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Retrospective analysis of tacrolimus concentrations and factors influencing their levels in adult kidney transplant recipients treated with Dailiport

ABSTRACT

Introduction: One of the standard immunosuppressive drugs used after kidney transplantation is the calcineurin inhibitor — tacrolimus. Precise maintenance of appropriate blood concentrations of this drug is crucial to ensure clinical efficacy and to minimize adverse effects. However, data on achieving target concentration levels of Dailiport — one of the newly registered generic prolonged-release tacrolimus formulations in Poland — are lacking, particularly regarding factors influencing this process in real-world clinical practice outside controlled clinical trials.

Objective: The aim of this study is to provide these insights based on a retrospective analysis of kidney transplant patients from a single clinical center.

Material and methods: A retrospective analysis of tacrolimus blood concentrations was conducted in 23 kidney transplant recipients. The observation period was 6 months.

Results and conclusions: The analysis revealed typical fluctuations in tacrolimus blood concentrations, with a statistically significant trend toward stabilization at the target level after the first month of treatment (comparison: month 1 vs. months 2–3 and months 4–6). Due to the lack of identified additional factors influencing the achievement of target concentrations, further studies on larger patient cohorts, incorporating a broader range of potential influencing factors, are necessary.

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Keywords: kidney transplantation, tacrolimus, immunosuppression

INTRODUCTION

Kidney transplantation is the most effective treatments for end-stage renal disease, leading to improved survival and quality of life compared to dialysis therapy [1]. According to data from Poltransplant [2], in 2023, a total of 977 kidneys and 24 kidney-pancreas grafts were taken from deceased donors in Poland, along with 78 kidneys from living donors. As of December 2023, the number of patients awaiting kidney transplantation was 1,193. This highlights the clinical and societal significance of managing post-transplant patients.

The majority of kidney transplant recipients receive a triple-drug immunosuppressive regimen consisting of glucocorticosteroids, mycophenolate mofetil, and calcineurin inhibitors [3]. Tacrolimus is the preferred calcineurin inhibitor [3]. Despite its undeniable benefits, precise monitoring of blood tacrolimus concentrations is necessary to ensure adequate clinical efficacy while minimizing nephrotoxicity, neurotoxicity, and other adverse effects [4].

In the European Union, several oral tacrolimus formulations have been approved for use in transplantology, including Advagraf, Envarsus, Prograf, and, more recently, Dailiport. According to the Summary of Product Characteristics for Dailiport [5], it is a generic prolonged-release formulation administered once daily, intended for the prevention of kidney

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or liver transplant rejection in adult recipients. However, data on maintaining target Dailiport concentration levels and the factors influencing this process in real-world clinical practice, outside controlled clinical trials, remain lacking.

The aim of this study is to provide data on tacrolimus concentrations and the factors influencing these levels in adult kidney transplant recipients treated with Dailiport, based on a retrospective case analysis from a single clinical center.

MATERIAL AND METHODS

The medical records of all adult patients treated with Dailiport at the Department of Transplantation, Immunology, Nephrology, and Internal Diseases, Medical University of Warsaw were analyzed. The study included patients who received Dailiport immediately after kidney transplantation, regardless of the underlying cause of native kidney failure. The documentation covered the period from December 2022 to November 2023.

For each patient, the internal database recorded the following information: a unique identifier corresponding to the order of inclusion in the database, age and sex, details regarding graft rejection (biopsy-confirmed rejection episodes and the time post-transplant when rejection occurred; this group also included one patient whose transplanted kidney did not regain function due to a multifactorial process), information on any conversion to another tacrolimus formulation, and the results of trough tacrolimus (C_0) blood concentration measurements (ng/mL).

The measurements were assigned to specific time intervals: postoperative days 2–6, and 7; weeks 2–4 post-transplant; months 2–3 post-transplant; and months 4–6 post-transplant. The exact dates of concentration measurements were not recorded, and the number of measurements per patient varied depending on clinical needs during the course of treatment. All patients received standard therapy, and the study was retrospective in nature, which eliminated the need for approval from the Bioethics Committee.

The basic characteristics of the study group were presented using descriptive statistics. In the analysis of Dailiport concentrations, values were classified as within the reference range, below the reference range, or above the reference range, based on predefined reference values for each post-transplant period. The results were graphically represented using bar charts, illustrating both the number of measurements performed and the percentage of measurements outside the reference range.

Factors influencing deviations from the reference tacrolimus concentration were analyzed using a Multinomial Logistic Mixed-Effects Model [6]. The model included sex, patient age, time period of concentration measurement, and graft rejection episodes as potential factors affecting drug concentration levels. The results were expressed as odds ratio (OR) estimates with 95% confidence intervals (CI) for each factor compared to the reference category.

The model accounted for both fixed and random effects, allowing for the analysis of data containing multiple measurements from individual patients. Calculations were performed using R software [7], with the brms package [8].

RESULTS AND DISCUSSION

The study group consisted of 23 patients, of whom 35% were women. The mean age of the patients was 52 years. Graft rejection occurred in 22% of the participants, while conversion to another tacrolimus formulation was required in 17% of patients. Full demographic and clinical data are presented in Table 1.

Figures 1–3 present the analysis of tacrolimus concentration measurements for each patient during the first month, the second to third month, and the fourth to sixth month after transplantation, respectively. These charts illustrate both the number of measurements and their distribution relative to the reference

Table 1. Characteristics of the study group

	N = 23[1]
Sex	
Women	8 (34.8%)
Men	15 (65.2%)
Age	
Mean (Standard Deviation)	51.7 (13.1)
Median	51.0
[25%, 75%]	[40.5, 64.5]
Minimum–Maximum	32.0–73.0
Graft rejection	
No	18 (78.3%)
Yes	5 (21.7%)
Conversion to another tacrolimus formulation	
No	19 (82.6%)
Yes	4 (17.4%)

[1]n (%)

concentration values, allowing for a visual assessment of concentration dynamics over time.

Table 2 presents the results of the analysis of factors influencing the likelihood of tacrolimus concentrations falling outside the reference range. A statistically significant decrease in the odds of both subtherapeutic and supratherapeutic tacrolimus levels was observed during the second- to third- and fourth- to sixth-month post-transplant. No significant effect of patient sex or age on drug concentration was identified. Additionally, graft rejection was not statistically significantly associated with tacrolimus levels.

Maintaining optimal drug concentration during the early post-transplant period (first month) proved to be a significant challenge. Therapeutic blood levels of Dailiport were observed more frequently as the time from transplantation increased, which is consistent with the findings of other authors who report stabilization of tacrolimus concentrations after the initial months [9].

Despite the expected association between suboptimal drug concentrations and the risk of graft rejection, the present study did not demonstrate such a relationship. However, some publications suggest a significant impact of low tacrolimus levels on an increased risk of rejection [10], while the conclusions of other authors are in line with the current findings [11]. The lack of a detected association in the present study may be attributed to low statistical power due to the small sample size.

The main limitations of the present analysis include its retrospective design, the absence of a comparison between Dailiport and other tacrolimus formulations, and the aforementioned small cohort size. Additionally, the lack of precise information on measurement dates prevented a clear determination of the temporal relationship between graft rejection and changes in drug concentration.

CLINICAL IMPLICATIONS

In summary, typical fluctuations in tacrolimus concentrations were observed among patients, with a statistically significant trend toward stabilization at target levels after the first month of treatment. As the duration of treatment was the only identified factor influencing the achievement of target blood concentrations, further studies involving larger patient cohorts and a broader range of potential influencing factors are warranted.

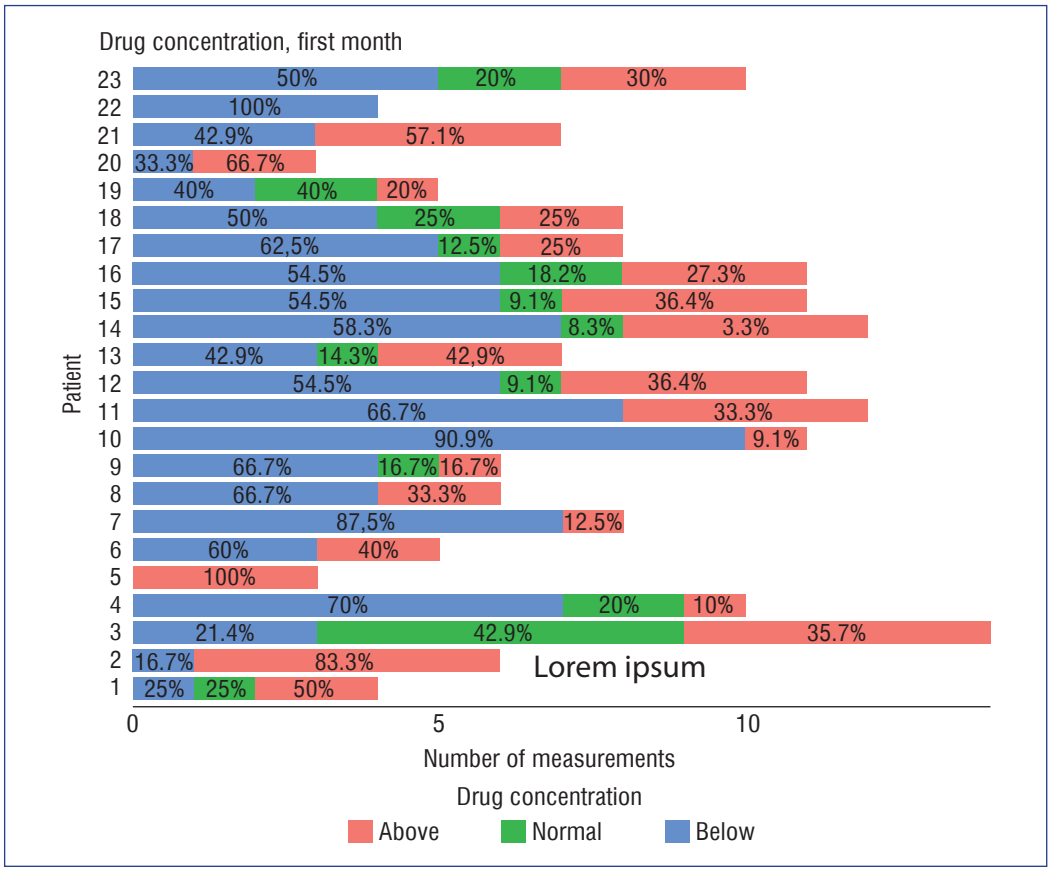

Figure 1. Tacrolimus concentration in the first month after transplantation

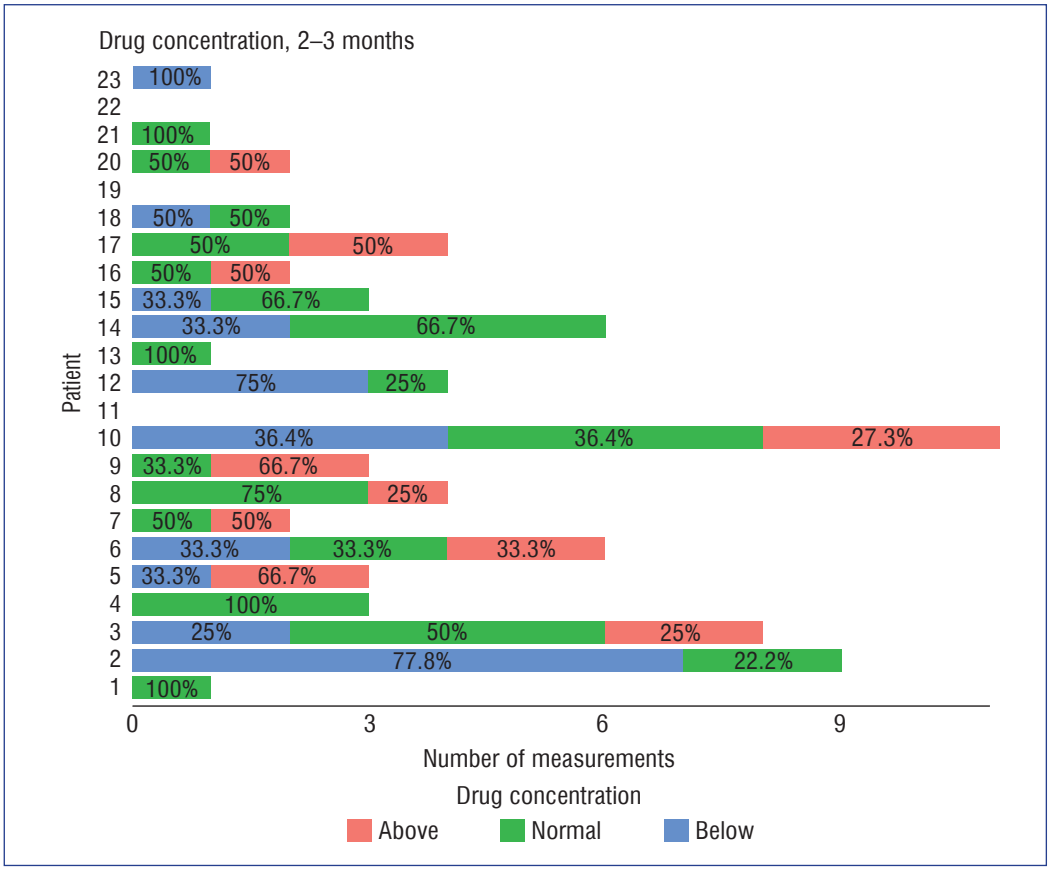

Figure 2. Tacrolimus concentration in the second to third month after transplantation

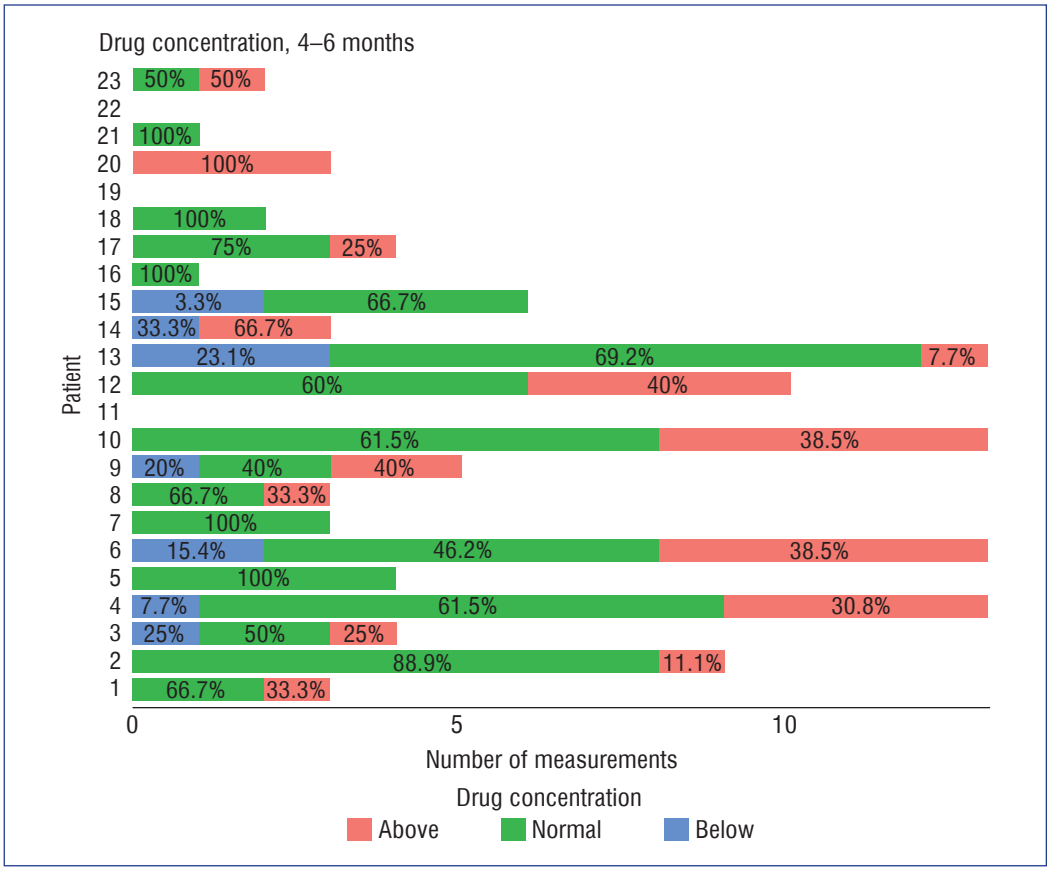

Figure 3. Tacrolimus concentration in the fourth to sixth month after transplantation

Table 2. Results of the analysis of factors influencing the odds of tacrolimus concentrations falling below or above the reference range

	Odds ratio (OR)	95% confidence interval	
		Lower	Upper
Above vs. within range			
Sex [male vs. female]	1.081	0.562	2.156
Age [per 1-year increase]	0.995	0.971	1.018
Time [month 2–3 vs. month 1]*	0.176	0.079	0.368
Time [month 4–6 vs. month 1]*	0.161	0.081	0.311
Graft rejection [yes vs. no]	1.001	0.417	2.452
Below vs. within range			
Sex [male vs. female]	0.765	0.380	1.464
Age [per 1-year increase]	0.995	0.971	1.019
Time [month 2–3 vs. month 1]*	0.153	0.073	0.316
Time [month 4–6 vs. month 1]*	0.031	0.013	0.069
Graft rejection [yes vs. no]	0.804	0.293	2.120

*Statistically significant result

ARTICLE INFORMATION AND DECLARATIONS

Data availability statement

The authors will make anonymized data available upon reasonable request.

Ethics statement

Due to the nature of the study, approval from a bioethics committee was not required.

Author contributions

KW, AB, MD — Conceptualization;
KW, AB — Data collection and analysis;
KW, AB, MD — Manuscript writing and critical review;
MD – Supervision.

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Conflict of interest

The authors declare that this study was commissioned by Sandoz AG. The authors received financial compensation for their work. The sponsor had no influence on the choice of methodology or the results presented. Daniel Rabczenko performed the aforementioned tasks as part of a paid service. Signature: SPEAK/MED/044/08-2024/1 SPEAK/MED/044/08-2024/2

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