

Clinical Study

Tacrolimus Dose Modification in Hematopoietic Cell Transplant Recipients Following a Change in Therapy from Fluconazole to Voriconazole

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Antifungal therapy with voriconazole or fluconazole in combination with the calcineurin inhibitor tacrolimus exhibits significant CYP3A4 drug interaction potential in allogeneic hematopoietic cell transplant (HCT) recipients. The package insert for voriconazole has dosing recommendations for tacrolimus when voriconazole is started, but these do not apply to patients already receiving fluconazole therapy. The purpose of this retrospective study is to estimate appropriate dose modification of tacrolimus following a change in therapy from fluconazole to voriconazole. We performed a retrospective case-series analysis of five patients. The mean steady-state concentration/dose (*C/D*) ratio of tacrolimus increased from 413 (range, 255–642) to 850 (range, 670–953) following a switch from fluconazole to voriconazole ($P = 0.006$). This data represents a mean 2-fold increase in *C/D* ratios following the switch, indicating that the dose of tacrolimus may be most accurately reduced by approximately 50% following this switch in therapy. This provides some guidance for practitioners to estimate dose adjustments but will require close pharmacokinetic monitoring and adjustments on an individual patient basis.

1. Introduction

Triazole antifungal agents are widely used for prophylaxis and treatment of invasive fungal infections in patients undergoing hematopoietic cell transplantation (HCT). Fluconazole is a commonly utilized agent because it exhibits excellent coverage of yeasts such as *Candida* species; however it is ineffective against molds and certain species of *Candida*. Due to its limited antifungal spectrum, fluconazole is utilized in patients who are at a low risk of acquiring invasive mold infections such as those due to *Aspergillus* species [1]. Alternatively, voriconazole is an extended-spectrum triazole antifungal agent that exhibits broad coverage of both yeasts and molds including *Aspergillus*. Therefore, patients undergoing HCT

that are initiated on fluconazole are sometimes later switched to voriconazole in the event of a suspected or confirmed breakthrough fungal infection.

Tacrolimus is a calcineurin inhibitor that is routinely used for prevention of graft versus host disease (GVHD) in patients undergoing allogeneic HCT. Both tacrolimus and triazole antifungal agents are metabolized by the cytochrome P450 enzyme system. Tacrolimus is primarily metabolized by the CYP3A4 isoenzyme subtype while the triazole antifungals fluconazole and voriconazole are metabolized by the CYP2C9, CYP2C19, and CYP3A4 isoenzymes in different degrees [2]. Due to this association, fluconazole and voriconazole act as competitive inhibitors of these enzyme systems resulting in a clinically significant drug interaction

when administered in combination with tacrolimus. An increase in tacrolimus bloodstream concentrations is the end result of this interaction, and the dose of tacrolimus must be carefully adjusted to compensate for these changes in metabolism in order to avoid pharmacologic adverse effects [3].

The package insert for voriconazole recommends decreasing the dose of tacrolimus to one-third of the previous dose, when voriconazole is started [2]. This does not account for patients already having a baseline interaction with fluconazole, and the appropriate adjustment is unknown in this very common scenario. Various dosing and monitoring strategies have been suggested for patients administered voriconazole and tacrolimus concurrently who have not been receiving fluconazole. In an attempt to counteract anticipated changes in tacrolimus concentrations, Trifilio et al. described the use of a preemptive dose reduction strategy based off of 48-hour steady-state levels [4]. The authors concluded that although preemptive dose reduction was an effective strategy, subsequent therapeutic drug monitoring and the need for further drug levels were still essential. Furthermore, Mori et al. utilized concentration/dose (C/D) ratios as a more accurate measure of the relationship between tacrolimus dose and subsequent serum concentrations. This study also demonstrated that tacrolimus dose adjustments may be best decided on an individual basis rather than uniformly [5].

To our knowledge, only one case-series analysis of three patients has been performed regarding tacrolimus dosing following a switch in therapy from fluconazole to voriconazole. Kawazoe et al. utilized C/D ratios to suggest that some patients may require a tacrolimus dose reduction up to one-fifth of regular dosing following this change in antifungal therapy [3]. Our case-series analysis of five patients attempts to add to the limited data currently available to clinicians regarding this interaction. The primary objective of this study is to help further describe the impact upon tacrolimus blood concentrations and dosing adjustments when antifungal therapy is switched from fluconazole to voriconazole in transplant recipients. This can aid clinicians in developing an empiric dose in similar situation.

2. Materials and Methods

This is a retrospective case-series analysis of patients who underwent allogeneic HCT at an academic medical center from May 2008 to March 2011. Recipients who were previously stabilized on tacrolimus and fluconazole therapy that were later switched from fluconazole to voriconazole were included in this study. Selection of patients was performed using a query of the electronic medical record to identify all HCT patients who received voriconazole concomitantly with tacrolimus during hospitalization. Patients were excluded from this analysis if they were initiated on pharmacotherapy known to cause additional drug interactions with tacrolimus, if steady-state concentrations were not achieved during either fluconazole (treatment for less than 7 days) or voriconazole (treatment for less than 24 hours) therapy at the time of tacrolimus drug level monitoring, and if patients were initiated on a different antifungal agent prior to voriconazole

therapy. Institutional review board approval was granted prior to study initiation.

It is standard practice at our institution to use fluconazole for antifungal prophylaxis in patients undergoing allogeneic HCT until day 100 following transplant. Fluconazole is administered at a dosage of 400 mg orally or intravenously depending on oral tolerability of medications. Patients in this study received 400 mg of fluconazole by either route prior to a switch in therapy to voriconazole. Voriconazole was initiated with a loading dose of 6 mg/kg IV for 2 doses followed by dosing of 4 mg/kg either intravenously or orally thereafter for the treatment of a confirmed or suspected breakthrough fungal infection.

Blood concentrations of tacrolimus were drawn as trough values prior to tacrolimus administration twice weekly. Whole blood samples were measured using a chemiluminescent immunoassay on the Abbott Architect analyzer (Abbott Diagnostics, Abbott Park, IL, USA). Transplant pharmacists and/or physicians adjusted tacrolimus doses relative to blood concentration reporting. Concentration/dose ratios described in units of (ng/mL)/(mg/kg) were calculated to accurately describe this interaction and to account for changes in dosage due to routine and preemptive clinical practice. Calculations of C/D ratios were performed 48 hours following a switch to voriconazole to ensure attainment of steady state and stabilization of tacrolimus blood levels. The C/D ratios during fluconazole and voriconazole therapy were compared to describe the extent of change in this drug interaction with tacrolimus.

Statistical analysis was performed using SPSS software, version 18.0 (IBM corporation, Armonk, NY, USA). Basic descriptive statistics were used to describe measures of central tendency. C/D ratios were reported in values of the mean \pm standard error of the mean. Comparisons between mean C/D ratios were made using dependent t -tests, and P values < 0.05 were considered statistically significant. The Pearson correlation coefficient was used to measure potential correlation between two variables.

3. Results

Of the 36 patients identified for further analysis, only five met inclusion criteria for this study. Nineteen patients were excluded because they were not administered fluconazole prior to voriconazole initiation, six patients had not yet reached steady state on either medication, and six patients were being coadministered medications with clinically significant drug interactions. Patient demographic information for the five patients that met inclusion criteria is summarized in Table 1. Our patient population consisted exclusively of female patients with a median age of 54 years old. Four out of five patients exhibited both stable renal and hepatic function throughout the study observation period.

Each patient included in this analysis received a minimum of 14 days of concomitant fluconazole and tacrolimus therapy prior to a switch to voriconazole. Only two patients (patients 3 and 4) received intravenous fluconazole because they could not tolerate oral therapy. Because tacrolimus levels

TABLE 1: Patient demographic information.

Patient	Age (years)	Gender	Race	Weight (kg)	Diagnosis	Donor Type	Scr (mg/dL) Median (range)	T. Bili (mg/dL) Median (range)
1	33	F	Caucasian	100.6	MDS	Matched Unrelated, Allogeneic	0.47 (0.27–1.0)	0.7 (0.4–0.9)
2	74	F	Caucasian	88.1	AML	Matched Unrelated, Allogeneic	0.63 (0.4–1.2)	0.8 (0.5–1.2)
3	43	F	Caucasian	77.1	AML	Matched Unrelated, Allogeneic	0.61 (0.4–0.85)	0.7 (0.5–1.0)
4	58	F	Caucasian	72.4	MDS	Matched Unrelated, Allogeneic	0.48 (0.36–0.75)	1.25 (0.6–2.8)
5	54	F	Caucasian	71.5	AML	Matched Related, Allogeneic	1.23 (0.67–2.6)	0.8 (0.4–1.3)

Scr: serum creatinine, T. Bili: total bilirubin, MDS: myelodysplastic syndrome, AML: acute myelogenous leukemia.

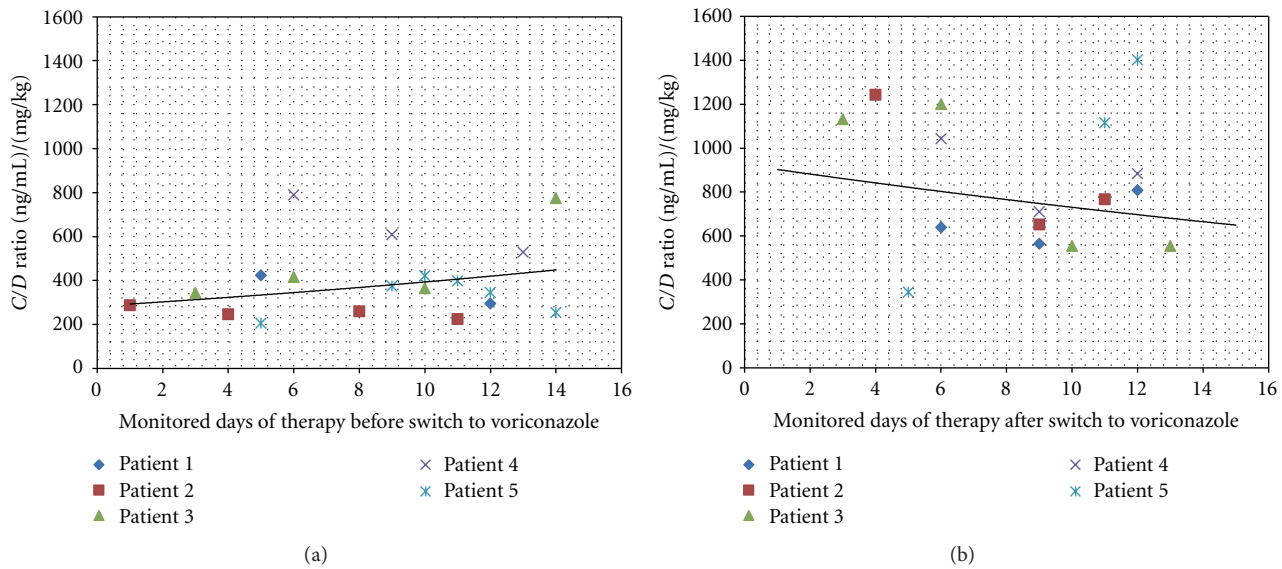


FIGURE 1: (a) *C/D* Ratios observed before the switch from fluconazole to voriconazole with concomitant tacrolimus therapy. (b) *C/D* ratios observed after the switch from fluconazole to voriconazole with concomitant tacrolimus therapy.

were drawn twice weekly, the time in-between levels was typically three to four days. However, tacrolimus levels were sometimes ordered more frequently if the previous level was outside of the target range (5–12 ng/mL).

As suspected, increases in tacrolimus blood concentrations and *C/D* ratios were observed following a switch in therapy from fluconazole to voriconazole. Individual changes in tacrolimus *C/D* ratios for each patient following a switch in therapy from fluconazole to voriconazole are illustrated in Figure 1. The pooled mean *C/D* ratios prior to and following this change in therapy were 413 (range, 255–642) and 850 (range, 670–953), respectively ($P = 0.006$). Overall, this data represents approximately a 2.0-fold increase in *C/D* ratios. Individual and aggregate values for patient *C/D* are ratios summarized in Table 2.

Only one of the five patients included in this analysis experienced total bilirubin levels outside of the normal range (0.2–1.3 mg/dL) during the observation period. Although the maximum total bilirubin level observed of this patient reached 2.8 mg/dL during therapy (Table 1), a positive correlation was not found between this marker of liver dysfunction and *C/D* ratios in this patient ($r = -0.154$). The primary

reason behind this liver injury was due to the development of steroid-refractory GVHD of the liver.

4. Discussion

It is common practice for HCT patients to be switched from fluconazole to voriconazole therapy for the empiric or definitive treatment of breakthrough fungal infections. Both of these triazole antifungal agents exhibit different degrees of CYP3A4 enzyme inhibition with tacrolimus. Currently there is little information to guide clinicians when accounting for dosage adjustments due to this change in therapy. Our small case-series study indicates that the mean *C/D* ratio of tacrolimus was increased an average of 2.0-fold, indicating that around a 50% dosage reduction may be necessary to achieve similar tacrolimus concentrations following a switch from voriconazole to fluconazole.

Due to both hepatic and intestinal CYP3A4 isoenzyme metabolism, studies have reported a more significant drug interaction with tacrolimus with the use of oral fluconazole compared to intravenous fluconazole [6]. It is common at our institution for patients undergoing HCT to receive

TABLE 2: Mean changes in C/D ratios following a switch from fluconazole to voriconazole.

Patient	Tacrolimus administration	Fluconazole and tacrolimus			Voriconazole and tacrolimus		
		Fluconazole Dose/Route	Mean C/D ratio (ng/mL)/(mg/kg)	SEM	Voriconazole Dose/Route	Mean C/D ratio (ng/mL)/(mg/kg)	SEM
1	PO, BID	400 mg PO QD	359.1	63.8	IV load, 400 mg PO BID	670.0	72.3
2	PO, BID	400 mg PO QD	254.8	13.2	IV load, 300 mg PO BID	886.9	180.7
3	IV, CI	400 mg IV QD	474.4	101.1	IV load, 300 mg PO BID	859.6	204.5
4	PO, BID	400 mg IV QD	642.0	77.1	IV load, 300 mg IV BID	878.5	96.2
5	PO, BID	400 mg PO QD	333.2	34.9	IV load, 300 mg IV BID	953.3	316.0
Pooled Mean	—	—	412.7	58.0	—	849.7	173.9

PO: oral administration, IV: intravenous administration.

QD: once daily, BID: two times daily, CI: continuous infusion.

C/D ratio: concentration/dose ratio.

SEM: standard error of the mean.

oral fluconazole as antifungal prophylaxis unless the patient cannot tolerate oral medications. In our small patient sample, our findings do not indicate increased tacrolimus C/D ratios for those receiving oral fluconazole versus intravenous fluconazole as depicted in Table 2. Only patients 3 and 4 received intravenous fluconazole prior to the switch from fluconazole to voriconazole. Because the initial interaction between intravenous fluconazole and tacrolimus would be expected to be less significant than that of oral fluconazole and tacrolimus, one would predict greater increases in tacrolimus concentrations following a conversion to voriconazole therapy. However, these patients each exhibited a minimal 20% average increase in C/D ratios, respectively.

The manufacturer recommends a tacrolimus dosage adjustment of one-third of the usual dose when initiating voriconazole without a fluconazole lead-in period [2]. Contrary to previous study data suggesting that the dosage reduction may need to be even further reduced to one-fifth following a switch from fluconazole to voriconazole [3], we have observed that a lower reduction of the tacrolimus dose was necessary in this case-series analysis. This observation would be expected based on the assumption that, although each agent produces CYP3A4 enzyme competitive inhibition, the relative potency of this interaction is greater for voriconazole than for fluconazole.

There are various differences between our trial and the smaller case series conducted by Kawazoe et al. that may explain our more modest observations of this drug-drug interaction following fluconazole therapy [3]. Fluconazole 400 mg is the standard prophylactic dose at our institution compared to doses of 200 mg and 100 mg used in the previous trial. Prescribers should be aware that the dose of fluconazole

could significantly affect the degree of interaction. Likewise, voriconazole was administered at an oral dosage of 4 mg/kg every 12 hours when a transition from IV to oral therapy was made which may impact the degree of interaction differently than a fixed dose of 200 mg every 12 hours which is utilized by some clinicians. In addition, we implemented 24-hour delay period to ensure that tacrolimus serum concentrations and resulting C/D ratios were calculated after voriconazole reached steady-state levels from a loading dose. Furthermore, the differences in patient populations between the two studies could introduce various differences in CYP isoenzyme polymorphisms that could significantly alter tacrolimus concentrations.

There are various significant limitations to our study. First, our case-series study design is descriptive in nature, and further trials with more robust study designs will be needed to look further into these findings. In addition, lack of standardization between dosage forms of each of the three medications given concomitantly may have produced some variation in tacrolimus drug levels. Furthermore, differences in voriconazole interpatient metabolism and concentrations were not accounted for in this study which could help to explain the magnitude of its drug interaction with tacrolimus.

5. Conclusions

Although the use of uniform or preemptive dose-reduction strategies of tacrolimus alone is a simple approximation due to wide interpatient variability, these are often implemented in clinical practice in an effort to reduce time to therapeutic targets and potentially reduce the incidence of

toxicity [4]. Our findings indicate that typical dosage adjustments following a switch from fluconazole to voriconazole may be more modest than previous estimates. The results of this case series analysis indicate that an approximate 50% reduction in tacrolimus dosing following a switch in therapy from fluconazole to voriconazole may be necessary to continue to achieve optimal steady-state concentrations. However, ongoing tacrolimus drug concentrations should be closely monitored and dosing should be adjusted accordingly. Although this data may provide a starting point for clinicians regarding this interaction, larger clinical studies are needed to confirm the reproducibility of these findings.

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