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Pharmacotherapy of Prograf (Tacrolimus) in Liver Transplant Recipients; Consideration of Its' Levels with Efficacy and Toxicity

Zahra Tolou-Ghamari[1,*]

[1]Isfahan Neurosciences Research Centre (INRC), Alzahra Research Centers, Isfahan University of Medical Sciences, Isfahan, Iran

[*]*Corresponding author*: Zahra Tolou-Ghamari, Isfahan Neurosciences Research Centre (INRC), Alzahra Research Centers, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: toloeghamari@pharm.mui.ac.ir

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Abstract

Context: Cytochrome P450 (CYP3A) enzymes are basic for the metabolism of several medications such as tacrolimus, as immunosuppression with tacrolimus in men prevents allograft rejection and reverses steroid-resistant rejection in transplanted recipients.
Evidence Acquisition: The aim of this study was to determine a proper guideline for tacrolimus (prograf) prescription after organ transplantation.
Methods: The key words relevant to topics of tarcolimus pharmacotherapy were searched. Consequently, articles related to efficacy and toxicity of tacrolimus in organ transplant recipients were selected and studied entirely.
Results: The results showed that tacrolimus dosage might vary with the indication for transplantation, time after grafting, and the genotype of CYP3A. Hepatic dysfunction may impair drug disposition as a result of decreased metabolic activity through parenchymal damage and compromised biliary excretion of parent drug and metabolites during cholestasis.
Conclusions: To avoid side effects, in prescribing tacrolimus such as acute rejection and toxicity, further investigation for more direct markers related to the differentiation between immunosuppressive activity due to parent drug and side effects due to metabolites within Iranian population of organ transplantation seems to be advantageous.

Keywords: Tacrolimus, Pharmacotherapy, Toxicity, Liver, Transplantation

1. Context

Prograf or Tacrolimus is an inhibitor of calcineurin that is widely used as an immunosuppressive agent after solid organ transplantation. Other names include FK-506 or fujimycin, trade names Prograf, Advagraf, and Protopic. The drug was discovered in 1987 from a soil bacterium, Streptomyces tsukubaensis, and was first recognized by the food and drug administration in 1994 for use in the recipients of liver. Other immunosuppressive agents such as cyclosporine (as an inhibitor of calcineurin), sirolimus or everolimus (as the serine/threonine kinase inhibitor), and mycophenolate mofetil (as inosine monophosphate dehydrogenase inhibitor) could be mentioned as the most common drugs used as other immunosuppressive pharmacotherapy approaches in organ transplant recipients.

Tacrolimus is an immunosuppressive drug used mainly after allogeneic organ transplantation to lower the risk of organ rejection. Pharmacotherapy used tacrolimus for the management of other T cell-mediated disease such as eczema, severe intractable uveitis after bone marrow transplantation exacerbations of disease, Kimura's disease, and vitiligo. Early studies on cultured rat CD4 + (helper) T-lymphocytes showed that tacrolimus was approximately 100 times as much potent as on a weight for weight basis than cyclosporin in inhibiting selectively a variety of cytokines, in particular interleukin-2. Subsequent experiments demonstrated that tacrolimus apparently inhibited thymocyte differentiation, T-cell proliferation and cytokine production with additional inhibition of B-cell activation and proliferation was also noted. The bioavailability of drug seems to be less than 20%. The biological half-life of tacrolimus was reported as 11.3 hours that ranged from 3.5 to 40.5 hours. The drug had a protein binding of 75 to 99%. It was metabolized in the liver mainly by cytochrome P3A4 and cytochrome P3A5, and excreted mostly by fecal. In the transplanted organ, intracellular calcium could be increased in the presence of activated T-cell. Calcium acts via calmodulin and, therefore, it could activate calcineurin. In these events, nuclear factor of activated T-cells (NF-AT) was dephosphorylated by the calcineurin that transfers to the nucleus of the T-cell and upsurges the action of genetic factor coding for interlukin-2 and connected cytokines. Up to now, eight tacrolimus metabolites have been described, but their clinical importance remains unclear (1-7).

2. Evidence Acquisition

In order to provide sufficient evidence for clarifying tacrolimus pharmacotherapy management, this study was conducted to compare the clinical outcomes after the prescription of tacrolimus in organ transplant recipients which was anticipated to reach a considerate level of the associations between efficacy, metabolites and adverse events in tacrolimus-treated patients.

3. Survey Method

The selected articles were achieved by methodically searching through United States national library of medicine (PubMed, NLM) database based on their reception until 2016. Searching terms included "tacrolimus", "tacrolimus metabolite 3", "tacrolimus metabolite 1", "tacrolimus rejection" and "tacrolimus rejection and its association to metabolites". References of the retrieved studies and reviews were scanned to obtain additional relevant articles. Consequently, 34 articles applicable to the selected terms were preferred, selected, studied, and used categorically for this article.

4. Results

According to a recent publication, more than 100 000 solid organ transplantations are performed every year worldwide (2). In spite of rapid development associated with the detection of tacrolimus concentrations after organ transplantation, differentiation between the amount of parent drug and drug metabolites seems to be a big challenge. It is well known that tacrolimus metabolic transformations mainly include hydroxylations and demethylations (1, 8) catalysed mostly by members of the cytochrome P450 (CYP) 3A family of haemoproteins (1, 9). Cytochrome P3A (CYP3A) is the most abundant CYP in human liver, but is also present in high concentrations in enterocytes and in kidney (1). CYP3A4 activity may vary 4 - 5 fold in human liver (but doses of tacrolimus may vary 14-fold in stable liver recipients reflecting genetic and environmental modulation of enzyme activities in both liver and intestine and contributions from other enzymes (1). Zegarska et al. in 2016 reported that a higher concentration of metabolite 3 (M-III) may have a nephrotoxic or myelotoxic effect and result in higher frequency of infections (1, 3).

The characteristics of the more active tacrolimus metabolites are shown in Table 1. There are at least 10 metabolites, and studies using mammalian liver microsomes showed that the O-demethylated metabolites at the 13 and 31 positions of tacrolimus are predominant and minor metabolites, respectively. After the incubation of M-II (the 31-O-demethylated metabolite of tacrolimus) with rat liver microsomes and analysis by mass spectrometry, M-V and M-VI were also isolated. M-II contained two methoxy substituents at both the 15- and 13- positions, so M-V and M-VI were the 15, 15'- or 13, 13'- 0-didemethylated metabolites, respectively. M-VII was the 13-, 15-O-didemethylated metabolite. Hydroxylated metabolites predominated in bile. One report suggested that the concentration of tacrolimus metabolites remained < 20 % of parent drug during the first dosage interval after liver transplantation while a second indicated that 28% of ELISA reactivity in blood was not attributable to parent tacrolimus. A glucuronide metabolite was also reported for tacrolimus (1).

Previous publications reported that dysfunction on the metabolism of tacrolimus by the liver, intestine, and kidneys could influence pharmacotherapy management after organ transplantation. Cytochrome P450 (CYP) 3A isoenzymes are abundant in liver and extrahepatic tissues, particularly the intestine and kidney. CYP3A-dependent metabolism in the intestine has already been implicated in determining the bioavailability of tacrolimus. Published articles suggested that CYP3A5 isoforms are strongly expressed in human kidney and that these show a high activity towards cyclosporin in human renal cortex microsomes. The relationship of renal CYP3A with cyclosporin-induced hypertension has also been demonstrated and there is additional evidence for interindividual differences in CYP3A activity both in kidney and intestine. Since cyclosporin and tacrolimus share a common dependence on CYP3A for metabolism, these observations may provide a basis for changes in CYP3A activity (resulting from either tissue damage and dysfunction or genetic determinants) making major contributions to the diversity of tacrolimus absorption and disposition (1-9).

5. Discussion

It is well known that calcineurin inhibitors could increase the risk of many diseases after transplantation by their association with nephrotoxicity, cardiotoxicity, and neurotoxicity. Therefore, due to narrow therapeutic window related to therapeutic range of such drugs, there is a necessity to monitor blood trough concentration. The concentration out of therapeutic range in a blood of transplanted recipient could result in rejection or toxic side effects (1, 2).

As shown in table 1, the immunosuppressive activity of tacrolimus metabolite -II (M-II) is comparable to that of tacrolimus, but other metabolites exhibit very weak or negligible pharmacological activities. The reactivity of the metabolites with the anti-tacrolimus monoclonal antibody used in blood level monitoring of tacrolimus are as

Table 1. Characterisation of Tacrolimus Metabolites

Tacrolimus Metabolites	FKBP12 Binding Affinity	Complex Formation Assay	MLR Suppression	Reactivity to Tacrolimus McAb
M-II (31-O-demethylated)	14.2	79.7	100	70 - 109
M-III (15-O-demethylated)	116.0	0	0	90.5
M-V (15, 31-O-di-demethylated)	20.0	0	0	92.3
Tacrolimus	100	100	100	100

Abbreviations: FKBP12, Tacrolimus binding protein; MLR, mixed lymphocyte reaction; M-II, metabolite 2; M-III, metabolite 3; M-V, metabolite 5; Mc Ab, monoclonal antibody.

follows: M-II, M-III, and M-V have comparable reactivity to that of tacrolimus, but M-I, M-IV, M-VI, M-VII, and M-VIII exhibit weak or negligible reactivity with the monoclonal antibody (1, 10, 11).

Induction of CYP3A5 via high-dose steroid pulse therapy could lead to an increase in the ratio of tacrolimus metabolites/tacrolimus (12). Another study showed that the CYP3A5 hereditary polymorphisms are connected with the singular differences in pharmacokinetics and pharmacodynamics as well as in trough concentration of prograf and its metabolites. The mean fluorescence intensity of human leukocyte antigen-D related with monocytes might be deliberated to be an important option for checking tacrolimus effectiveness (13). The study of prograf distribution, elimination and its main metabolites such as 13-O-desmethyl progrf and 15-O-desmethyl prograf in kidney transplant recipients in relation to diabetic population and inherited polymorphism of cytochrome P450 (CYP) 3A showed that dose-equalised concentrations of prograf or metabolites were greater in diabetic patients. Those that transfer CYP3A4*1B and CYP3A5 individually, or when evaluated as a shared CYP3A4-3A5 genotype, had meaningfully lower dose-normalized pre-dose (C0/dose) and 2-hour post-dose (C2/dose) concentrations of prograf and metabolites.

Non-diabetic population of organ recipients with at least one CYP3A4*1B and CYP3A5*1 allele had lower C0/dose as compared to the others within this group. Genetic polymorphism of CYP3A5 or CYP3A4 affect prograf or metabolites dose-normalized amounts but not metabolite to parent values ratios (14). A study of 50 kidney transplant recipients, those receiving low-dose tacrolimus in order to evaluate the cross-reactivity in tacrolimus chemiluminescent immunoassay and to characterize them according to CYP3A5 genetic polymorphism showed no significant difference related to drug concentration at 12 hours post dose between two genotypes of CYP3A5*1/*3 and CYP3A5*3/*3. However, dose-equalized concentrations at 12 hours post dose were significantly higher in the CYP3A5*3/*3 genotype carrying group rather than CYP3A5*1/*3, but the ratio of 13-O-demethylate/tacrolimus was significantly lower correspondingly (15).

Another investigation of two liver transplant recipients established that the minor metabolite 2 was first established in the human bile, signifying that the presence of metabolite 2 in bile could link with the widespread metabolism of prograf and/or the prerequisite of larger oral dosage (16).

Kuypers et al. in 2007, reported that the CYP3A4*1/CYP3A5*1 and CYP3A4*1B/CYP3A5*1 genotypes were meaningfully more regularly related with the increase of biopsy-proven prograf -related nephrotoxicity than the CYP3A4*1/ CYP3A5*3 genotype (37.5 versus 11.2%; P = 0.03 and 42.8 versus11.2%; P = 0.02). The absence of a time-related rise in dose-corrected prograf exposure observed with the CYP3A4*1/CYP3A5*1 and its genotypes is associated with prograf-related nephrotoxic side effects, probably as a consequence of advanced concentrations toward toxic metabolites (17, 18).

Finally, as in clinical practice, monitoring predose trough blood concentrations seems to be essential for guiding optimal dosing of tacrolimus (1-25), therefore in the Iranian population of transplantation, in order to achieve the best long-term results, focus on different methods of therapeutic drug monitoring appears to be advantageous.

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