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Review Article

Effects on Pharmacokinetics of Tacrolimus in Liver Transplant Patients

Yuan Zhang[1#], JianWei Yang[2#], Li Qin Zhu[1]* and Nan Wang[3]

[1]*Department of Pharmacy, Tianjin First Central Hospital, China*

[2]*Department of Pharmacy, Peking University People's Hospital, China*

[3]*Department of Pharmacy, Tianjin Third Central Hospital, China*

[#] *Both authors contributed equally*

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***Corresponding author**

Li Qin Zhu, Department of Pharmacy Tianjin First Central Hospital, China,

Tel: 86-022-23626417;

Fax: 86-022-23626417;

Email: zlq0713@aliyun.com

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Abstract

Tacrolimus is widely used in clinic for the treatment of anti-rejection in liver or kidney transplant patients. It is characterized by narrow therapeutic range and great individual variation. Moreover, the complexity of interactions between tacrolimus and other drugs and the particularity of disease in patients with different physiological state seriously affect the blood concentrations of tacrolimus. Factors investigated that might influence the pharmacokinetics of tacrolimus included postoperative days, age, height, body weight, race, hematocrit, type of graft, hepatic function, renal function, drug interaction and genetic polymorphisms. The aim of this review is to critically analyze the effects of different factors on the pharmacokinetics of tacrolimus in liver transplantation patients.

Core Tip: To achieve a steady target concentration of tacrolimus is essential for liver transplant patients. In clinic, we should not only focus on the concentration of therapeutic drug monitoring results, but also pay attention to the influences of other factors on the concentration of tacrolimus.

Introduction

Tacrolimus is an immunosuppressive agent which is used to prevent organ rejection in patients who received a liver, kidney, or heart transplant and improve solid organ survival [1]. However, tacrolimus is characterized by its narrow therapeutic index and significant inter-individual variability in Pharmacokinetics (PK).

For most drugs, initial dosage for different individuals is associated with many factors, such as weight and age. If drug blood concentrations can be measured, the dosage of the drug may be adjusted to the blood value to get an acceptable range. With regards to immunosuppressive drugs, like tacrolimus, dose that is too low could cause organ rejection, and a dose that is too high could cause toxicity [2,3]. Achieving a steady target blood concentration is critical to avoid rejection and adverse drug effects [4].

Many factors might influence the pharmacokinetics of tacrolimus. A number of demographic investigations have also been performed to seek the correlation between pharmacokinetic parameters of tacrolimus and patients' demographic data. It's crucial to investigate the factors affecting the metabolism and blood concentration of tacrolimus.

A Population Pharmacokinetic (PPK) model can be used to predict the regimen most likely to achieve a given target drug concentration based on patient characteristics (covariate values).

Population pharmacokinetic studies in adult [5-8] and pediatric [9-12] liver transplant patients have been performed. Several factors including Postoperative Days (POD), age, height, body weight, race, hematocrit, type of graft, hepatic function, renal function, drug interactions and genetic polymorphisms have previously been reported to contribute to tacrolimus pharmacokinetics variability, either in pediatric [9,11-14] or adult liver transplantation [5-8,10,15-18]. Covariates reported to influence the apparent Clearance (CL/F) of tacrolimus include patient hepatic and renal function, body size, age (in pediatrics), Postoperative Days (POD), and type of graft (whole or cut-down graft). Covariates reported to infect the apparent Volume of Distribution (V/F) of tacrolimus include patient size and hematocrit level [19].

This review is aim to get further understanding of factors that influence the pharmacokinetics of tacrolimus and to provide theoretical reference for clinical rational use of tacrolimus.

Postoperative Days (POD)

Postoperative days (POD) was identified as a major covariate that described the recovery of tacrolimus hepatic CL/F. As we know, this covariate has already been identified in pharmacokinetic population studies in full or living-donor-liver adults [6,8,20-23] and pediatric transplant patients [19].

In several pharmacokinetic studies to date, The CL/F in adult patients with living-donor liver transplantation was also significantly correlated with postoperative days [6]. It's also reported that the CL/F of tacrolimus could increase significantly during the first few weeks after transplantation and then increase rapidly a plateau from approximately zero immediately after surgery in adult full liver transplant patients [5,9]. Possible explanations for this include enzyme induction by concomitant steroid therapy, donor organ recovery, or altered plasma protein levels.

Similarly, the CL/F of tacrolimus was related to postoperative days in pediatric patients who received living-donor liver transplantation. In study of population pharmacokinetic and pharmacodynamic analysis of tacrolimus in pediatric living-donor liver transplant patients by Fukudo et al [9] indicated that CL/F of tacrolimus increased with time in the immediate postoperative period but did not change further after postoperative day 21. The CL/F in adult patients with living-donor liver transplantation was increased by 1.8% per day after surgery, and this value was three times in pediatric patients after living-donor liver transplantation [19]. Several authors had described a need for increased tacrolimus dosage with the extension of postoperative days [9,24-26]. In liver transplant patients, increased tacrolimus apparent clearance with postoperative days may be partly a function of improvement in liver metabolic activity [5]. It could also be attributed to an induction of metabolic activity by concomitant steroid usage and changes in hematocrit.

Age

There is a widespread view approved an age-dependent change in tacrolimus CL/F in the pediatric liver transplant patients [12]. The possible explanation for this is the metabolic function of the liver over the developmental phase of the child growth. An age-normalized decrease in clearance was reported with increasing patients age (34% for every 1 year change in age from the median population age of 2.5 years across the age range of 1.1 to 13.9 years) [11]. Therefore, pediatric transplant patients require 2 to 4 fold higher doses of tacrolimus than adults to maintain similar trough concentrations [27]. The comparatively higher doses required in pediatric patients have been attributed to differences in CYP3A. Differences in bowel length, hepatic blood flow and P-glycoprotein expression also need to be considered [28].

Height

It's indicated that V/F of tacrolimus is a linear function of height. Height has the greatest influence on apparent volume of distribution based on whole blood concentration ($V_{d,B}/F$) and it alone explains 20.5% of the observed variability in $V_{d,B}/F$ [29].

Body Weight

The study by Yasuhara et al. used a population approach to investigate the pharmacokinetics of tacrolimus in 33 children who had received a living- related (1.e. cut-down) liver transplant [19]. They found marked inter-individual variability in the pharmacokinetics of tacrolimus, part of which was explained by a decrease in clearance (per kilogram of body weight) with increasing body weight.

It's also investigated that apparent whole blood clearance after oral administration (CLB/F) is a linear function of body weight [29]. Body weight has the greatest influence on CLB/F and in alone explains 35.6% of the observed variability in CLB/F which was similar with the result of Johan E. (a 1 kg increase in body weight resulted in a 1.7% increase in CLB/F) [13]. Hence, bodyweight-based dosage adjustment of tacrolimus appears necessary. In pediatric liver transplantation, early post transplantation clearance suggested a revised dosage strategy allowing an initial loading dose following by a maintenance dose that increased with time based on allometric scaling [10]. Allometric scaling of CL to weight has been shown to better reflect physiological changes in drug elimination compared with linear scaling especially in pediatric population [30,31].

This finding is of particular clinical relevance because it indicates that dosing on an mg/kg basis would decrease the variability in concentration-time profiles of tacrolimus into a narrower range for the pediatric and adult Asian liver transplant patients. Therefore, the current practice of administering oral tacrolimus according to bodyweight is justified in liver transplant patients.

Race

A number of population pharmacokinetics researches of tacrolimus in different population had been developed, for example, the Asian liver transplant patients [7,11,29], the Caucasian liver transplantat patients [32], the African American patients[33], Korea liver transplant patients [34] and so on. It's indicated that the Caucasian patients require lower tacrolimus dosages (mg/kg) than African American patients [35]. While, as the three studies [4,29,59] were performed on Caucasian patients, it appears that race does not have an effect on the CL/F of tacrolimus because the population mean values of CL/F of these patients are comparable to those in Asian patients of similar age groups. In a comparison of 41 non-black and 13 black patients, no significant difference was found in clearance or volume of distribution. However, the black patients had lower bioavailability compared to non-black patients (9.9% *vs* 19%) [36]. Similarly, in a study of comparison among 10 African American, 12 Latin American and 12 White patients, there was no significant difference in pharmacokinetics of tacrolimus [37]. Tacrolimus maximum concentrations (C_{max}) and bioavailability, however, was significantly reduced among White patients. Difference among ethnic groups may results from racial differences in intestinal CYP3A or P-glycoprotein activity [38].

Hematocrit (Hct)

Tacrolimus pharmacokinetics is characterized by high binding to red blood cells which explained the significant influence of hematocrit levels on the CL/F of tacrolimus [39]. In a kidney transplantation study, hematocrit predicts variability in tacrolimus whole blood concentrations but is not expected to influence unbound (therapeutically active) concentrations [40]. Hematocrit levels have previously been reported to contribute to tacrolimus PK variability in pediatric liver transplant patients [41]. The CL/F value decrease with the increase of hematocrit in patients [22]. Minematsu et al investigated the effects of hematocrit on tacrolimus pharmacokinetics [42]. They analyzed data on tacrolimus distribution among human blood cells in vitro and retrospectively analyzed dosages and whole blood concentrations of tacrolimus to predict plasma tacrolimus concentrations in living donor transplant patients [42]. It was concluded that hematocrit might be an important factor affecting the pharmacokinetics of tacrolimus in living donor liver transplantation patients [42].

Type of Graft

In the study of population pharmacokinetics of tacrolimus in child who receive cut-down or full liver transplants by Staatz et al [12], children who received a cut-down liver from an adult exhibited on average 7-fold lower CL/F than children who received a whole liver from a child donor. The author postulated that the transplant organ retains the metabolic characteristics of the donor, with a child donor liver exhibiting greater drug clearance than an adult donor liver. This hypothesis is supported by one study in adults that suggests tacrolimus dosage may be donor age dependent [43].

Hepatic Function

Tacrolimus is primarily metabolized in the liver and intestinal mucosa by the cytochrome P450 (CYP450) 3A enzyme, and eliminated through biliary excretion. Therefore, patients with poor liver function will have reduced tacrolimus CL/F compared with patients with normal liver function.

In adult liver transplant patients, hepatic dysfunction has been shown to have major influence on the elimination of tacrolimus [44]. Abnormal liver function can decrease tacrolimus clearance by up to two-thirds and increase elimination half life 3-fold. Results from the present study suggest that glutamic oxalacetic transaminase (AST) maybe the most useful marker for reduced liver function [44,45].

It had been reported that CL/F estimates decreased with increased patient age and AST value, and increased with the increasing of Gamma-Glutamyl Transpeptidase (GGT) value [19]. Similarly, the results from Fukudo et al [9] also reported that CL/F was found to decrease exponentially with the increase of AST, a marker of acute liver damage, which was consistent with the finding that the CL/F of tacrolimus was inversely associated with the AST concentration [19].

Furthermore, after adult liver transplantation, the concentrations of liver enzymes (ALT, AST, GGT) remain considerably elevate for the first couple of weeks, which does not necessarily reflect poor graft function. This could explain the lack of an effect of liver function indices on tacrolimus CL/F in this study. The study of toward better outcomes with tacrolimus therapy: population pharmacokinetics and individualized dosage prediction in adult liver transplantation investigated by Staatz et al [8] showed that AST concentration was identified as the most important factor influencing the pharmacokinetics of tacrolimus. CL/F was greater in patients with AST concentrations less than 70 U/L.

In a study of the pharmacokinetics of tacrolimus in 18 pediatric liver patients with 287 concentration measurements by Garcia Sanchez et al [46], a correlation was found between clearance and bilirubin and Alanine Aminotransferase (ALT) levels. The clearance increased with increasing bilirubin and ALT levels. The CL/F of patients with hepatic dysfunction, defined as Total Bilrubin (TBIL) over 2.5mg/dL, was 72.8% of that in patients with TBIL below 2.5mg/dl [6]. This finding showed that tacrolimus concentration was related to TBIL.

On the contrary, in pediatric liver transplant patients, a decrease in tacrolimus CL/F accompanied with an increase in hepatic enzymes (AST) [12]. These differences could be caused by the difference ages of the patients (adult versus pediatric), time in the post-transplantation period (early versus late) investigated in these studies. Alkaline Phophatase (ALP), a variable that reflects hepatocellular alterations and biliary excretion, was also found to have an effect on CLB/F. It was indicated that the inter-individual variability in the CLB/F of tacrolimus was explained by elevated ALP of the patients and it had been found that a rise in ALP≥200U/L was independently associated with a reduction in tacrolimus CLB/F of 2.93L/h [7].

However, no association could be demonstrated with liver function in tacrolimus apparent clearance in adult liver transplant patients by Hamim Zahir et al [16] that had systematic investigated the possible influence of covariates on the variability. Likewise, in the study of tacrolimus pharmacokinetics in the early post-liver transplantation period and clinical applicability via Bayesian prediction has reported that hepatic enzymes alone failed to explain variability in clearance [18], possibly because this covariate varied with time after liver transplantation and because of confounding with other clinical condition.

Renal Function

Tacrolimus is primarily metabolized in the liver and intestinal mucosa by the cytochrome P450 3A enzyme, and eliminated through biliary excretion. However, renal clearance of tacrolimus is <1% of total body clearance [47]. Results from other previous studies of influence of renal function on the clearance of tacrolimus have been contradictory.

The most useful marker of reduced renal function, Serum Creatinine (SCr) of the patients has been found to influence the CLB/F of tacrolimus [7]. Specifically, a 1 μmol/L increase in SCr was associated with 0.6% reduction in CLB/F of tacrolimus (at two extremes of SCr, patients with SCr 60μmol/L and 120μmol/L, would have a CLB/F of 14.1L/h and 9.3L/h, respectively) [7]. Hence, SCr-based dosage adjustment of tacrolimus appears unnecessary. Renal clearance of tacrolimus is <1% of total body clearance [47]. Therefore, the influence of SCr on tacrolimus CL/F is unlikely to influence its renal clearance. However, Fukatsu et al [6] indicated that the CL/F of patients with renal dysfunction, which was defined as SCr over 1mg/dL, was 80.9% of that in patients with SCr below this level. The conflicting results of the different studies may be due to the different ranges of SCr encountered in the patients of the different studies.

Genetic Polymorphisms

There is great inter-individual variability in the dose required to achieve the target blood level, and many patients require multiple modifications of the dose to reach the range. One of the main determinants of these differences is a CYP3A5 gene polymorphism. It's reported that about 80% Caucasians are poor metabolizers and require lower doses compared to the extensive metabolizers [48].

CYP3A5 is the main metabolic enzyme for tacrolimus [49]. Therefore, CYP3A5 polymorphisms might account for the individual variability in tacrolimus pharmacokinetics. It is reported that both donor and recipient CYP3A5 gene polymorphisms were associated with tacrolimus pharmacokinetics [49-51]. A meta-analysis and systematic review published in 2013 has shown that CYP3A5 gene polymorphisms in liver transplant donors influences the tacrolimus C/D ratio in patients [52]. Moreover, in the particular case of liver transplantation, both the intestinal recipient and donor graft CYP3A5 expression may influence tacrolimus metabolism in a sequential manner, as has been shown in liver transplant adults [40, 53], which

was in accordance with the result of Li et al. [17]. CYP3A5 expressers require a 1.8-fold higher tacrolimus dose than non-expressers [54]. Li et al. also found a significant rise in total bilirubin resulted in 47% reduction of CL/F compared with the normal bilirubin level in CYP3A5 non-expressor patients engrafted with CYP3A5 non-expressor liver in pediatric organ transplant [17]. The abnormally higher bilirubin value might reflect the lower CYP3A activity, leading to the reduction of CL/F value after liver transplantation [17].

Zhu et al. investigated the effect of CYP3A5 genotypes, multidrug resistance 1 (MDR1, ABCB1) C3435T and G2677T/A polymorphism on pharmacokinetics of tacrolimus in Chinese adult liver transplant patients and found CYP3A5 genotypes significantly influenced the CL/F of tacrolimus [55]. A retrospective, single-centre study have concluded that CYP3A5 genotypes and recipient ages were independently associated with tacrolimus pharmacokinetics in pediatric liver transplantation cases and an ABCB1 1236C>T genotype could heighten the effects of CYP3A5 [56].

A study on 50 Chinese liver transplant donors and patients also found that daily tacrolimus dose requirements were significantly higher in patients who carried the wild type ABCB1 3435CC rather than the C3435T allele at the weeks 1 and 2 and at 1 mo post-transplantation [57]. Several studies have evidenced that no correlation between ABCB1 genotype and tacrolimus dose requirements [55,32,58,34].

For CYP3A4, Guy-Viterbo V et al. have shown that donor CYP3A4 genotypes significantly influenced the CL/F of tacrolimus [59]. No study has shown significant correlation between CYP3A4*1B and tacrolimus pharmacokinetics in children [54]. Gijsen et al have reported that tacrolimus dose requirement was significantly lower for CYP3A4*22 carriers when compared with CYP3A4*1/*1 carriers in children who had heart transplant [54]. The CYP3A4*22 may be a novel candidate to consider in further liver transplantations.

NR1I3, known as constitutively activated receptor or constitutive androstane receptor, was first identified in 1994 [60]. Drug-metabolizing enzymes and transproters, including Phase I and Phase II drug-metabolizing enzymes such as CY3As, CY2Bs, CYPZCs and GSTs, and drug transporters such as MDR1, MRP2 and MRP3, are regulated by NR1I3 [61,62]. NR1I3 is a key regulator of drug-metabolizing of enzymes and transporters [63]. It can mediate the induction of CYP3A5 expression, by transactivation of the CYP3A5 promoter in human liver and intestine [64]. Thus, besides drug-metabolizing enzymes and drug transporters, their regulators such as NR1I3 gene polymorphisms may affect tacrolimus pharmacokinetics. Chen et al. reported that NR1I3 gene polymorphisms were associated with tacrolimus pharmacokinetics [49]. Several studies also have demonstrated that NR1I2 gene polymorphisms were associated with tacrolimus pharmacokinetics [65-67].

Drug Interaction

Tacrolimus inhibits cytotoxic lymphocytes, which are largely responsible for graft rejection in allograft patients [68]. Pharmacodynamic drug interactions (increased nephro- or neurotoxic effects) may occur between tacrolimus and coadministered drugs which were known to have these effects [69]. Therefore, its metabolism extensively by the cytochrome P-450 enzyme system and p-glycoprotein presents a multitude of challenges in regard to drug interactions [70].

Tacrolimus is substrate of CYP3A. As a result, administration of a drug that is a cytochrome P450 substrate/inhibitor to a liver transplant recipient can lead to dangerously high immunosupressant blood levels, while intake of cytochrome P450 inducer can predispose to subtherapeutic dosing and rejection [71]. Drugs that are either inhibitors or induces of this metabolism system may increase or decrease serum concentrations of tacrolimus (Table 1).

It is reported that the AUC of tacrolimus increased 70.3- and 17.1-fold when co-administered with telaprevir and boceprevir in healthy individuals, respectively [72,73]. When using tacrolimus with telaprevir, it is suggested to use 10% of the initial total daily dose once the morning trough level goes below 3 or 4 ng/ml [71]. While the tacrolimus dose should be started at approximately 25% of the initial dose and the interval guided by a daily assessment of trough levels when using with boceprevir [74]. The results of a population pharmacokinetics study have shown that concurrent therapy with sulfonyl ureas influenced tacrolimus CL/F in liver transplantation patients [75]. Since voriconazole and other azole antifungal agents inhibit CYP3A activity, Zhang et al.'s observations suggested that voriconazole at clinically relevant concentrations will inhibit the hepatic metabolism of tacrolimus and increase the concentration of tacrolimus more than two-fold [76]. A case report from Spriet et al. illustrates the impact of the inhibition might be more pronounced if both drugs were administrated orally [77].

Table 1: Cytochrome P450 3A4 inhibitor and inducers[a].

Inhibitors (increase tacrolimus levels)	Inducers(decrease tacrolimus levels)
Amiodarone	Barbiturates
Amprenavir	Bosentan
Aprepitant	Carbamazepine
Cimetidine	Efavirenz
Ciprofloxacin	Glucocorticoids
Clarithromycin	Modafinil
Delavirdine	Nafcillin
Diltiazem	Nevirapine
Doxycycline	Oxcarbazepine
Echinacea	Phenytoin
Enoxacin	Primidone
Erythromycin	Rifampin
Fluconazole	Pioglitazone
Fluvoxamine	Topiramate
Grapefruit Juice	
Indinavir	
Itraconzole	
Ketoconazole	
Miconazole	
Nefazodone	
Miconazole	
Nefazodone	
Nelfinavir	
Ritonavie	
Saquinavir	
Star Fruit	
Telithromycin	
Verapamil	
Voriconazole	

[a]Based on data from Health and DNA Wed Site.

Table 2: Drug-interactions reported in recent years.

Author	Year	Drug	Co-administration Influence on the PK parameters of tacrolimus
Garg V et al. [73]	2011	Telarevir	Increased tacrolimus dose-normalized exposure by 70-fold; increased the terminal elimination half-life of tacrolimus from 40.7h to 196h
Hulskotte E et al. [72]	2012	Boceprevir	Increased the AUC_{inf} and C_{max} of TAC 17- and 9.9- fold; CL was 18 times lower
Zhang X et al. [75]	2012	Sulfonylureas	Reduce the CL/F of tacrolimus
Zhang S et al. [76]	2012	Voriconazole	Inhibited the metabolism of tacrolimus by 50%
Guy-Viterbo V et al. [59]	2014	Fluconazole	Influenced tacrolimus CL/F
Hurst A L et al. [70]	2015	Nicardipine	Increased the concentrations of tacrolimus

Hurst et al. conclude that concomitant use of tacrolimus and nicardipine could result in high tacrolimus concentrations in four pediatric liver transplant patients due to the inhibition of cytochrome p450 enzymes responsible for the metabolism of tacrolimus [70]. Another study has shown that fluconazole administration significantly influenced tacrolimus apparent clearance [59]. Table 1 showed the CYP450 3A4 inhibitor and inducers. The studies of drug interaction with tacrolimus in recent years were showed in Table 2.

Conclusion

Owing to the various factors that are likely to affect the concentrations of tacrolimus, the clinicians and patients require extensive education to facilitate adherence to the immunosuppressive regimen after transplantation. Tacrolimus dosage regimen should be made according to results of the therapeutic drug monitoring, combination scheme and the patient's physical condition.

References

1. Scott LJ, Mckeage K, Keam SJ, Plosker GL. Tacrolimus: a further update of its use in the management of organ transplantation, Drugs. 2003; 63: 1247-1297.
2. Robles-Piedras AL, Gonzalez-Lopez EH. Tacrolimus levels in adult patients with renal transplant. Proc West Pharmacol Soc. 2009; 52: 33-34.
3. Wei-long Shi, Hui-Lin Tang, and Suo-Di Zhai. Effects of the CYP3A4*1B Genetic Polymorphism on the pharmacokinetics of tacrolimus in adult renal transplant recipients: AMeta-Analysis. National Institutes of Health List. 2015; 10: e0127995.
4. FT Musuamba, M Mourad, V Haufroid, IK Delattre, RK. Verbeeckm, and ABCB1 genotypes, and analytical method influence tacrolimus pharmacokinetics; a population pharmacokinetic study. Therapeutic Drug Montoring. 2009; 31: 34-742.
5. Antignac M, Hulot JS, Boleslawski E, Hannoun L, Touitou Y, Farinotti R, et al. Population pharmacokinetics of tacrolimus in full liver transplant patients: modeling of the post-operative clearance. Eur J Clin Pharmacol. 2005; 61: 409-416.
6. Fukatsu S, Yano I, Igarashi T, Hashida T, Takayanagi K, Saito H, et al. Population pharmacokinetics of tacrolimus in adult recipients receiving living-donor liver transplantation. Eur J Clin Pharmacol. 2001; 57: 479-484.
7. Sam WJ, Tham LS, Holmes MJ, Aw M, Quak SH, Lee KH, et al. Population pharmacokinetics of tacrolimus in whole blood and plasma in Asian liver transplant patients, Clin Pharmacokinet. 2006; 45: 59-75.
8. Staatz CE, Willis C, Taylor PJ, Lynch SV, Tett SE. Toward better outcomes with tacrolimus therapy: population pharmacokinetics and individualized dosage prediction in adult liver transplantation. Liver Transpl. 2003; 9: 130-137.
9. Fukudo M, Yano I, Masuda S, Goto M, Uesugi M, Katsura T, et al. Population pharmacokinetic and pharmacogenomic analysis of tacrolimus in pediatric living-donor livertransplant recipients. Clin Pharmacol Ther. 2006; 80: 331-345.
10. Garcia Sanchez MJ, Manzanares C, Santos-Buelga D, Alberto Blázquez, Javier Manzanares, Pedro Urruzuno, et al. Covariate effects on the apparent clearance of tacrolimus in paediatric liver transplant patients undergoing conversion therapy. Clin Pharmacokinet. 2001; 40: 67-71.
11. Sam WJ, Aw M, Quak SH, SM Lim, BG Charles, SY Chan, et al. Population pharmacokinetics of tacrolimus in Asian paediatric liver transplant patients. Br J Clin Pharmacol. 2000; 50: 531-541.
12. Staatz CE, Taylor PJ, Lynch SV, Willis C, Charles BG, Tett SE. Population pharmacokinetics of tacrolimus in children who receive cut-down of full liver transplants. Transplantation. 2001; 72: 1056-1061.
13. Johan E Wallin, Martin Bergstrand, Henryk E Wilczek, Nydert PS, Karlsson MO, Staatz CE. Population pharmacokinetics of tacrolimus in pediatric liver transplantation: Early posstransplantation clearance. Ther Drug Monit. 2011; 33: 663-672.
14. DJ Moes, SA van der Bent, JJ Swen, van der Straaten T, Inderson A, Olofsen E, et al. Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in stable liver transplant recipients. Eur J Clin Pharmacol. 2015; 31.
15. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmadynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet. 2004; 43: 623-653.
16. Hamim Zahir, Andrew J Mclachlan, Ameeta Nelson, Mc Caughan G, Gleeson M, Akhlaghi F. Population pharmacokinetic estimation of tacrolimus apparent clearance in adult liver Transplant recipients. The Drug Monit. 2005: 27: 422-430.
17. Li D, Lu W, Zhu JY, et al. Population pharmacokinetics of tacrolimus and CYP3A5, MDR1 and IL-10 polymorphisms in adult liver transplantant patients. J Clin Pharm Ther. 2007; 32: 505-515.
18. Oteo I, Luklas JC, Leal N, Suarez E, Valdivieso A, Gastaca M, et al. Tacrolimus pharmacokinetics in the early post-liver transplantation period and clinical applicability via Bayesian prdediction. Eur J Clin Pharmacol. 2013; 69: 65-74.
19. Yasuhara M, Hashida T, Toraguchi M, et al. Pharmacokinetics and pharmacodynamics of FK506 in peadiatric patients receiving living-related donor liver transplantations. Transplant Proc. 1995; 27: 1108-1110.
20. Holt DM, Armstrong VW, Griesmacher A, Morris RG, Napoli KL, Shaw LM. International federation of clinical chemistry/ International association of therapeutic drug monitoring and clinical toxicology working group on immunosuppressive drug monitoring. Ther Drug Monit. 2002; 24: 59-67.
21. Hu RH, Lee PH, Tsai MK. Clinical influencing factors for daily dose, trough level, and relative clearance of tacrolimus in renal transplant recipients. Transplant Proc. 2000; 32: 1689-1602.
22. Parke J, Holford NH, Charles BG. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. Comput Methods Programs Biomed. 1999; 59: 19-29.
23. Pou L, Brunet M, Andres I, Rodamilans M, Lopez R, Corbella J. Influence of posttransplant time on dose and concentration of tacrolimus in liver transplant patients. Transpl Int. 1998; 11: S270-S271.
24. Staatz C, Taylor P, Tett S. Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol Dial Transplant. 2001; 16: 1905-1909.

25. Molinaro M, Regazzi MB, Pasquino S, et al. Pharmacokinetics of tacrolimus during the early phase after heart transplantation. Transplant Proc. 2001; 33: 2386-2389.

26. Lemahieu WP, Maes BD, Vanrenterghem Y. Different evolution of trough and dose levels during the first year after transplantation for tacrolimus versus cyclosporine. Transplant Proc. 2005; 37: 2051-2053.

27. MacFarlane GD, Venkataramanan R, McDiarmid SV, Pirsch JD, Scheller DG, Ersfeld DL, et al. Therapeutic drug monitoring of tacrolimus in pediatric liver transplant patients. Pediatr Transplant. 2001; 5:119-124.

28. Mittal N, Thompson JF, Kato T, Tzakis AG. Tacrolimus and diarrhea: pathogenesis of altered metabolism. Pediatr Transplant. 2001; 5: 75-79.

29. Wai john San, Lai San Tham, Michael J Holmes, Aw M, Quak SH, Lee KH, et al. Population pharmacokinetics of tacrolimus in whole blood and plasma in Asian liver transplant patients. Clin Pharmacokinet. 2006: 45: 59-75.

30. Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: general principles. Eur J pediatr. 2006; 165: 741-746.

31. Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: modeling covariate effects. Eur J Pediatr. 2006; 165: 819-829.

32. Provenzani A, Notarbartolo M, Labbozzetta M, Poma P, Biondi F, Sanguedolce R, et al. The effect of CYP3A5 and ABCB1 single nucleotide polymorphisms on tacrolimus dose requirements in Caucasian liver transplant patients. Ann Transplant. 2009; 14: 23-31.

33. Neylan JF. Effect of rece and immunosuppression in renal transplantation: three-year survival results from a US multicentre, randomized trial. FK506 Kidney Transplant Study Group. Transplant Proc. 1998; 30: 1355-1358.

34. Jun KR, Lee W, Jang MS, Chun S, Song GW, Park KT, et al. Tacrolimus concentrations in relation to CYP3A and ABCB1 polymorphisms among solid organ transplant recipients in Korea. Transplantation. 2009; 87: 1225-1231.

35. Feipe CR, Silva HT, Machado PG, Garcia R, da Silva Moreira SR, Pestana JO. The impact of ethic miscegenation on tacrolimus clinical pharmacokinetics and therapeutic drug monitoring. Clin Transplant. 2002; 16: 262-272.

36. Fitzsimmons WE, Bekersky I, Dressler D, Raye K, Hodosh E, Mekki Q, et al. Demographic consideration in tacrolimus pharmacokinetics. Transplant Proc. 1998; 30: 1359-1364.

37. Mancinelli LM, Frassetto L, Floren LC, Dressler D, Carrier S, Bekersky I, et al. The pharmacokinetics and metabolic disposition of tacrolimus: a comparsion across ethnic groups. Clin Pharmacol Ther. 2001; 69: 24-31.

38. Uber PA, Mehra MR, Scott PL, et al. Ethic disparities in the pharmacokinetic characteristics in heart transplantation. Transplant Proc. 2001; 33: 1581-1582.

39. Guy-Viterbo V, Scohy A, Verbeeck RK, Reding P Wallemacq, Flora Tshinanu Musuamba. Population pharmacokinetic analysis of tacrolimus in the first year after pediatric liver transplantation. European journal of clinical pharmacology. 2013; 69: 1533-1542.

40. Størset E, Holford N, Midtvedt K, Sara Bremer, Stein Bergan, Anders Åsberg. Importance of hematocrit for a tacrolimus target concentration strategy. European journal of clinical pharmacology. 2014; 70: 65-77.

41. Musuamba FT, Guy-Viterbo V, Reding R, Verbeeck RK, Wallemacq P. Population pharmacokinetic analysis of tacrolimus early after pediatric liver transplantation. Therapeutic drug monitoring. 2014; 36: 54-61.

42. Minematsu T, Sugiyama E, Kusama M, S Hori, Y Yamada, H Ohtani, et al. Effect of hematocrit on pharmacokinetics of tacrolimus in adult living donor liver transplant recipients. Transplantation proceedings. Elsevier. 2004; 36: 1506-1511.

43. Teperman LW, Morgan GR, Diflo T, et al. Tacrolimus dose is donor age dependent. American Society of transplant surgeons 24th Scientific Meeting. 1998. A-176.

44. Abu-Elmagd K, Fung JJ, Alessiani M, Jain A, Venkataramanan R, Warty VS, et al. The effect of graft function on FK506 plasma levels, dosage and renal function, with particular reference to the liver. Transplantation. 1991; 52: 71-77.

45. Staatz CE, Willis C, Taylor PJ, Tett SE. Population pharmacokinetics of tacrolimus in adult kidney transplant recipients. Clin Pharmacol Ther. 2002; 72: 660-669.

46. Garcia Sanchez MJ, Manzanares C, Santos-Buelga D, Blázquez A, Manzanares J, Urruzuno P, et al. Covariate effects on the apparent clearance of tacrolimus in paediatric liver transplant patients undergoing concentration therapy. Clin Pharmacokinet. 2001; 40: 63-71.

47. Venkataramannan R, Jain A, Warty VS, et al. Pharmacokinetics of FK506 in transplant patient. Transplant Proc. 1991; 23: 2730-2740.

48. Beatriz Tavira, Carmen Diaz-Corte, Diego Coronel, Francisco Ortega, Eliecer Coto. Pharmacogenetics of tacrolimus: from bench to bedside? Official Publication of the Spanish Nephrology Society. 2014; 34: 11-17.

49. Chen D, Guo F, Shi J, Zhang C, Wang Z, Fan J, et al. Association of hemoglobin levels, CYP3A5, and NR1I3 gene polymorphisms with tacrolimus pharmacokinetics in liver transplant patients. Drug metabolism and pharmacokinetics. 2014; 29: 249-253.

50. Uesugi M, Masuda S, Katsura T, Oike F, Takada Y, Inui K, et al. Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients. Pharmacogenetics and genomics. 2006; 16: 119-127.

51. Ji E, Choi L, Suh K S, Cho JY, Han N, Oh JM. Combinational effect of intestinal and hepatic CYP3A5 genotypes on tacrolimus pharmacokinetics in recipients of living donor liver transplantation. Transplantation. 2012; 94: 866.

52. Rojas L E, Herrero M J, Bosó V, Salvador F Aliño. Meta-analysis and systematic review of the effect of the donor and recipient CYP3A5 6986A> G genotype on tacrolimus dose requirements in liver transplantation. Pharmacogenetics and genomics. 2013; 23: 509-517.

53. Uesugi M, Masuda S, Katsura T, Oike F, Takada Y, Inui K. Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients. Pharmacogenetics and genomics. 2006; 16: 119-127.

54. Lancia P, Jacqz-Aigrain E, Zhao W. Choosing the right dose of tacrolimus. Arch Dis Child. 2015; 100: 406-413.

55. Zhu L Q, Yang J W, Zhang Y, Jing Y, Zhang Y, Li G. Effects of CYP3A5 genotypes, ABCB1 C3435T and G2677T/A polymorphism on pharmacokinetics of Tacrolimus in Chinese adult liver transplant patients. Xenobiotica. 2015; 45: 840-846.

56. Yang TH, Chen YK, Xue F, Xia Q. Influence of CYP3A5 genotypes on tacrolimus dose requirement: age and its pharmacological interaction with ABCB1 genetics in the Chinese pediatric liver transplantation. International journal of clinical practice. 2015, 69: 53-62.

57. Wei-lin W, Jing J, Shu-sen Z, Li-hua W, Ting-bo L, Song-feng Y, et al. Tacrolimus dose requirement in relation to donor and recipient ABCB1 and CYP3A5 gene polymorphisms in Chinese liver transplant patients. Liver transplantation 2006; 12: 775-780.

58. Shi Y, Li Y, Tang J, Zhang J, Zou Y, Cai B, et al. Influence of CYP3A4, CYP3A5 and MDR-1 polymorphisms on tacrolimus pharmacokinetics and early renal dysfunction in liver transplant recipients. Gene. 2013; 512: 226-231.

59. Guy-Viterbo V, Baudet H, Elens L, Haufroid V, Lacaille F, Girard M, et al. Influence of donor-recipient CYP3A4/5 genotypes, age and fluconazole on tacrolimus pharmacokinetics in pediatric liver transplantation: a population approach. Pharmacogenomics. 2014; 15: 1207-1221.

60. Baes M, Gulick T, Choi HS, Martinpli MG, Simha D, Moore DD. A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. Mol. Cell, Biol. 1994; 14:1544-1552.

61. Handschin C, Meyer UA. Induction of drug metabolism: the role of nuclear receptors. Pharmacol. Rev. 2003; 55:649-673.

62. Swales, K. and Negishi, M. CAR, driving into the future. Mol. Endocrinol. 2004; 18: 1589-1598.

63. Tojima H, Kakizaki S, Yamazaki Y, Takizawa D, Horiguchi N, Sato K, et al. Ligand dependent hepatic gene expression profiles of nuclear receptors CAR and PXR. Toxicol, Lett. 2012; 212: 288-297.

64. Burk O, Koch I, Raucy J, Hustert E, Eichelbaum M, Brockmoller J, et al. The induction of cytochrome P450 3A5 (CYP3A5) in the human liver and intestine is mediated by the xenobiotic sensors pregnane X receptor (PXR) and constitutively activated receptor (CAR). J. Biol. Chem. 2004; 279: 38379-38385.

65. Barraclough KA, Isbel NM, Lee KJ, Bergmann TK, Johnson DW, McWhinney BC, et al. NR1I2 polymorphisms are related to tacrolimus dose-adjusted exposure and BK viremia in adult kidney transplantation. Transplantation. 2012; 94: 1025-1032.

66. Press RR, Ploeger BA, den Hartigh J, T van der Straaten, Hans van Pelt, Meindert Danhof, et al. Explaining variability in tacrolimus pharmacokinetics to optimize early exposure in adult kidney transplant recipients. Therapeutic drug monitoring. 2009; 31: 187-197.

67. Benkali K, Prémaud A, Picard N, Rérolle JP, Toupance O, Hoizey G, et al. Tacrolimus population pharmacokinetic-pharmacogenetic analysis and Bayesian estimation in renal transplant recipients. Clinical pharmacokinetics. 2009; 48: 805-816.

68. Scott LJ, Mckeage K, Keam SJ, Plosker GL. Tacrolimus: a further update of its use in the management of organ transplantation, Drugs. 2003; 63: 1247-1297.

69. Michele Vicari-Christensen, Suzanne Repper, Sharon Basile, Danella Young. Tacrolimus: Review of pharmacokinetics pharmacodynamics, and pharmacogenetics to facilitate Practitioners' understanding and offer strategies for educating patients and promoting adherence. Progress in Transplantation. 2009; 19: 277-284.

70. Hurst AL, Clark N, Carpenter TC, Sundaram SS, Reiter PD. Supra-therapeutic tacrolimus concentrations associated with concomitant nicardipine in pediatric liver transplant recipients. Pediatric transplantation. 2015; 19: E83-E87.

71. Tischer S, Fontana RJ. Drug-drug interactions with oral anti-HCV agents and idiosyncratic hepatotoxicity in the liver transplant setting. Journal of hepatology. 2014; 60: 872-884.

72. Hulskotte E, Gupta S, Xuan F, van Zutven M, O'Mara E, Feng HP, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. Hepatology. 2012; 56: 1622-1630.

73. Garg V, van Heeswijk R, Eun Lee J, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011; 54: 20-27.

74. Pungpapong S, Aqel BA, Koning L, Murphy JL, Henry TM, Ryland KL, et al. Multicenter experience using telaprevir or boceprevir with peginterferon and ribavirin to treat hepatitis C genotype 1 after liver transplantation. Liver Transpl. 2013; 19: 690-700.

75. Zhang XQ, Wang ZW, Fan JW, Li YP, Jiao Z, Gao JW, et al. The impact of sulfonylureas on tacrolimus apparent clearance revealed by a population pharmacokinetics analysis in Chinese adult liver-transplant patients. Therapeutic drug monitoring. 2012; 34: 126-133.

76. Zhang S, Pillai V C, Mada S R, Strom S, Venkataramanan R. Effect of voriconazole and other azole antifungal agents on CYP3A activity and metabolism of tacrolimus in human liver microsomes. Xenobiotica. 2012; 42: 409-416.

77. Spriet I, Grootaert V, Meyfroidt G, Debaveye Y, Willems L. Switching from intravenous to oral tacrolimus and voriconazole leads to a more pronounced drug–drug interaction. European journal of clinical pharmacology. 2013: 1-2.