

## Review Article

# Tacrolimus toxicity in organ transplantation: an overview

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## Abstract

Tacrolimus is a macrolide lactone antibiotic, and acts as a calcineurin inhibitor. It is widely used to prevent organ transplant rejection. It has been approved as first-line treatment after organ transplantation. Tacrolimus has narrow therapeutic range and wide individual variability in its pharmacokinetics. In organ transplantation, immunosuppression is associated with important risks, in particular, related to infections and cardiovascular diseases, which are the predominant causes of death in those with a functioning graft. This review focuses on toxicity of tacrolimus after transplantation. Tacrolimus toxicity is a major determinant of morbidity and mortality in organ recipients after transplantation. Therefore, reducing toxicities has become a priority. To decrease the incidence of side effects, and expand graft survival, the appropriate initial and maintenance dose of tacrolimus is essential. Clinical conditions that influence tacrolimus pharmacokinetics, such as hemorrhage, systemic inflammation and shock, all result in higher variations of tacrolimus concentrations. In addition, unbound plasma concentration is a major important reasonable parameter for monitoring of receiving optimal tacrolimus dosing in the unstable patient. Therefore, the approach of tacrolimus monitoring is vital and will support to avoid tacrolimus toxicity in the early days after transplantation.

**Keywords:** Tacrolimus, Organ transplantation, Toxicity, Tacrolimus monitoring.

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## Introduction

Organ transplantation is the treatment of choice for terminal and irreversible organ failure. Development of immunosuppressive medications is the key to successful organ transplantation. Immunosuppressive drugs are used for maintenance and reversal of established rejection. In 1984, tacrolimus was isolated from the fermentation of *Streptomyces*, and was investigated as a novel immunosuppressant [1]. In 1994, the FDA accepted the use of tacrolimus for the prevention of rejection in liver transplantation [2, 3]. Its application has since expanded to other types of transplants, and today it is

an important immunosuppressive used in transplant patients. The half-life of tacrolimus is 8.7-11.3 h [4-6]. Steady state concentrations are expected in two to three days. It has been shown that absorption of tacrolimus is unpredictable between individuals. After oral administration, tacrolimus is rapidly absorbed with mean time of peak concentrations of 1.5 to 2 hours. Bioavailability of tacrolimus is approximately 21%, although there is large individual instability [7]. Tacrolimus has a wide range of toxicities. This article reviews toxicity of tacrolimus in organ transplantation.

## Mechanism of tacrolimus

Tacrolimus can cause impairment of gene expression in target cells. It binds to an immunophilin, FK506 binding protein 12 (FKBP12). This complex inhibits phosphatase activity of calcineurin. Calcineurin is a heterodimeric  $\text{Ca}^{2+}$ /calmodulin-stimulated protein phosphatase, consisting of a catalytic A subunit (CnA) and a tightly associated  $\text{Ca}^{2+}$ -binding regulatory B subunit (CnB), and plays a key role in T-cell activation by regulating the activity of NFAT (nuclear factor of activated T cells) and calcium signaling [8]. Inhibition of calcineurin phosphatase suppresses translocation of an activated T-cell transcription factor that promotes interleukin-2-mediated proliferation of helper T-cells, which plays a critical role in the immune response associated with allograft rejection [4].

## Metabolism of Tacrolimus

Cytochrome P450 3A4 (CYP3A4) is the major iso-enzyme involved in the metabolism of tacrolimus. Extended metabolism by CYP3A4 in the gastrointestinal tract is responsible for presystemic elimination of about half of the absorbed dose, whereas first-pass metabolism by CYP3A4 in the liver accounts for an additional 10% of elimination. The amount of absorption of tacrolimus from the gastrointestinal tract is also affected by the activity of P-glycoprotein (P-gp) in enterocytes. P-gp is encoded by the Multidrug Resistance Gene 1 (MDR1) [9, 10]. P-gp, an adenosine triphosphate (ATP)-driven efflux pump, is a transmembrane transporter that is closely associated with CYP3A4 and secretes tacrolimus and its metabolites back into the lumen of the gut. The expression of Pgp and CYP3A can be influenced by genetics [11, 12].

## Side effects of Tacrolimus

Tacrolimus is associated with nephrotoxicity, neurotoxicity, gastrointestinal toxicity, hyperkalemia, hypertension, myocardial hypertrophy, hyperlipidemia and a higher incidence of new-onset diabetes mellitus after transplantation [13-17].

## Tacrolimus induced nephrotoxicity

Tacrolimus can cause acute and chronic nephrotoxicity [18]. It has been illustrated that in 17 to 44% of renal transplant recipients and in 18 to 42% of liver transplant recipients undergo chronic renal

failure within 5 years [19, 20]. The occurrence of nephrotoxicity have not been systematically studied in Heart and lung, transplant recipients. Tacrolimus nephrotoxicity can be best managed by either discontinuation or reduction of the medication [21, 22]. The molecular mechanism of tacrolimus nephrotoxicity is not fully understood. It has been shown that tacrolimus binding proteins are present at a high concentration in the kidney. Vascular endothelial cells, tubular epithelial cells, interstitial fibroblasts, and arteriolar myocytes are targets for tacrolimus nephrotoxicity. Vasospasm results in decreased glomerular filtration, may have a key factor in the vascular toxicity of tacrolimus. The occurrence of epithelial and arteriolar myocyte vacuolization suggests a direct toxic effect of the drug on the renal tubule and smooth-muscle cells [13, 23].

It has also been reported that higher concentrations of 15-O-demethyl (M-III), one of major tacrolimus metabolites, may have a nephrotoxic or myelotoxic effect and result in higher incidence of infections [24].

## Tacrolimus induced neurotoxicity

It has been shown that tacrolimus induced neurotoxicity in 20% to 40% of solid organ transplant recipients [25]. The clinical appearance of tacrolimus neurotoxicity varies from headaches and tremors to confusion, agitation, hallucinations or overt psychosis. Although the molecular mechanism of tacrolimus neurotoxicity is less well understood, but there is evidence that it may be similar to hypertensive encephalopathy. On the other hand, not all patients with immunosuppressive induced leukoencephalopathy have hypertension [26].

Hypertension is one of the most common adverse effects of tacrolimus. Hypertension is as a risk factor for posterior reversible encephalopathy syndrome (PRES), a rare, but serious side effect of tacrolimus therapy [14].

The pathophysiology of PRES is still unknown, but there are some theories. PRES seems to be related to impaired cerebral autoregulation and dysfunction of the cerebrovascular blood-brain barrier [27]. Cerebral autoregulation can be defined the maintenance of constant blood flow to the brain by vasoconstriction or vasodilatation of resistance arterioles, resulting in a constant blood flow to the brain. Acute elevation of

blood pressure could overcome the capacity of the normal autoregulation. This can cause cerebral vasodilation with a resulting hyperperfusion and/or regional vasoconstriction of the brains arteries. Hyperperfusion could lead to endothelial dysfunction, resulting in an extravasation of proteins and fluid, i.e., causing a vasogenic edema. Therefore, controlling blood pressure to near baseline levels may play a critical role in minimizing neurological toxicities of tacrolimus during the transplant process [27-29].

It is important to mention that tacrolimus is lipophilic, but it does not cross the blood-brain barrier (BBB) because the P-glycoprotein efflux pump may block its entry. In some people, a polymorphism in the MDR1 gene causes a reduction or loss in efflux pumps allowing tacrolimus to enter the BBB. Brain myelin has a high lipid content which may be a preferential binding site for tacrolimus. Studies in stem cell transplant and organ transplant patients taking tacrolimus have shown a correlation between patients with MDR1 polymorphisms and neurotoxicity with tacrolimus [30-32].

### **Tacrolimus induced hypertension**

In organ transplantation, hypertension is an important risk factor for allograft vasculopathy, peripheral artery disease, and decreased allograft and patient survival [33, 34].

The mechanisms responsible for tacrolimus induced hypertension are not completely understood but are believed to initiate in the vasculature.

Endothelial dysfunction and more specifically a decrease in production of the vasodilator nitric oxide (NO) by endothelial NO synthase (eNOS) probably play a primary role in the pathogenesis of hypertension [35].

Studies have considered the role of endothelial dysfunction and NO bioavailability in tacrolimus-induced hypertension. It has been demonstrated that two weeks treatments of rats with tacrolimus increases systolic blood pressure and decreases mesenteric endothelium-dependent relaxation responses, as well as aortic eNOS activity [36, 37].

The production of NO from eNOS is mediated by the Ca<sup>2+</sup>/calmodulin and is regulated by multiple factors, including changes in phosphorylation condition [38].

Tacrolimus inhibits FKBP12/12.6 in blood

vessels leading to reduced vasodilation and/or increased vasoconstriction [15]. It is illustrated that FKBP12.6 deficient mice develop hypertension, and genetic and pharmacologic removal of FKBP12/12.6 from intracellular calcium channels dose-dependently decreases nitric oxide production and endothelial function [39]. In addition to its negative effects on endothelial nitric oxide production, tacrolimus increases transforming growth factor- $\beta$  (TGF- $\beta$ ) levels and elevated levels of TGF- $\beta$  are associated with hypertension [40].

### **Tacrolimus induced myocardial hypertrophy**

Cardiotoxicity due to tacrolimus is a lethal complication after organ transplantation. Decreasing the tacrolimus trough concentration or changing tacrolimus therapy to another immunosuppressive therapy caused regression or improvement in cardiac involvement.

A number of mechanisms have been suggested to explain the cardiotoxicity of tacrolimus. It is demonstrated that tacrolimus changes intracellular calcium handling and causes myocardial hypertrophy. FK506 binding protein is expressed in skeletal and cardiac muscles. FK506 binding protein stabilizes the ryanodine receptor. Ryanodine receptor is an intracellular calcium release channel in the terminal cisternae of the sarcoplasmic reticulum of muscle and non-muscle cells [41].

In presence of tacrolimus, FK506 binding protein binds to tacrolimus and is released from the ryanodine receptor, thus increasing calcium release from the sarcoplasmic reticulum. It has been shown that calcium overload associated with the onset and progression of cardiac hypertrophy [42]. In addition, tacrolimus may induce capillary leak syndrome, and causes interstitial edema followed by myocardial hypertrophy in rabbits. Tacrolimus resulted vasculitis in several dogs and baboon organs, including the heart [43]. This vasculitis may be related to the myocardial toxicity of tacrolimus. Although it is an important immunosuppressive drug in organ transplantation, blood concentration must be carefully maintained [44]. It is likely that the cardiotoxicity associated with tacrolimus is related to high blood levels of this medication, particularly at levels greater than 20 ng/mL

[16].

Repeated echocardiography is helpful to detect and avoid tacrolimus-induced cardiac hypertrophy [44].

## **Tacrolimus induced diabetes mellitus**

Tacrolimus can cause diabetes mellitus after transplantation. It prevents the transcription of the insulin gene in the beta-cell via inhibition of calcineurin after binding to FKBP12 [45]. The FKBP12 is highly concentrated in the B cells of the pancreas. Tacrolimus leads to decreased insulin synthesis, secretion and sensitivity [46]. Tacrolimus impairs the glucose uptake in cells due to a reduction in the number of glucose transporter type 4 (GLUT-4) receptor molecules on the cell membrane surface of adipocytes [47]. GLUT-4 is the insulin-regulated protein present primarily in adipose tissue and striated muscle, providing the translocation of glucose into the cell [48].

Thus, failure in GLUT-4 translocation leads to hyperglycemia. Tacrolimus also decreases glucokinase activity in pancreatic islets, thereby suppressing glucose-induced insulin release [49].

It has also been demonstrated that Tacrolimus can cause islet cell injury in the form of cytoplasmic swelling, vacuolization, and altered insulin staining [17]. Moreover, it has been shown that, Tacrolimus treatment resulted in dose- and time-dependent increases in the production of reactive oxygen species by beta cells. In addition, the antioxidant status decreased in beta cells after tacrolimus treatment. (57).

High concentration of tacrolimus, elder age, family history for diabetes mellitus are the most significant risk factors for the development of post-transplant diabetes mellitus. Diabetes mellitus is a severe complication as it may cause weight loss, infections, and cardiac allograft vasculopathy that is associated with increased rejection risk [46]. However, the diabetogenicity of tacrolimus is often reversible with dosage reduction of tacrolimus [54].

It has been shown that mesenchymal stem cell (MSCs) transplantation is a new approach to control hyperglycemia in diabetes mellitus [50, 51]. In addition, inhibition of oxidative stress may block both

the initiation and progression of diabetic complications [52, 53]. Interestingly, it has been demonstrated that therapeutic concentrations of immunosuppressive drugs affect MSCs function. MSCs also affect the efficacy of immunosuppressive medication such as Tacrolimus. These findings may be important for potential clinical use of MSC in combination with immunosuppressant, so that preincubation/pretreatment of MSC with Tacrolimus increased the immunosuppressive capacity of MSC. (58).

## **Conclusions and Future Perspectives**

Tacrolimus has a narrow therapeutic window, and its blood concentration should be maintained at an optimal range in transplanted patients for the following reasons. If the concentration is inadequate, the transplanted organ will be rejected as a result of the insufficient immunosuppression by tacrolimus. If the concentration is greater than therapeutic range, adverse effects will be observed due to the excess concentration of tacrolimus [55].

Tacrolimus has significant inter-individual and intra-individual pharmacokinetic variability that makes it impossible to give a standard dosing regimen to all adults to achieve target blood concentrations. Therapeutic drug monitoring (TDM) and pharmacokinetic based design of individualized dosage regimens are recommended to optimize treatment outcome. TDM in transplanted patients is conducted by measuring the whole blood levels of tacrolimus by an enzyme immunoassay (EIA) using the monoclonal antibody raised against tacrolimus [56].

It could be suggested that co administration of immunosuppressant drugs like Tacrolimus with mesenchymal stem cell may potentiate Tacrolimus immunosuppressive effect in addition to enhancing MSCs intrinsic immunomodulatory/immunosuppressive effect to prevent rejection in a synergistic pattern.

## **Conflicts of interest**

The authors declare that there are no conflicts of interest.



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