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Tacrolimus therapeutic drug monitoring in Tunisian renal transplant recipients: Effect of post-transplantation period ☆

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ABSTRACT

Background: Most previous studies having focused on therapeutic drug monitoring of tacrolimus in renal transplant recipients have assessed the clinical response of patients. The aim of this study is to investigate the influence of post-transplant delay on tacrolimus dose, trough levels (C0) and dose/C0 ratio in a Tunisian renal transplant population.
Patients and methods: A retrospective study including 110 renal transplant patients has been performed. Tacrolimus trough concentrations were adjusted according to the target range proposed by the European consensus conference on tacrolimus optimization. Samples for determination of tacrolimus blood level were subdivided according to the post-transplantation period into three groups.
Results: The initial dose required was 0.17 ± 0.05 mg/kg/day during the first 3 months after transplantation. A reduction of 36 and 65% of tacrolimus initial dose during the second (3–12 months) and third period after transplantation (>12 months), respectively, was required to maintain the concentration level within therapeutic range. These results were different from those found in other studies performed in different populations. We hypothesize that these differences in dosing requirement may be due to an interethnic polymorphism in the expression of enzymes involved in tacrolimus metabolism.
Conclusion: These results could provide a simple therapeutic strategy to optimize tacrolimus prescription after renal transplantation in Tunisian population.

1. Introduction

Tacrolimus is a potent immunosuppressant drug that is well established for primary immunosuppression in kidney transplantation. It was introduced in the late 1980s as an alternative to cyclosporine-A for the prevention of graft rejection following solid organ transplantation [1]. Based on its high inter and intra-individual pharmacokinetic variability, therapeutic drug monitoring is essential to avoid graft rejection and drug toxicity.

In order to obtain an optimal efficacy and a minimal toxicity, the European experts on tacrolimus have recently proposed new target ranges of trough concentration based on both drug combination and post-transplantation delay. This consensus conference on Tacrolimus optimization concluded that tacrolimus whole blood concentrations should range from 10 to 15 ng/ml during the first 3 months after transplantation, and then from 8 to 12 ng/ml during the second period after transplantation (3 months–12 months), and from 5 ng/ml to 10 g/ml thereafter [2].

Only few studies have assessed the corresponding recommended tacrolimus dose corresponding to therapeutic concentrations ranges according to time post-transplantation [3–5] and, to our knowledge, there have been no reports of such studies performed on Tunisian kidney transplant recipients.

The aim of this study is to investigate the influence of post-transplant delay on tacrolimus dose, trough levels (C0) and dose/C0 ratio in a Tunisian renal transplant population.

2. Patients and methods

We performed a retrospective study including one hundred and ten Tunisian patients undergoing renal transplantation. Their tacrolimus blood samples were obtained between March 2009 and December 2011. All patients were treated with a combined immunosuppressive therapy based on tacrolimus, mycophenolic acid and prednisone. The initial tacrolimus dose (Prograf®, Hikma) was 0.15 mg/kg per day administered in two divided doses, and started the same day of renal transplantation. Subsequent tacrolimus doses were adjusted to

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Table 1
Patients' characteristics.

	Group 1 ($n = 141$)	Group 2 ($n = 170$)	Group 3 ($n = 146$)
Age (year)	31.6 ± 11.9	26 ± 9.3	33.0 ± 8.0
Gender (M/F)	41/18	18/8	16/9
Weight (kg)	58.2 ± 13.8	61.5 ± 13.3	65.9 ± 11.1
Tac doses (mg/kg/day)	0.17 ± 0.06	0.11 ± 0.06	0.06 ± 0.04
Tac concentration (ng/ml)	10.53 ± 4.47	10.61 ± 4.62	9.48 ± 5.59
Dose/concentration (mg/μg/l)	0.019 ± 0.015	0.012 ± 0.009	0.009 ± 0.006
Creatinine clearance (ml/min)	84.7 ± 44.7	97.6 ± 43.6	104.7 ± 51.7

Results are expressed as mean ± SD.
Tac = tacrolimus.

maintain the whole-blood concentration within the recommended target range.

Concomitant immunosuppressive drugs based on Mycophenolate Mofetil and methylprednisolone at a dose of 2000 mg/day and 500 mg/day, respectively, were administered in all patients. Corticosteroid dose was progressively reduced to 20 mg/day of prednisone in day 7, to reach a long-term maintenance dose of 10 mg/day at the end of the second week post-transplantation.

The samples were subdivided according to the post-transplantation period into three groups. Group 1 (G1), 2 (G2) and 3 (G3) are blood samples collected from patients with a less than 3-month post-transplantation delay, those with a 3 to 12-month delay and those with a more than 12-month delay, respectively.

Blood samples for the determination of trough tacrolimus concentrations were taken immediately prior to the morning dose. C0 was adjusted according to the target range proposed by the European consensus conference on tacrolimus optimization [2]: between 10 and 15 ng/ml during the first 3 months after transplantation (G1), 8 and 12 ng/ml in the subsequent 9 months (G2) and between 5 and 10 ng/ml thereafter (G3).

Tacrolimus blood concentrations were determined by an enzyme multiplied immunoassay technique (EMIT, V-twin*). The assay's detection limit was 2 ng/ml.

Statistical analyses were performed using the platform-independent basic-statistics GUI for R (Rcmdr R package) software version 1.9–4. A univariate analysis using ANOVA test was carried out to compare continuous parameters in different groups. A Chi square test was performed to compare gender in three groups. Then, we have performed a multivariate analysis using a backward stepwise multiple regression analysis (Generalized Linear Model, Rcmdr R package) in order to evaluate the effect of covariates (age, gender, weight, creatinine clearance, post-transplantation time) on tacrolimus dose requirement. Covariates were dichotomizated according to the median value in order to investigate which group of age, weight and creatinine clearance or post transplantation period could affect tacrolimus dose. The best final model was selected using the Akaike information criterion (AIC).

3. Results

3.1. Patients' data

One hundred and ten Tunisian patients (75 men and 35 women) undergoing renal transplantation were included in the study. Their mean age was 31.6 ± 11.9 years and their mean weight was 58.2 ± 13.8 kg (Table 1).

3.2. Correlation between concentration and tacrolimus doses

A total of 446 blood samples for the determination of tacrolimus trough concentration were obtained during the period of the study. The mean number of samples per patient was 8.1, ranging from 1 to 17 samples per patient.

Correlation analyses between trough concentration levels and tacrolimus doses were performed. No significant correlations were found between blood concentration and tacrolimus doses either in all samples (Fig. 1A) or in the three groups (Fig. 1B, C, D)

3.3. Determination of tacrolimus doses corresponding to concentrations within therapeutic range

Among 447 Tac samples, 136 (30%) were under the predefined target ranges (85, 41 and 21 for G1, G2, G3, respectively), 110 (25%) were over target ranges (18, 45 and 47, for G1, G2and G3, respectively) and 200 (45%) tacrolimus concentrations were within therapeutic ranges: 68 in G1, 54 in G2 and 78 in G3 (Fig. 2).

Analyses of concentrations within therapeutic ranges, doses corresponding to therapeutic concentrations, and D/C0 in each group are detailed in Table 2.

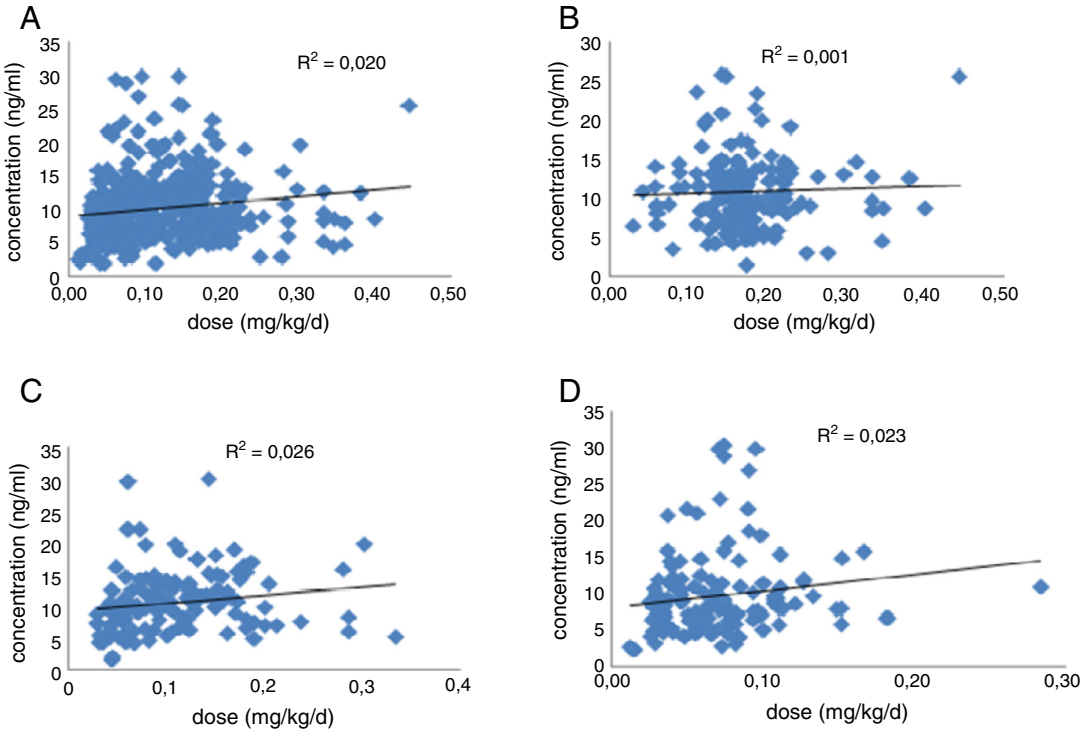

Fig. 1. Correlation between tacrolimus doses and blood concentrations: A. Total blood samples; B. Group 1; C. Group 2; D. Group 3.