

ORIGINAL ARTICLE

Evaluation of clotrimazole prophylaxis on tacrolimus trough concentrations in kidney transplant recipients

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JJN1-200, Cleveland, OH 44195, USA.
Email: wingse2@ccf.org**Abstract**

Background: Clotrimazole troches are used as prophylaxis against oropharyngeal candidiasis post-transplant and have limited systemic absorption. Following several occurrences of tacrolimus concentration fluctuations after clotrimazole discontinuation, its use as prophylaxis was discontinued post-kidney transplant.

Methods: We conducted a retrospective cohort study to evaluate the effect of clotrimazole prophylaxis on tacrolimus trough concentrations post-kidney transplant. The study included adult patients who received a kidney transplant at Cleveland Clinic Main Campus from August 1, 2019 to July 1, 2020 and were maintained on per-protocol, standard-dose tacrolimus through 90 days post-transplant. Patients were excluded if they received cyclosporine, systemic antifungals, strong CYP3A4 inhibitors or inducers, or a simultaneous multiorgan transplant. The primary objective was to compare tacrolimus trough concentrations before and after completion of clotrimazole prophylaxis. Secondary objectives were to compare the time to first post-transplant goal tacrolimus trough concentration, the rate of for-cause allograft biopsies within 90 days after transplant, and the incidence and type of candidiasis within 30 days after transplant, pre- and post-protocol change.

Results: Following clotrimazole discontinuation, the median tacrolimus trough concentration decreased from 10.5 ng/ml (IQR 8.4–12.2) to 6.6 ng/ml (IQR 5–8.7, $p < 0.0001$). No statistically significant differences in the rate of for-cause allograft biopsies (4.9% vs. 9.7%, $p = 0.264$) or incidence of candidiasis (1.2% vs. 5.4%, $p = 0.217$) were observed between those who received clotrimazole and those who did not receive clotrimazole.

Conclusions: Our study provides further evidence of a significant drug–drug interaction between tacrolimus and clotrimazole among kidney transplant recipients that can potentially lead to negative allograft outcomes.

KEYWORDS

clotrimazole, drug–drug interaction, tacrolimus, transplant

Abbreviations: CYP3A4, cytochrome P450 3A4; CYP3A5, cytochrome P450 3A5; IQR, interquartile range; TDD, total daily dose.

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1 | INTRODUCTION

Following kidney transplantation, patients are placed on a maintenance regimen of immunosuppression to prevent rejection of the newly transplanted organ and to preserve graft function. Tacrolimus is a calcineurin inhibitor with a narrow therapeutic index that is considered first-line for maintenance immunosuppressive treatment.¹ As a result of chronic medication-induced immunosuppression, transplant recipients are at a higher risk of developing opportunistic infections, including oropharyngeal candidiasis.² Clotrimazole is an azole antifungal that is indicated for both the treatment and prophylaxis of oropharyngeal candidiasis.³ As an azole antifungal, clotrimazole is an inhibitor of both cytochrome P450 3A4 and 3A5 enzymes (CYP3A4 and CYP3A5). This leads to a potentially significant drug interaction with tacrolimus, which is primarily metabolized via CYP3A4 and CYP3A5. Since clotrimazole is administered as a troche, systemic concentrations are limited.⁴ However, multiple studies that included heart, pancreas, and kidney transplant recipients have reported a clinically significant interaction between clotrimazole and tacrolimus, in which tacrolimus concentrations are elevated during concomitant treatment and decrease following discontinuation of clotrimazole.^{5–7} The proposed mechanism of this interaction is through inhibition of intestinal CYP3A4-mediated metabolism and P-glycoprotein efflux of tacrolimus by clotrimazole.^{6,8} Previous studies all included small numbers of subjects, and limited literature exists describing this potential drug–drug interaction in a larger population of kidney transplant recipients. Following routine occurrences of tacrolimus concentration fluctuations after clotrimazole discontinuation, routine use of clotrimazole as prophylaxis was stopped and removed from the kidney transplant protocol at our institution. The purpose of this study was to evaluate the effect of clotrimazole as fungal prophylaxis on tacrolimus trough concentrations post-kidney transplant, within the population prior to the protocol change, as well as to explore patient and allograft outcomes following the protocol change.

2 | METHODS

2.1 | Study design

This retrospective cohort study included patients ≥ 18 years of age who received a kidney transplant at Cleveland Clinic Main Campus from August 1, 2019 to July 1, 2020 and remained on per-protocol, standard-dose tacrolimus through 90 days post-transplant. Standard-dose tacrolimus was defined as tacrolimus adjusted to attain a target trough concentration of 8–12 ng/ml. Patients could receive tacrolimus immediate-release (generic, Prograf®) or extended-release formulation (Envarsus XR®), with trough concentrations collected 12 or 24 h post-dose, as appropriate. Patients were excluded if they received cyclosporine, systemic antifungals, strong CYP3A4 inhibitors or inducers, or a simultaneous multiorgan transplant. Those patients who underwent transplant prior to the protocol change received clotrimazole oropharyngeal candidiasis prophylaxis. Clotrimazole was initiated

post-transplant, as a 10 mg troche three times daily, and continued until ureteral stent removal (typically between 4–6 weeks post-transplant). Those patients who underwent a transplant following the protocol change on January 31, 2020 did not receive oropharyngeal candidiasis prophylaxis. Patient demographics, including transplant and immunosuppression characteristics, were collected via manual review of electronic medical records. Additional data collected included the tacrolimus trough concentration prior to and at least four days after clotrimazole discontinuation, dates of tacrolimus initiation and first at-goal trough concentration, for-cause allograft biopsies within 90 days post-transplant, and documented candidiasis within 30 days post-transplant. This study was approved by the Institutional Review Board of the Cleveland Clinic Foundation.

2.2 | Objectives

The primary objective of this study was to compare tacrolimus trough concentrations before and after the completion of clotrimazole prophylaxis in kidney transplant recipients. Secondary objectives were to compare the time to first post-transplant goal tacrolimus trough concentration, the rate of for-cause allograft biopsies within 90 days after transplant, and the incidence and type of candidiasis within 30 days after transplant, pre- and post-adult kidney transplant protocol change.

2.3 | Statistical analysis

Baseline characteristics were reported using descriptive statistics, including median with interquartile range (IQR) for continuous variables and counts with percentage for categorical variables. The primary outcome, comparing tacrolimus trough concentrations before and after clotrimazole discontinuation among those who received routine clotrimazole prophylaxis (pre-protocol change group), was analyzed using the Wilcoxon signed-rank test. The secondary outcome, comparing the time to first goal tacrolimus trough concentration among those who received clotrimazole and those who did not receive clotrimazole, was analyzed using the Mann–Whitney *U*-test. The rate of for-cause allograft biopsies and incidence of candidiasis were analyzed with the Fisher's exact test. Reported *p*-values are two-sided, with statistical significance defined as a *p*-value ≤ 0.05 . Statistical analysis was performed using Stata software version 14.1 (StataCorp, TX, USA).

3 | RESULTS

A total of 174 patients met inclusion criteria, with 81 patients having received clotrimazole prophylaxis and 93 patients having received no clotrimazole prophylaxis. Baseline characteristics were similar between groups (Table 1). The average patient was a white male, with a median age of 58 years. The most common causes of kidney disease included hypertension (40.2%) and diabetes (32.2%). Compared

TABLE 1 Baseline characteristics

Characteristic	Clotrimazole (n = 81)	No clotrimazole (n = 93)
Age (years)	55 (42–63)	61 (47–68)
Gender		
Male	55 (67.9)	51 (54.8)
Female	26 (32.1)	42 (45.2)
Race		
White	57 (70.4)	64 (68.8)
Black	16 (19.8)	18 (19.4)
Asian	1 (1.2)	5 (5.4)
More than one race	6 (7.4)	5 (5.4)
Cause(s) of renal disease		
Hypertension	35 (43.2)	35 (37.6)
Diabetes	23 (28.4)	33 (35.5)
Focal segmental glomerulosclerosis	10 (12.4)	11 (11.8)
Polycystic kidney disease	6 (7.4)	11 (11.8)
IgA nephropathy	7 (8.6)	7 (7.5)
Kidney transplant type		
Donor after brain death	25 (30.9)	53 (57.0)
Donor after cardiac death	24 (29.6)	19 (20.4)
Living donor	32 (39.5)	21 (22.6)
Induction regimen		
Basiliximab	33 (40.7)	17 (18.3)
Antithymocyte globulin (rabbit)	48 (59.3)	74 (79.6)
Serum creatinine at discharge (mg/dl)	3.60 (2.54–5.45)	4.41 (2.39–6.73)
Initial tacrolimus TDD (mg)	6 (4–6)	5 (4–6)
Time to first trough (days)	5 (4–6)	5 (4–6)

Abbreviation: TDD, total daily dose. Values are presented as median (interquartile range) or number (percent).

to those who received a kidney transplant prior to the protocol change, those who received a kidney transplant after the protocol change were more likely to have received a deceased donor transplant (60.5% and 77.4%, respectively) and induction with antithymocyte globulin (59.3% and 79.6%, respectively). The median initial tacrolimus total daily dose (TDD) was 6 mg (IQR 4–6) among patients who received clotrimazole prophylaxis and 5 mg (IQR 4–6) among patients who did not.

Following discontinuation of clotrimazole, within the pre-protocol change group, the median tacrolimus trough concentration decreased significantly from 10.5 ng/ml (IQR 8.4–12.2) to 6.6 ng/ml (IQR 5–8.7, $p < 0.0001$), as seen in Figure 1. Additionally, 54 patients (66.7%) had a trough concentration less than 8 ng/ml. The median tacrolimus TDD prior to, and following, clotrimazole discontinuation was 5 mg (IQR 3–6) and 5 mg (IQR 4–6), respectively ($z = -3.359$, $p = 0.0008$). It took a median of 12 days (IQR 7–17) to re-attain a goal tacrolimus trough concentration after clotrimazole prophylaxis was discontinued.

The median time to first goal tacrolimus trough concentration, after initiation post-transplant, was 10 days (IQR 7–14) among patients who received routine clotrimazole prophylaxis and 13 days (IQR 8–

20) among patients who did not receive clotrimazole prophylaxis ($p = 0.0023$, Table 2). No statistically significant difference was seen in the rate of for-cause allograft biopsies between groups (4.9% vs. 9.7%, $p = 0.264$). Of those who underwent a for-cause allograft biopsy, no patients in the clotrimazole group had results definitive for acute cellular rejection versus three patients in the no-clotrimazole group. Similarly, there was no statistically significant difference observed in the incidence of candidiasis between groups (1.2% vs. 5.4%, $p = 0.217$, Table 2). The most frequently observed type of candidiasis was oropharyngeal, occurring in four patients who did not receive clotrimazole prophylaxis. One patient within the clotrimazole group developed esophageal candidiasis.

4 | DISCUSSION

In this retrospective cohort study of kidney transplant recipients, we evaluated the effect of clotrimazole prophylaxis on tacrolimus trough concentrations. Maintaining therapeutic concentrations of tacrolimus

**TABLE 2** Secondary outcomes

Outcome	Clotrimazole (n = 81)	No clotrimazole (n = 93)	p-Value
Time to first goal tacrolimus trough (days)	10 (7–14)	13 (8–20)	0.0023
For-cause allograft biopsy	4 (4.9) [†]	9 (9.7)	0.264
Definitive for acute cellular rejection	0 (0)	3 (3.2)	–
Borderline for acute rejection	0 (0)	2 (2.2)	–
Adjustments to immunosuppression	1 (1.2)	6 (6.5)	–
Candidiasis	1 (1.2)	5 (5.4)	0.217
Oropharyngeal	0 (0)	4 (4.3)	–
Esophageal	1 (1.2)	0 (0)	–

Note: Values are presented as median (interquartile range) or number (percent).

[†]One patient within the clotrimazole group had two for-cause biopsies within 90 days post-transplant.

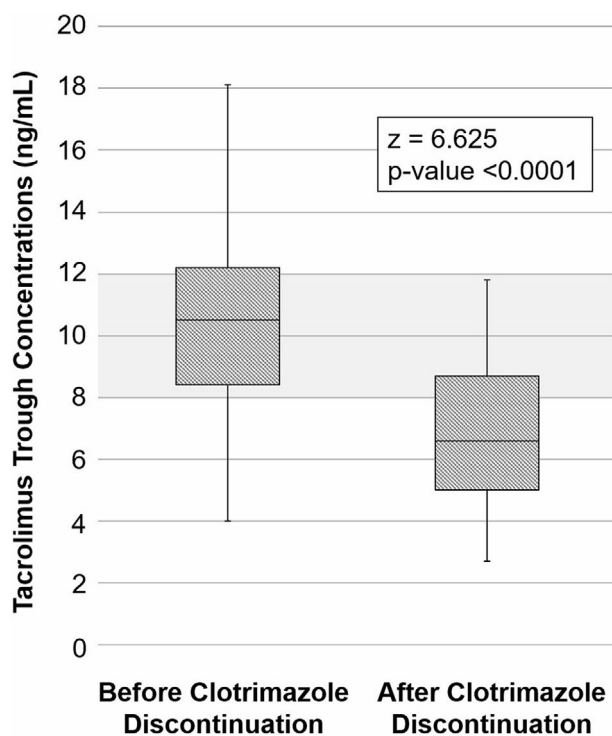


FIGURE 1 Tacrolimus trough concentrations before and after clotrimazole discontinuation. Median tacrolimus trough concentrations before and after clotrimazole discontinuation were 10.5 ng/ml (IQR 8.4–12.2) and 6.6 ng/ml (IQR 5–8.7), respectively. The goal tacrolimus trough concentration of 8–12 ng/ml is highlighted in gray

post-transplant is vital to prevent rejection of the transplanted organ and preserve graft function.¹ The mechanism of the proposed interaction between clotrimazole and tacrolimus is inhibition of CYP3A4 and CYP3A5 by clotrimazole, leading to decreased tacrolimus metabolism. When clotrimazole is discontinued, and the proposed drug–drug interaction is no longer present, we observed a decrease in tacrolimus concentrations.

Prior to the present study, the effect of clotrimazole on tacrolimus trough concentrations post-kidney transplant was evaluated by Vasquez et al. in a small subset of 35 kidney transplant recipients. Compared to patients who received nystatin for oropharyngeal candidiasis prophylaxis, those who received clotrimazole had mean tacrolimus trough concentrations that were significantly higher 3, 5, and 7 days post-transplant ($p < 0.05$), as well as mean tacrolimus doses on day 7 that were significantly reduced ($p < 0.05$).⁵ A similar finding was described by Viesselmann et al. within a cohort of 65 pancreas transplant recipients, 43 of whom were also kidney transplant recipients. When compared to the mean tacrolimus trough concentration prior to clotrimazole discontinuation, the mean trough concentration following discontinuation was significantly lower (7.1 ± 2.6 ng/ml vs. 9.6 ± 3.0 ng/ml, $p = 0.000003$). Further, the observed decrease in tacrolimus trough concentrations was found to be significantly greater among those patients who experienced an episode of rejection 3–12 months post-transplant.⁶ Following clotrimazole discontinuation, the apparent clearance of tacrolimus is increased, as described within the heart transplant population by Uno et al.⁷ Our current study expands upon previous literature by evaluating the proposed interaction within a larger transplant population of 174 patients. Prior to clotrimazole discontinuation, the majority of patients had a tacrolimus trough concentration that fell within the therapeutic range (8–12 ng/ml). Following clotrimazole discontinuation, not only did the median tacrolimus trough concentration significantly decrease, similar to the findings of Viesselmann et al., but also the majority of patients were subtherapeutic. This was observed despite overall higher tacrolimus TDDs following clotrimazole discontinuation. This emphasizes the clinically significant drug–drug interaction, as subtherapeutic tacrolimus concentrations place transplant recipients at an increased risk for graft rejection.¹

Post-protocol change, with the cessation of clotrimazole prophylaxis, goal tacrolimus trough concentrations were achieved later than pre-protocol change, when patients received clotrimazole until ureteral stent removal. This observation is likely due to the lack of the drug–drug interaction within the no-clotrimazole group paired with similar starting tacrolimus doses as were utilized pre-protocol change.

Tacrolimus dosing within this study was observed to be more conservative than per package labeling recommendations, and at the clinical discretion of the transplant nephrologists.⁹

Our study also allowed for evaluation of patient and allograft outcomes, with and without routine clotrimazole prophylaxis. No statistically significant difference was observed in the rate of for-cause allograft biopsies among patients who received routine clotrimazole prophylaxis and those who did not. However, there were numerically more patients within the no-clotrimazole group who underwent a for-cause allograft biopsy (nine vs. four in the clotrimazole group). Among those who received a for-cause allograft biopsy, three were found to have acute cellular rejection and two had results consistent with high suspicion for rejection. This trend contradicts our initial hypothesis that fewer for-cause biopsies would be seen within the group post-protocol change, due to steady tacrolimus concentrations. However, the observed numerical increase in for-cause allograft biopsies may be related to the observed delay in achieving an initial therapeutic tacrolimus trough concentration. The decision to stop using clotrimazole prophylaxis did not have clinical impact on candidiasis as there was not a statistically significant difference in its incidence between groups, although there were more cases of oropharyngeal candidiasis among those who did not receive prophylaxis (4.3% incidence). This observed incidence is lower than that seen in a similar single-center study conducted by Ky et al., in which oropharyngeal candidiasis within 3 months post-kidney transplant was seen in 7.8% of those not receiving nystatin prophylaxis.¹⁰

An inherent limitation of this study is its retrospective design, which limited the overall sample size and the ability to control for adjustments in tacrolimus dosing. Specifically, adjustments between the time of tacrolimus initiation and first recorded trough, as well as adjustments between the time of clotrimazole discontinuation and the first recorded trough post-discontinuation were unable to be captured. Additionally, variability in monitoring frequency existed amongst patients.

Overall, the results of our present study provide further evidence of a significant drug–drug interaction between tacrolimus and clotrimazole, which can potentially lead to negative allograft outcomes, among the largest population of kidney transplant recipients described to date. The median tacrolimus trough concentration following clotrimazole discontinuation significantly decreased, resulting in subtherapeutic tacrolimus trough concentrations. Removal of routine clotrimazole prophylaxis did not significantly affect the rate of for-cause allograft biopsies or incidence of candidiasis among included patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Emily Wings, Michael Spinner, and Jamie Eckardt conceived the study design. Emily Wings conducted data collection. Emily Wings, Michael

Spinner, and Jamie Eckardt performed statistical analysis, wrote and revised the manuscript, and gave final approval of the completed manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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