kirk AD, et al. Evaluation of tacrolimus abbreviated area-under-the-curve monitoring in renal transplant patients who are potentially at risk for adverse events. Clin Transplant 2010;24(4):557-563.

33. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993 Mar;69(3):236-239.

34. Davis S, Gralla J, Klem P, Tong S, Wedermyer G, Freed B, et al. Lower tacrolimus exposure and time in therapeutic range increase the risk of de novo donor-specific antibodies in the first year of kidney transplantation. Am J Transplant 2018 Apr;18(4):907-915.

35. Leino AD, Park JM, Pasternak AL. Impact of CYP3A5 phenotype on tacrolimus time in therapeutic range and clinical outcomes in pediatric renal and heart transplant recipients. Pharmacotherapy 2021 Aug;41(8):649-657.

36. Adie SK, Bitar A, Konerman MC, Dorsch MP, Andrews CA, Pogue K, et al. Tacrolimus time in therapeutic range and long-term outcomes in heart transplant recipients. Pharmacotherapy 2022 Feb;42(2):106-111.

37. Song T, Yin S, Jiang Y, Huang Z, Liu J, Wang Z, et al. Increasing Time in Therapeutic Range of Tacrolimus in the First Year Predicts Better Outcomes in Living-Donor Kidney Transplantation. Front Immunol 2019 Dec;10:2912.

38. Yin S, Huang Z, Wang Z, Fan Y, Wang X, Song T, et al. Early Monitoring and Subsequent Gain of Tacrolimus Time-In-Therapeutic Range May Improve Clinical Outcomes After Living Kidney Transplantation. Ther Drug Monit 2021 Dec;43(6):728-735.

39. Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem 2008 Nov;392(6):1093-1108.

40. Lamba J, Hebert JM, Schuetz EG, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for CYP3A5. Pharmacogenet Genomics 2012 Jul;22(7):555-558.

41. Xie HG, Wood AJ, Kim RB, Stein CM, Wilkinson GR. Genetic variability in CYP3A5 and its possible consequences. Pharmacogenomics 2004 Apr;5(3):243-272.

42. Neyshaburinezhad N, Ghasim H, Rouini M, Daali Y, Ardakani YH. Frequency of Important CYP450 Enzyme Gene Polymorphisms in the Iranian Population in Comparison with Other Major Populations: A Comprehensive Review of the Human Data. J Pers Med 2021 Aug;11(8):8..

43. CYP3A5_allele_functionality_reference.xlsx [Internet]. [cited 2024 Nov 27]. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.cpicpgx.org%2Fdata%2Freport%2Fcurrent%2Fallele_function_reference%2FCYP3A5_allele_functionality_reference.xlsx&wdOrigin=BROWSELINK

44. PharmGKB [Internet]. [cited 2024 Nov 27]. Gene-specific Information Tables for CYP3A5. Available from: https://www.pharmgkb.org/page/cyp3a5RefMaterials

45. Hajjej A, Almawi WY, Arnaiz-Villena A, Hattab L, Hmida S. The genetic heterogeneity of Arab populations as inferred from HLA genes. PLoS One 2018 Mar;13(3):e0192269.

46. CPIC® Guideline for Tacrolimus and CYP3A5 – CPIC [Internet]. [cited 2024 Nov 27]. Available from: https://cpicpgx.org/guidelines/guideline-for-tacrolimus-and-cyp3a5/

47. Mutawi TM, Zedan MM, Yahya RS, Zakria MM, El-Sawi MR, Gaedigk A. Genetic variability of *CYP2D6, CYP3A4* and *CYP3A5* among the Egyptian population. Pharmacogenomics 2021 Apr;22(6):323-334.

48. Iwamoto T, Monma F, Fujieda A, Nakatani K, Gayle AA, Nobori T, et al. Effect of Genetic Polymorphism of CYP3A5 and CYP2C19 and Concomitant Use of Voriconazole on Blood Tacrolimus Concentration in Patients Receiving Hematopoietic Stem Cell Transplantation. Ther Drug Monit 2015 Oct;37(5):581-588.

49. Niioka T, Kagaya H, Saito M, Inoue T, Numakura K, Habuchi T, et al. Capability of utilizing CYP3A5 polymorphisms to predict therapeutic dosage of tacrolimus at early stage post-renal transplantation. Int J Mol Sci 2015 Jan;16(1):1840-1854.

50. Rojas L, Neumann I, Herrero MJ, Bosó V, Reig J, Poveda JL, et al. Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J 2015 Feb;15(1):38-48.

51. Bruckmueller H, Werk AN, Renders L, Feldkamp T, Tepel M, Borst C, et al. Which Genetic Determinants Should be Considered for Tacrolimus Dose Optimization in Kidney Transplantation? A Combined Analysis of Genes Affecting the CYP3A Locus. Ther Drug Monit 2015 Jun;37(3):288-295.

52. Ghafari S, Dashti-Khavidaki S, Khatami MR, Ghahremani MH, Seyednejad SA, Beh-Pajooh A. Association Between CYP3A5 Genetic Polymorphisms with Tacrolimus Dose Requirement and Allograft Outcomes in Iranian Kidney Transplant Recipients. Iran J Kidney Dis 2019 Nov;13(6):414-416.

53. Sy SK, Singh RP, Shilbayeh S, Zmeili R, Conrado D, Derendorf H. Influence of CYP3A5 6986A > G and ABCB1 3435C > T Polymorphisms on Adverse Events Associated With Tacrolimus in Jordanian Pediatric Renal Transplant Patients. Clin Pharmacol Drug Dev 2013 Jan;2(1):67-78.

54. Shilbayeh S, Zmeili R, Almardini RI. The impact of CYP3A5 and MDR1 polymorphisms on tacrolimus dosage requirements and trough concentrations in pediatric renal transplant recipients. Saudi J Kidney Dis Transpl 2013 Nov;24(6):1125-1136.

55. Alotaibi N. CYP3A5 Polymorphisms Leading to Tacrolimus Toxicity Following an Adult Renal Transplant. Saudi J Kidney Dis Transpl 2023 May;34(3):250-253.

56. Jithesh PV, Abuhaliqa M, Syed N, Ahmed I, El Anbari M, Bastaki K, et al; Qatar Genome Program Research Consortium. A population study of clinically actionable genetic variation affecting drug response from the Middle East. NPJ Genom Med 2022 Feb;7(1):10.

57. Mulder TA, van Eerden RA, de With M, Elens L, Hesselink DA, Matic M, et al. *CYP3A4*22* Genotyping in Clinical Practice: Ready for Implementation? Front Genet 2021 Jul;12:711943.

58. Pratt VM, Cavallari LH, Fulmer ML, Gaedigk A, Hachad H, Ji Y, et al. CYP3A4 and CYP3A5 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. J Mol Diagn 2023 Sep;25(9):619-629.

59. Oetting WS, Wu B, Schladt DP, Guan W, Remmel RP, Mannon RB, et al. Genome-wide association study identifies the common variants in CYP3A4 and CYP3A5 responsible for variation in tacrolimus trough concentration in Caucasian kidney transplant recipients. Pharmacogenomics J 2018 May;18(3):501-505.

60. Kuypers DR. "What do we know about tacrolimus pharmacogenetics in transplant recipients?". Pharmacogenomics 2018 May;19(7):593-597.

61. Zhou Y, Lauschke VM. The genetic landscape of major drug metabolizing cytochrome P450 genes-an updated analysis of population-scale sequencing data. Pharmacogenomics J 2022 Dec;22(5-6):284-293.

62. Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001 Apr;27(4):383-391.

63. Uçkun Z, Baskak B, Özdemir H, Özel-Kizil ET, Devrimci-Özgüven H, Süzen HS. Genotype and Allele Frequency of *CYP3A4 -392A>G* in Turkish Patients with Major Depressive Disorder. Turk J Pharm Sci 2018 Aug;15(2):200-206.

64. Shi WL, Tang HL, Zhai SD. Effects of the CYP3A4*1B Genetic Polymorphism on the Pharmacokinetics of Tacrolimus in Adult Renal Transplant Recipients: A Meta-Analysis. PLoS One 2015 Jun;10(6):e0127995.

65. Alatorre-Moreno EV, Saldaña-Cruz AM, Pérez-Guerrero EE, Morán-Moguel MC, Contreras-Haro B, López-de La Mora DA, et al. Association of CYP3A4-392A/G, CYP3A5-6986A/G, and ABCB1-3435C/T Polymorphisms with Tacrolimus Dose, Serum Concentration, and Biochemical Parameters in Mexican Patients with Kidney Transplant. Genes (Basel) 2024 Apr;15(4):497.

66. Concha J, Sangüesa E, Ribate MP, García CB. CYP3A4*1B but Not CYP3A5*3 as Determinant of Long-Term Tacrolimus Dose Requirements in Spanish Solid Organ Transplant Patients. Int J Mol Sci 2024 Oct;25(20):11327.

67. Li Z, Wang X, Li D, Cheng S, Li Z, Guo H, et al. Effects of CYP3A4*22 and POR*28 variations on the pharmacokinetics of tacrolimus in renal transplant recipients: a meta-analysis of 18 observational studies. BMC Nephrol 2024 Feb;25(1):48.

68. Hannachi I, Ben Fredj N, Chadli Z, Ben Fadhel N, Ben Romdhane H, Touitou Y, et al. Effect of CYP3A4*22 and CYP3A4*1B but not CYP3A5*3 polymorphisms on tacrolimus pharmacokinetic model in Tunisian kidney transplant. Toxicol Appl Pharmacol 2020 Jun;396:115000.

69. ABCB1 ATP binding cassette subfamily B member 1 [Homo sapiens (human)] - Gene - NCBI [Internet]. [cited 2025 Jun 14]. Available from: https://www.ncbi.nlm.nih.gov/gene/5243

70. Vafadari R, Bouamar R, Hesselink DA, Kraaijeveld R, van Schaik RH, Weimar W, et al. Genetic polymorphisms in ABCB1 influence the pharmacodynamics of tacrolimus. Ther Drug Monit 2013 Aug;35(4):459-465.

71. Azam F, Khan M, Khaliq T, Bhatti AB. Influence of ABCB1 gene polymorphism on concentration to dose ratio and adverse effects of tacrolimus in Pakistani liver transplant recipients. Pak J Med Sci 2021;37(3):689-694.

72. Hodges LM, Markova SM, Chinn LW, Gow JM, Kroetz DL, Klein TE, et al. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). Pharmacogenet Genomics 2011 Mar;21(3):152-161.

73. Rotarescu CA, Maruntelu I, Rotarescu I, Constantinescu AE, Constantinescu I. Analysis of ABCB1 Gene Polymorphisms and Their Impact on Tacrolimus Blood Levels in Kidney Transplant Recipients. Int J Mol Sci 2024 Oct;25(20):20.

74. Syarifah S, Widyawati T, Hasni D, Sari MI, Rusdiana R, Hamdi T. The Relation of Haplotype ATP-binding Cassette B1 and Glutathione S-transferase P1 *A313G* Genes with Hematological Toxicity in Indonesian Breast Cancer Patients Receiving Chemotherapy. Oman Med J 2022 Mar;37(2):e357-e357.

75. Al-Diab O, Yousef A, Al Manassrah E, Masadeh A, Olemat M, Qosa H, et al. Genotype and Haplotype Analysis of *ABCB1* at 1236, 2677 and 3435 among Jordanian Population. Trop J Pharm Res 2015 Jul;14(6):1013.

76. Peng W, Lin Y, Zhang H, Meng K. Effect of ABCB1 3435C>T Genetic Polymorphism on Pharmacokinetic Variables of Tacrolimus in Adult Renal Transplant Recipients: A Systematic Review and Meta-analysis. Clin Ther 2020 Oct;42(10):2049-2065. .

77. Li Z, Wang X, Li D, Cheng S, Dong Y, Yang H, et al. The Impact of ABCB1 SNPs on Tacrolimus Pharmacokinetics in Liver or Kidney Transplant Recipients: A Meta-analysis. Curr Pharm Des 2023;29(29):2323-2335.

78. Sallustio BC, Noll BD, Hu R, Barratt DT, Tuke J, Coller JK, et al. Tacrolimus dose, blood concentrations and acute nephrotoxicity, but not CYP3A5/ABCB1 genetics, are associated with allograft tacrolimus concentrations in renal transplant recipients. Br J Clin Pharmacol 2021 Oct;87(10):3901-3909.

79. Fernando ME, Sellappan M, Srinivasa Prasad ND, Suren S, Thirumalvalavan K. Influence of CYP3A5 and ABCB1 Polymorphism on Tacrolimus Drug Dosing in South Indian Renal Allograft Recipients. Indian J Nephrol 2019;29(4):261-266.

80. Tsironi A, Lazaros K, Mendrinou E, Papasotiriou M, Siamoglou S, Kydonopoulou K, et al. Impact of *CYP3A4* and *ABCB1* genetic variants on tacrolimus dosing in Greek kidney transplant recipients. Front Pharmacol 2025 Mar;16:1538432.

81. Gijsen VM, Madadi P, Dube MP, Hesselink DA, Koren G, de Wildt SN. Tacrolimus-induced nephrotoxicity and genetic variability: a review. Ann Transplant 2012;17(2):111-121.

82. Brazeau DA, Attwood K, Meaney CJ, Wilding GE, Consiglio JD, Chang SS, et al. Beyond Single Nucleotide Polymorphisms: *CYP3A5*3*6*7* Composite and *ABCB1* Haplotype Associations to Tacrolimus Pharmacokinetics in Black and White Renal Transplant Recipients. Front Genet 2020 Aug;11:889.

83. Abdullah-Koolmees H, van Keulen AM, Nijenhuis M, Deneer VH. Pharmacogenetics Guidelines: Overview and Comparison of the DPWG, CPIC, CPNDS, and RNPGx Guidelines. Front Pharmacol 2021 Jan;11:595219.

84. Passey C, Birnbaum AK, Brundage RC, Oetting WS, Israni AK, Jacobson PA. Dosing equation for tacrolimus using genetic variants and clinical factors. Br J Clin Pharmacol 2011 Dec;72(6):948-957.

85. Passey C, Birnbaum AK, Brundage RC, Schladt DP, Oetting WS, Leduc RE, et al. Validation of tacrolimus equation to predict troughs using genetic and clinical factors. Pharmacogenomics 2012 Jul;13(10):1141-1147.

86. Boughton O, Borgulya G, Cecconi M, Fredericks S, Moreton-Clack M, MacPhee IA. A published pharmacogenetic algorithm was poorly predictive of tacrolimus clearance in an independent cohort of renal transplant recipients. Br J Clin Pharmacol 2013 Sep;76(3):425-431.

87. Elens L, Hesselink DA, van Schaik RH, van Gelder T. The CYP3A4*22 allele affects the predictive value of a pharmacogenetic algorithm predicting tacrolimus predose concentrations. Br J Clin Pharmacol 2013 Jun;75(6):1545-1547.

88. Francke MI, Andrews LM, Le HL, van de Wetering J, Clahsen-van Groningen MC, van Gelder T, et al. Avoiding Tacrolimus Underexposure and Overexposure with a Dosing Algorithm for Renal Transplant Recipients: A Single Arm Prospective Intervention Trial. Clin Pharmacol Ther 2021 Jul;110(1):169-178.

89. Zuo X cong, Ng CM, Barrett JS, Luo A jing, Zhang B kui, Deng C hui, et al. Effects of CYP3A4 and CYP3A5 polymorphisms on tacrolimus pharmacokinetics in Chinese adult renal transplant recipients: a population pharmacokinetic analysis. Pharmacogenet Genomics. 2013 May;23(5):251–61. PubMed PMID: 23459029.

90. Pasternak A. Establishing a CYP3A5 genotype–guided tacrolimus dosing protocol in adult kidney transplant recipients [Internet]. Available from: https://academic.oup.com/ajhp/article/83/3/e134/8237253?login=false

91. Venkat VL, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. Pediatr Transplant 2008 Feb;12(1):67-72.

92. Koh Y, Yap CW, Li SC. A quantitative approach of using genetic algorithm in designing a probability scoring system of an adverse drug reaction assessment system. Int J Med Inform 2008 Jun;77(6):421-430.

93. Spahn C, Toda N, Groat B, Aimer O, Rogers S, Oni-Orisan A, et al; Pharmacogenomics Global Research Network (PGRN) Publications Committee. Transforming Pharmacovigilance With Pharmacogenomics: Toward Personalized Risk Management. Clin Pharmacol Ther 2025 Dec;118(6):1286-1296.

94. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant 2011 Nov;11(11):2279-2296.

95. Clarkson MR, Magee CN, Brenner BM, eds. Chapter 40 - Clinical Aspects of Renal Transplantation. In: Pocket Companion to Brenner and Rector's The Kidney (Eighth Edition) [Internet]. Philadelphia: W.B. Saunders; 2011 [cited 2025 Jun 18]. p. 827–50. Available from: https://www.sciencedirect.com/science/article/pii/B9781416066408000403 doi:10.1016/B978-1-4160-6640-8.00040-3

96. Srinivas TR, Schold JD, Meier-Kriesche HU. CHAPTER 105 - Outcomes of Renal Transplantation. In: Floege J, Johnson RJ, Feehally J, editors. Comprehensive Clinical Nephrology (Fourth Edition) [Internet]. Philadelphia: Mosby; 2010 [cited 2025 Jun 18]. p. 1222–31. Available from: https://www.sciencedirect.com/science/article/pii/B9780323058766001052 doi:10.1016/B978-0-323-05876-6.00105-2

97. Genvigir FD, Campos-Salazar AB, Felipe CR, Tedesco-Silva H Jr, Medina-Pestana JO, Doi SQ, et al. *CYP3A5*3* and *CYP2C8*3* variants influence exposure and clinical outcomes of tacrolimus-based therapy. Pharmacogenomics 2020 Jan;21(1):7-21.

98. Asempa TE, Rebellato LM, Hudson S, Briley K, Maldonado AQ. Impact of CYP3A5 genomic variances on clinical outcomes among African American kidney transplant recipients. Clin Transplant 2018 Jan;32(1).

99. Căluşi T, Sorohan B, Georgescu DE, Spânu D, Iordache A, Purcaru F. Delayed Graft Function and Tacrolimus Overdosage: A Case Report. Chir Buchar Rom 1990. 2025 Apr;120(eCollection):1–6. PubMed PMID: 40285539.

100. Kuypers DR, de Jonge H, Naesens M, Vanrenterghem Y. A prospective, open-label, observational clinical cohort study of the association between delayed renal allograft function, tacrolimus exposure, and CYP3A5 genotype in adult recipients. Clin Ther 2010 Nov;32(12):2012-2023.

101. Yang H, Sun Y, Yu X, Hu X, Wang W, Zhang X, et al. Clinical Impact of the Adaptation of Initial Tacrolimus Dosing to the CYP3A5 Genotype After Kidney Transplantation: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Pharmacokinet 2021 Jul;60(7):877-885.

102. Glowacki F, Lionet A, Buob D, Labalette M, Allorge D, Provôt F, et al. CYP3A5 and ABCB1 polymorphisms in donor and recipient: impact on Tacrolimus dose requirements and clinical outcome after renal transplantation. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2011 Sep;26(9):3046–50. PubMed PMID: 21677300.

103. Abdel-Kahaar E, Winter S, Tremmel R, Schaeffeler E, Olbricht CJ, Wieland E, et al. The Impact of *CYP3A4*22* on Tacrolimus Pharmacokinetics and Outcome in Clinical Practice at a Single Kidney Transplant Center. Front Genet 2019 Sep;10:871.

104. Salgado PC, Genvigir FD, Felipe CR, Tedesco-Silva H Jr, Medina-Pestana JO, Doi SQ, et al. Association of the *PPP3CA* c.249G>A variant with clinical outcomes of tacrolimus-based therapy in kidney transplant recipients. Pharmgenomics Pers Med 2017 Mar;10:101-106.

105. Justiz Vaillant AA, Misra S, Fitzgerald BM. Acute Transplantation Rejection. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jun 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535410/ PubMed PMID: 30571031.

106. Debette-Gratien M, Woillard JB, Picard N, Sebagh M, Loustaud-Ratti V, Sautereau D, et al. Influence of Donor and Recipient CYP3A4, CYP3A5, and ABCB1 Genotypes on Clinical Outcomes and Nephrotoxicity in Liver Transplant Recipients. Transplantation 2016 Oct;100(10):2129-2137.

107. Chen L, Prasad GV. CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment. Pharmgenomics Pers Med 2018 Mar;11:23-33.

108. Charfi R, Bacha MM, Ben Fadhal M, Ferchichi K, El Jebari H, Gaies E, et al. The effects of the CYP3A5*3 variant on tacrolimus pharmacokinetics and outcomes in Tunisian kidney transplant recipients. Tunis Med 2023 Oct;101(10):738-744.

109. Cheng F, Li Q, Wang J, Hu M, Zeng F, Wang Z, et al. Genetic Polymorphisms Affecting Tacrolimus Metabolism and the Relationship to Post-Transplant Outcomes in Kidney Transplant Recipients. Pharmgenomics Pers Med 2021 Nov;14:1463-1474.

110. Hu R, Barratt DT, Coller JK, Sallustio BC, Somogyi AA. Effect of tacrolimus dispositional genetics on acute rejection in the first 2 weeks and estimated glomerular filtration rate in the first 3 months following kidney transplantation. Pharmacogenet Genomics 2019 Jan;29(1):9-17..

111. Gómez-Bravo MA, Salcedo M, Fondevila C, Suarez F, Castellote J, Rufian S, et al. Impact of donor and recipient CYP3A5 and ABCB1 genetic polymorphisms on tacrolimus dosage requirements and rejection in Caucasian Spanish liver transplant patients. J Clin Pharmacol 2013 Nov;53(11):1146-1154.

112. Terrazzino S, Quaglia M, Stratta P, Canonico PL, Genazzani AA. The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics 2012 Aug;22(8):642-645.

113. Thishya K, Sreenu B, Raju SB, Kutala VK. Impact of Pharmacogenetic Determinants of Tacrolimus and Mycophenolate on Adverse Events in Renal Transplant Patients. Curr Drug Metab 2021;22(5):342-352.

114. Abderahmene A, Khalij Y, Moussa A, Ammar M, Ellouz A, Amor D, et al. The pharmacogenetics of tacrolimus in renal transplant patients: association with tremors, new-onset diabetes and other clinical events. Pharmacogenomics J 2024 Jan;24(1):3.

115. Jia J, Zhao R, Danzheng J. Association between CYP3A5 Gene Polymorphism and Post-Transplant Acute Immune Rejection in Renal Transplant Recipients Receiving Tacrolimus Therapy: A Correlation Study. Arch Esp Urol 2024 Jul;77(6):688-694.

116. Lusco MA, Fogo AB, Najafian B, Alpers CE. AJKD Atlas of Renal Pathology: Calcineurin Inhibitor Nephrotoxicity. Am J Kidney Dis 2017 May;69(5):e21-e22.

117. Kaye AD, Shah SS, Johnson CD, De Witt AS, Thomassen AS, Daniel CP, et al. Tacrolimus- and Mycophenolate-Mediated Toxicity: Clinical Considerations and Options in Management of Post-Transplant Patients. Curr Issues Mol Biol 2024 Dec;47(1):1.

118. Bentata Y. Tacrolimus: 20 years of use in adult kidney transplantation. What we should know about its nephrotoxicity. Artif Organs 2020 Feb;44(2):140-152.

119. Farouk SS, Rein JL. The Many Faces of Calcineurin Inhibitor Toxicity-What the FK? Adv Chronic Kidney Dis 2020 Jan;27(1):56-66.

120. Vandewiele S, Herman J, van den Heuvel L, Knops N. A longitudinal study of long-term renal outcome after pediatric liver transplantation in relation to CNI exposure. Pediatr Transplant 2024 Feb;28(1):e14677.

121. Quteineh L, Verstuyft C, Furlan V, Durrbach A, Letierce A, Ferlicot S, et al. Influence of CYP3A5 genetic polymorphism on tacrolimus daily dose requirements and acute rejection in renal graft recipients. Basic Clin Pharmacol Toxicol 2008 Dec;103(6):546-552.

122. Kuypers DR, de Jonge H, Naesens M, Lerut E, Verbeke K, Vanrenterghem Y. CYP3A5 and CYP3A4 but not MDR1 single-nucleotide polymorphisms determine long-term tacrolimus disposition and drug-related nephrotoxicity in renal recipients. Clin Pharmacol Ther 2007 Dec;82(6):711-725.

123. Udomkarnjananun S, Townamchai N, Chariyavilaskul P, Iampenkhae K, Pongpirul K, Sirichindakul B, et al. The Cytochrome P450 3A5 Non-Expressor Kidney Allograft as a Risk Factor for Calcineurin Inhibitor Nephrotoxicity. Am J Nephrol 2018;47(3):182-190.

124. Zheng X, Huai C, Xu Q, Xu L, Zhang M, Zhong M, et al. FKBP-CaN-NFAT pathway polymorphisms selected by in silico biological function prediction are associated with tacrolimus efficacy in renal transplant patients. Eur J Pharm Sci 2021 May;160:105694.

125. Hurt CN, Greene GJ, Friedewald J, Waterman AD, Ladner D, Tang X, et al. Development of a Patient-Reported Outcome Measure of Side Effects for Patients Taking Calcineurin Inhibitors: The FACIT-CNI-Ntx. Am J Kidney Dis 2025 Jun;85(6):704-715.e1.

126. King CP, Cossart AR, Isbel NM, Campbell SB, Staatz CE. The association between tacrolimus exposure and tremor, headache and insomnia in adult kidney transplant recipients: A systematic review. Transplant Rev (Orlando) 2024 Jan;38(1):100815.

127. Faravelli I, Velardo D, Podestà MA, Ponticelli C. Immunosuppression-related neurological disorders in kidney transplantation. J Nephrol 2021 Apr;34(2):539-555.

128. Biddle K, Ahmed SH. Tacrolimus. Pract Diabetes 2019;36(1):33-35.

129. van Hooff JP, Christiaans MH, van Duijnhoven EM. Tacrolimus and posttransplant diabetes mellitus in renal transplantation. Transplantation 2005 Jun;79(11):1465-1469. .

130. Du Q, Li T, Yi X, Song S, Kang J, Jiang Y. Prevalence of new-onset diabetes mellitus after kidney transplantation: a systematic review and meta-analysis. Acta Diabetol 2024 Jul;61(7):809-829.

131. Tarnowski M, Słuczanowska-Głabowska S, Pawlik A, Mazurek-Mochol M, Dembowska E. Genetic factors in pathogenesis of diabetes mellitus after kidney transplantation. Ther Clin Risk Manag 2017 Apr;13:439-446.