

# Prograf Concentrations in Liver Transplantation: Correlation With Headache and Other Neurotoxic Complications?

Zahra Tolou-Ghamari<sup>1,\*</sup> and Behnam Sanei<sup>2</sup>

<sup>1</sup>Isfahan Urology and Renal Transplantation Research Center, Al-Zahra Research Centers, Isfahan University of Medical Sciences, Isfahan, IR Iran

<sup>2</sup>Department of General Surgery, Saint Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, IR Iran

\*Corresponding author: Zahra Tolou-Ghamari, Isfahan Neurosciences Research Centre and Isfahan Urology and Renal Transplantation Research Center, Al-Zahra Research Centers, Isfahan University of Medical Sciences, Isfahan, IR Iran. Tel: +98-3137922591, Fax: +98-313668001, E-mail: toloeghamari@pharm.mui.ac.ir

Received 2015 August 25; Revised 2015 September 22; Accepted 2015 September 29.

## Abstract

**Background:** Immunosuppressive tacrolimus is widely used in liver transplantation but could be potentially neurotoxic if blood levels increase to more than 15 mg/L.

**Objectives:** The aim of this study was to investigate the drug levels that might be related to the neurotoxic effects of tacrolimus.

**Patients and Methods:** Based on a cross-sectional method, preliminary data was obtained from fifty patients after liver transplantation. To determine the effectiveness or side effects, evidence-based results were obtained using Prograf therapy. Further data was obtained by reviewing the patients' medical records. Trough levels of tacrolimus were determined by microparticle enzyme immunoassay. Statistical analysis was performed using SPSS.

**Results:** There was no correlation between the dose and the trough level in the population (n = 45) studied (P = 0.270, r = 0.168). In 80% of patients, the tacrolimus dose was 5 mg and trough levels of tacrolimus showed as highly variable. The mean trough level was 13.2 mg/L (range: 0.1 - 41.4 mg/L). In 35% of patients, the level of tacrolimus C<sub>0</sub> was more than 15 mg/L, which appeared to indicate a neurotoxic side effect.

**Conclusions:** In the Iranian population of organ transplantation polypharmacy should be based on a rational basis of scheduled therapeutic drug monitoring. To confirm the presence of a correlation between Prograf levels with early or late rejection, nephrotoxicity or neurotoxicity, further studies in a greater number of liver recipients are recommended.

**Keywords:** Tacrolimus, Headache, Neurotoxic, Liver Transplant, C<sub>0</sub>

## 1. Background

Simplifying the therapeutic regimen of liver transplant recipients, could be a support to the avoidance of severe rejection and graft failure (1). With appropriate planning, liver recipients could have improved opportunities related to the quality and quantity of life (QOL), similar to normal healthy control subjects, without significant biochemical laboratory changes in liver and renal function (2). Currently, liver transplantation is an established treatment for patients with end-stage liver diseases (ESLD) in Iran. Through available records related to liver transplantations, there has been significant improvement in the development of immunosuppressive agents such as tacrolimus (3). Tacrolimus has a variable and low bioavailability (F), high volume of distribution (V<sub>d</sub>), extensive hepatic metabolism, that mostly excreted into the bile. The metabolism of this drug is catalyzed by cytochrome P450 3A (CYP3A) and is susceptible to modulation by CYP3A inducers and inhibitors. The therapeutic blood tacrolimus level is recommended to be from 5 - 15 ng/mL (3-12). Tacrolimus inhibits thymocyte differentiation, damages thymic epithelial cells, and prevents apoptosis

of antigen and mitogen stimulated T-cells. According to previous publications, neurotoxicity, akinetic mutism, nephrotoxicity, new onset diabetes (after transplant), gastro-intestinal toxicity, hepatotoxicity, and thrombotic microangiopathy could be linked to high levels of tacrolimus after liver transplantation (3-20).

Neurotoxicity associated with tacrolimus may start at therapeutic concentrations, as vasogenic edema (reversible) and cytotoxic edema (irreversible) That could cause changes in the subcortical white matter and posterior cerebral artery. Posterior reversible encephalopathy syndrome is the primary and rapid result of calcineurin inhibitor neurotoxicity. The characteristic neurological patterns related to the recipients of organ transplantation could be described as: altered mental status, headache, visual turbulences, and seizures (15-20). Pharmacotherapy management of tacrolimus early in the post-transplantation period needs well-focused attention, regarding the monitoring of drug concentration (3, 21, 22). In order to create more long-term survivors and excellent outcomes, the number of studies and articles related to

tacrolimus therapy in the Iranian liver transplant population are growing. Neurological complications are not unusual and could contribute to a longer intensive care unit and hospital stay. Therefore, every attempt should be made towards early detection of immunosuppressive therapy-related adverse effects.

## 2. Objectives

The aim of this study was to investigate the evidence-based pharmacotherapy of Prograf levels that might be related to neurotoxic borders in liver transplant recipients.

## 3. Patients and Methods

This study was conducted at the Isfahan neurosciences research centre. A preliminary cross-sectional study of fifty liver transplant recipients comprised of 16 females and 34 males with a median age of 49 years (range: 25 - 64 years) was performed. Furthermore, an evidence-based Prograf therapy treatment, linked to studies of complications, was performed in a retrospective manner by reviewing recipients' medical records. Trough levels of tacrolimus were determined using the microparticle enzyme-mediated immunoassay technique. The patients' clinical, pharmacological, and demographic data were recorded in Excel and statistical analysis of the variables was performed using SPSS for Windows. This study was approved by the ethical committee of Isfahan neuroscience research centre and Isfahan deputy of research, with the code number of 291224.

## 4. Results

The distribution of immunosuppressive trough levels in the population studied was highly variable. As shown in Figure 1, the mean dosage of the drug was 4.6 mg (range: 1 - 5 mg). Out of 45 patients, the doses of tacrolimus in 80% were 5 mg. Because the management of tacrolimus was connected with marked unpredictability and a

large disparity in C<sub>0</sub>, thus, the efficiency and neurotoxicity seem to be associated with blood levels. As shown in Figure 2, the mean C<sub>0</sub> of tacrolimus was 13.2 mg/L, with a minimum value of 0.1 and a maximum value of 41.4 mg/L. Trough levels of tacrolimus in 20.4% of patients was lower than the suggested therapeutic level. In 35% of the patients studied, the level was more than 15 mg/L (neurotoxic border). There was no correlation between dose and trough levels ( $P = 0.270$ ,  $r = 0.168$ ). The pattern of pharmacotherapy for selected patients is described as follows (Box 1): A twenty-four-year-old male with code 45, due to autoimmune hepatitis, received prednisone, and azathioprine eight years prior to liver transplantation. After surgery, the patient presented with a herpetic lesion on his lip that had been treated with intravenous acyclovir followed by the oral form. The drug regimen after transplantation was as follows: Prograf 3 mg every 12 hours, tablet; CellCept 1 gm every 12 hours, capsule; fluconazole 100 mg every 12 hours, tablet; co-trimoxazole 1 g daily, tablet; folic acid 5 mg 1 daily, tablet; prednisone 20 mg every morning, tablet; pantoprazole 40 mg every 12 hours, tablet; calcium D every 8 hours, tablet; and acyclovir every 12 hours. Tacrolimus C<sub>0</sub> was reported as 6 mg/mL. In another twenty-eight-year-old male transplanted due to primary sclerosing colangitis (PSC) with code 89, the drug regimen was as follows: amp cefitizidime 1 gm; metronidazol 500 gm every 6 hours; pantoprazole 40 gm every 12 hours; methylprednisolone 1 gm a day after transplant for two days; heparin 10000 iu for 24 hours; and mesalasin-albumin 1 vial. Evidence of acute rejection was noted in the patient's medical record, and then the patient was treated with 3 gm methylprednisolone. The patient was discharged with the following drug regimen: tacrolimus 7 mg; CellCept 2 gm; and prednisone 20 mg. Tacrolimus C<sub>0</sub> was reported as 5 mg/mL. Another patient, with code 68, underwent liver transplantation due to Wilson's disease. After the operation, the patient showed psychosis and episodes of rejection. The drug regimen was as follows: Prograf 4 mg every 12 hours; CellCept 2 gm every 12 hours; and prednisone 20 mg every 12 hours.

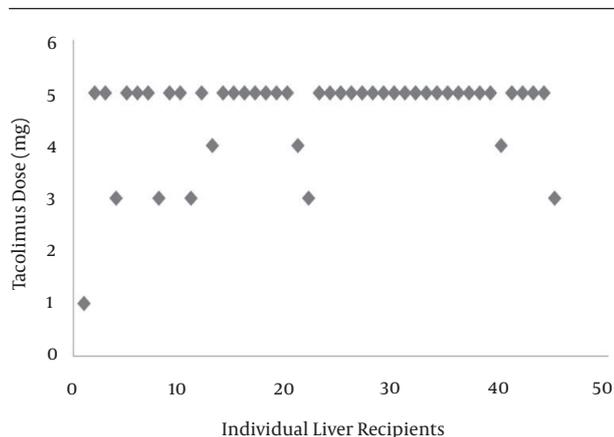
### Box 1. Drug Details in a Number of Prescriptions in Iranian Liver Graft Recipients

#### Types of Drugs Prescribed in Each Individual; Expected Behaviors in Combination Therapy (1-32)

Prograf, CellCept, fluconazole, co-trimoxazole, tab prednisolone pantoprazole, acyclovir; poly pharmacy could increase the CNS toxicity of tacrolimus, the risk of rejection still remains challenging and is; tacrolimus and CellCept, both may increase CellCept levels, risk of toxicity, may increase risk of immunosuppression, skin and other malignancies, infections, sepsis (renal excretion decrease by nephrotoxic agents; additive effects); co-administration of pantoprazole (proton pump inhibitors PPIs with CellCept) has been reported to reduce the exposure to mycophenolic acid, therefore, the risk of rejection still remains challenging and is; a fairly significant interaction exists between co-trimoxazole and CellCept, therefore, combinations usually should be avoided; sulfamethoxazole may decrease the blood levels and effects of mycophenolic acid

Cefitizidim, metronidazole, pantoprazole, methylprednisolone; co-administration of tacrolimus with metronidazole may result in elevated tacrolimus concentrations, possibly leading to tacrolimus toxicity

Citalopram, pantoprazole, co-trimoxazole, CellCept, Prograf, prednisolone, sirolimus; citalopram and tacrolimus both, may increase risk of QT continuation, cardiac arrhythmias (additive effects); using tacrolimus together with prednisone may increase the blood levels and effect one or both medications



- ence of Clinical Status. University of London: University of London; 1999.
4. Backman L, Nicar M, Levy M, Distant D, Eisenstein C, Renard T, et al. FK506 trough levels in whole blood and plasma in liver transplant recipients. Correlation with clinical events and side effects. *Transplantation*. 1994;**57**(4):519–25. [PubMed: 7509516]
  5. Fung JJ, Alessiani M, Abu-Elmagd K, Todo S, Shapiro R, Tzakis A, et al. Adverse effects associated with the use of FK 506. *Transplant Proc*. 1991;**23**(6):3105–8. [PubMed: 1721372]
  6. Kahan BD. The evolution of therapeutic immunosuppression and the potential impact of drug concentration monitoring. *Ther Drug Monit*. 1995;**17**(6):560–3. [PubMed: 8588220]
  7. Peddi VR, Demmy AM, Munda R, Alexander JW, First MR. Tacrolimus eliminates acute rejection as a major complication following simultaneous kidney and pancreas transplantation. *Transplant Proc*. 1998;**30**(2):509–11. [PubMed: 9532151]
  8. Yang TH, Chen YK, Xue F, Han LZ, Shen CH, Zhou T, et al. Influence of CYP3A5 genotypes on tacrolimus dose requirement: age and its pharmacological interaction with ABCB1 genetics in the Chinese paediatric liver transplantation. *Int J Clin Pract Suppl*. 2015; **183**:53–62. doi: 10.1111/ijcp.12667. [PubMed: 26176181]
  9. Sikma MA, van Maarseveen EM, van de Graaf EA, Kirkels JH, Verhaar MC, Donker DW, et al. Pharmacokinetics and Toxicity of Tacrolimus Early After Heart and Lung Transplantation. *Am J Transplant*. 2015;**15**(9):2301–13. doi: 10.1111/ajt.13309. [PubMed: 26053114]
  10. Staatz CE, Tett SE. Clinical Pharmacokinetics of Once-Daily Tacrolimus in Solid-Organ Transplant Patients. *Clin Pharmacokinet*. 2015;**54**(10):993–1025. doi: 10.1007/s40262-015-0282-2. [PubMed: 26038096]
  11. Snell GI, Ivulich S, Mitchell L, Westall GP, Levvey BJ. Evolution to twice daily bolus intravenous tacrolimus: optimizing efficacy and safety of calcineurin inhibitor delivery early post lung transplant. *Ann Transplant*. 2013;**18**:399–407. doi: 10.12659/aot.883993. [PubMed: 23921892]
  12. O'Regan JA, Canney M, Connaughton DM, O'Kelly P, Williams Y, Collier G, et al. Tacrolimus trough-level variability predicts long-term allograft survival following kidney transplantation. *J Nephrol*. 2015. doi: 10.1007/s40620-015-0230-0. [PubMed: 26374111]
  13. Arnold R, Pussell BA, Pianta TJ, Lin CS, Kiernan MC, Krishnan AV. Association between calcineurin inhibitor treatment and peripheral nerve dysfunction in renal transplant recipients. *Am J Transplant*. 2013;**13**(9):2426–32. [PubMed: 23841745]
  14. Moscato D, Nonnato A, Adamo R, Vancheri M, Caropreso A. Therapeutic monitoring of tacrolimus: aberrant results by an immunoassay with automated pretreatment. *Clin Chim Acta*. 2010;**411**(1-2):77–80. [PubMed: 19835852]
  15. Penninga L, Penninga EI, Moller CH, Iversen M, Steinbruchel DA, Gluud C. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. *Cochrane Database Syst Rev*. 2013;**5**:Cd008817. doi: 10.1002/14651858.CD008817.pub2. [PubMed: 23728681]
  16. Yamaguchi K, Fukuoka N, Kimura S, Shinohara N, Tatsumichi T, Tai T, et al. [Case of encephalopathy seemingly caused by tacrolimus at blood concentration near the upper limit of therapeutic range]. *Yakugaku Zasshi*. 2012;**132**(7):845–8. [PubMed: 22790031]
  17. Chopra A, Das P, Rai A, Kuppuswamy PS, Li X, Huston J, et al. Catastonia as a manifestation of tacrolimus-induced neurotoxicity in organ transplant patients: a case series. *Gen Hosp Psychiatry*. 2012;**34**(2):209.e9–11. doi: 10.1016/j.genhosppsych.2011.08.008. [PubMed: 21937118]
  18. Sierra-Hidalgo F, Martinez-Salio A, Moreno-Garcia S, de Pablo-Fernandez E, Correas-Callero E, Ruiz-Morales J. Akinetic mutism induced by tacrolimus. *Clin Neuropharmacol*. 2009;**32**(5):293–4. doi: 10.1097/WNF.0b013e3181a77fab. [PubMed: 19820432]
  19. Wu Q, Marescaux C, Wolff V, Jeung MY, Kessler R, Lauer V, et al. Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. *Eur Neurol*. 2010;**64**(3):169–77. doi: 10.1159/000319032. [PubMed: 20699617]
  20. Saner FH, Nadalin S, Radtke A, Sotiropoulos GC, Kaiser GM, Paul A. Liver transplantation and neurological side effects. *Metab Brain Dis*. 2009;**24**(1):183–7. doi: 10.1007/s11011-008-9119-0. [PubMed: 19139982]
  21. Tolou Ghamari Z, Palizban AA, Wendon J, Tredger JM. Pharmacokinetics of tacrolimus on days one or two after liver transplantation. *Transplant Med*. 2004;**16**:112–6.
  22. Tolou-Ghamari Z, Palizban A, Tredger J. Modelling Tacrolimus AUC in Acute and Chronic Liver Disease Immediately after Transplant. *Jahrg*. 2004;**16**: S. 109–11.
  23. Li CJ, Li L. Tacrolimus in preventing transplant rejection in Chinese patients—optimizing use. *Drug Des Devel Ther*. 2015;**9**:473–85. doi: 10.2147/dddt.s41349. [PubMed: 25609922]
  24. Ozbilgin M, Egeli T, Unek T, Ozkardesler S, Avkan-Oguz V, Sagol O, et al. Incidence of Late Acute Rejection in Living Donor Liver Transplant Patients, Risk Factors, and the Role of Immunosuppressive Drugs. *Transplant Proc*. 2015;**47**(5):1474–7. doi: 10.1016/j.transproceed.2015.04.076. [PubMed: 26093746]
  25. Nakamura-Yanagidaira T, Takahashi Y, Sano K, Murata T, Hayashi T. Development of spontaneous neuropathy in NF-kappaB50-deficient mice by calcineurin-signal involving impaired NF-kappaB activation. *Mol Vis*. 2011;**17**:2157–70. [PubMed: 21850191]
  26. Tolou-Ghamari Z, Wendon J, Tredger JM. In vitro pentamer formation as a biomarker of tacrolimus-related immunosuppressive activity after liver transplantation. *Clin Chem Lab Med*. 2000;**38**(11):1209–11. doi: 10.1515/CCLM.2000.190. [PubMed: 11156362]
  27. Tolou-Ghamari Z, Palizban AA, Michael Tredger J. Clinical monitoring of tacrolimus after liver transplantation using pentamer formation assay and microparticle enzyme immunoassay. *Drugs R D*. 2004;**5**(1):17–22. [PubMed: 14725486]
  28. Al Masri O, Fathallah W, Quader S. Recovery of tacrolimus-associated brachial neuritis after conversion to everolimus in a pediatric renal transplant recipient—case report and review of the literature. *Pediatr Transplant*. 2008;**12**(8):914–7. doi: 10.1111/j.1399-3046.2008.00961.x. [PubMed: 18503483]
  29. Monostory K, Toth K, Kiss A, Hafra E, Csikany N, Paulik J, et al. Personalizing initial calcineurin inhibitor dosing by adjusting to donor CYP3A-status in liver transplant patients. *Br J Clin Pharmacol*. 2015;**80**(6):1429–37. doi: 10.1111/bcp.12747. [PubMed: 26271661]
  30. Fujii N, Ikeda K, Koyama M, Aoyama K, Masunari T, Kondo E, et al. Calcineurin inhibitor-induced irreversible neuropathic pain after allogeneic hematopoietic stem cell transplantation. *Int J Hematol*. 2006;**83**(5):459–61. doi: 10.1532/IJH97.05154. [PubMed: 16787880]
  31. Page RL, Klem PM, Rogers C. Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother*. 2005;**39**(6):1109–13. [PubMed: 15855244]
  32. Park SI, Felipe CR, Pinheiro-Machado PG, Garcia R, Fernandes FB, Casarini DE, et al. Tacrolimus pharmacokinetic drug interactions: effect of prednisone, mycophenolic acid or sirolimus. *Fundam Clin Pharmacol*. 2009;**23**(1):137–45. [PubMed: 19267777]