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).

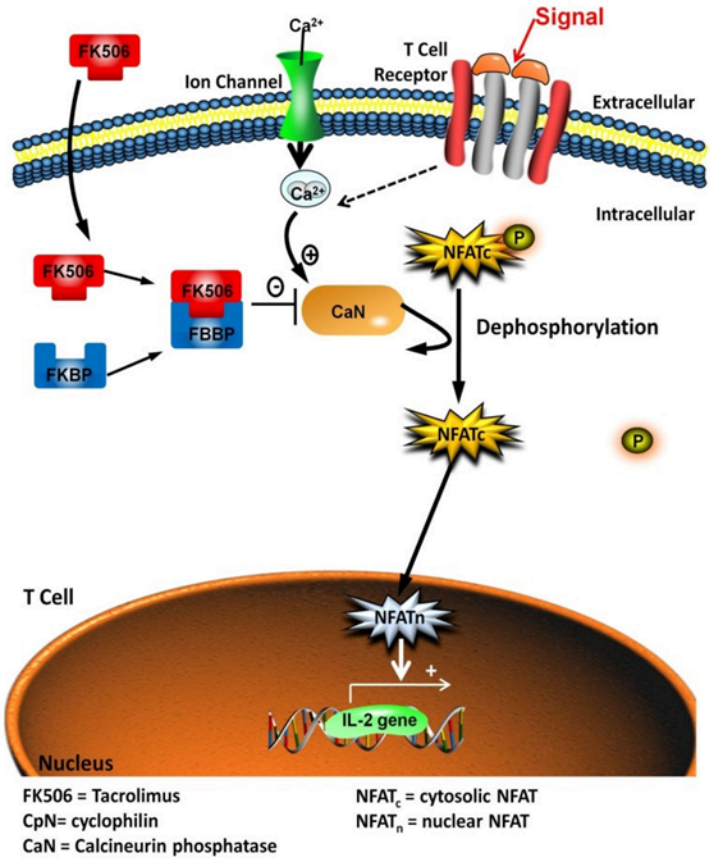

Figure 1: explains the mechanism of action of Tacrolimus (FK506). Adapted from (J Clin Med. 2016 Apr 26;5[5]:50)[8]

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]

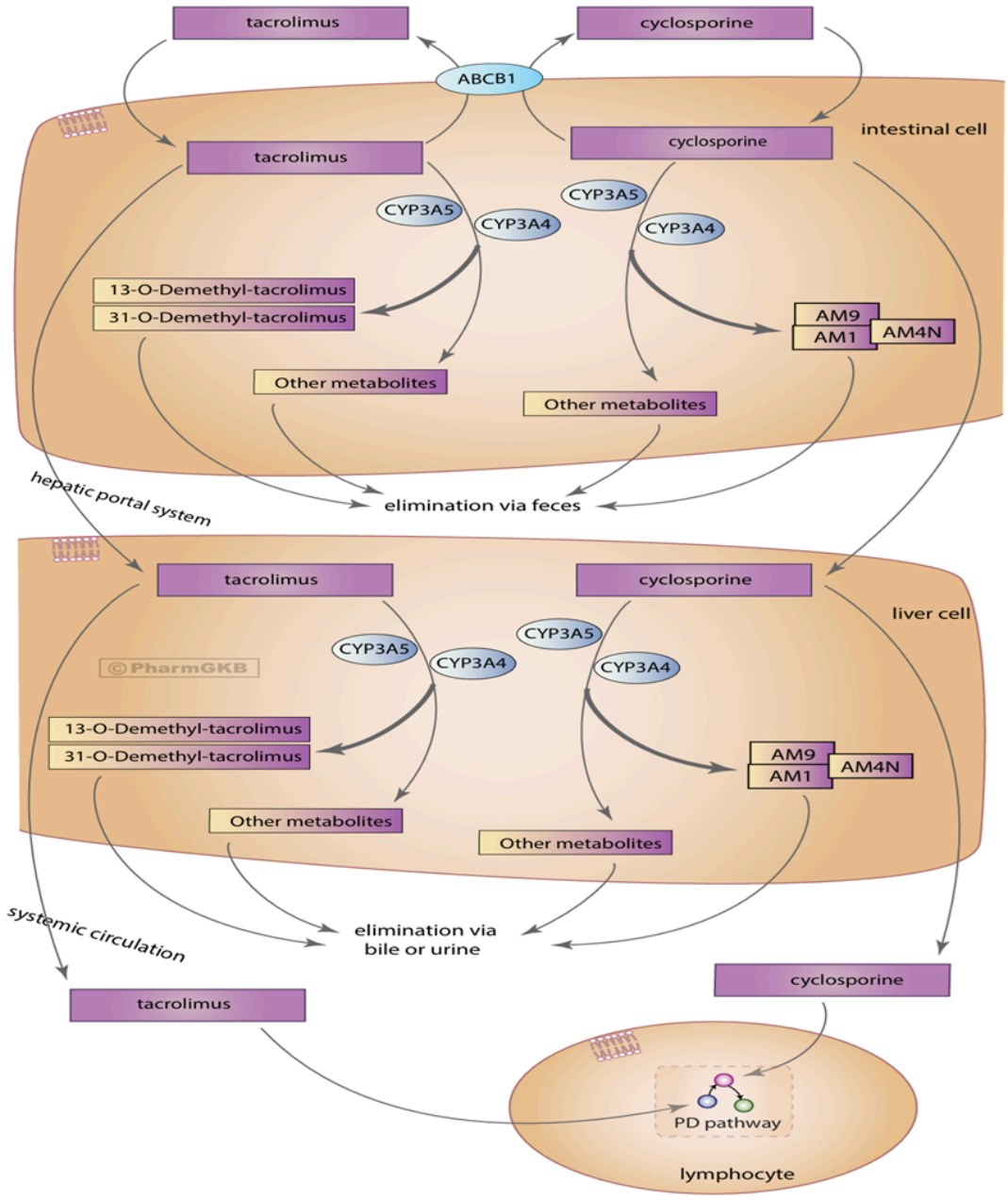

Figure 2: Schematic representation of tacrolimus metabolism (adopted from PharmGKB http://www.pharmgkb.org/pathway/ PA165986114).

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.

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