

Comparative effects of fluconazole, posaconazole, and isavuconazole upon tacrolimus and cyclosporine serum concentrations

J Oncol Pharm Practice

0(0) 1–6

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DOI: 10.1177/10781552211029046

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Abstract

Introduction: Calcineurin inhibitors are commonly used in hematopoietic stem cell transplant (HSCT) patients to prevent graft versus host disease, but as CYP3A4 substrates they are frequently involved in drug-drug interactions. The purpose of this study is to characterize the effects of isavuconazole, fluconazole, and posaconazole on tacrolimus and cyclosporine serum concentrations and dose adjustments in allogeneic HSCT patients.

Methods: This retrospective study included patients admitted to Oregon Health and Science University between April 2008 and December 2018 who underwent hematopoietic stem cell transplantation and received concomitant tacrolimus or cyclosporine and fluconazole, isavuconazole or posaconazole therapy. Data on patient characteristics, drug dosing, and serum drug concentrations were collected through chart review, and descriptive statistics were used to summarize the results.

Results: A total of 139 patients were included in this study. We found fluconazole initiation leads to a 25% reduction in both tacrolimus and cyclosporine doses in order to maintain goal serum concentrations. Posaconazole and isavuconazole initiation requires tacrolimus dose reductions by 53% and 21%, respectively.

Conclusions: Based on our experience, FLC, POS, and ISA initiation may require CNI dose reductions and close monitoring of CNI levels to ensure levels remain within goal serum concentrations. Larger studies are needed to fully quantify the percentage in CNI dose reductions and characterize differences among these antifungals.

Keywords

Drug interaction, hematopoietic stem cell transplant, calcineurin inhibitor, azole antifungal, dosage adjustments

Date received: 9 December 2020; revised: 9 June 2021; accepted: 10 June 2021

Introduction

Calcineurin inhibitors (CNI) are commonly used in hematopoietic stem cell transplant (HSCT) patients to prevent graft versus host disease.¹ While these immunosuppressants are effective for graft versus host disease prophylaxis, as CYP3A4 substrates they are subject to drug-drug interactions. Patients undergoing HSCT are also at risk for invasive fungal infections and require antifungal prophylaxis, often with azole antifungals.^{2,3} The azole antifungals inhibit CYP3A4 and increase CNI serum concentrations, putting patients at risk for toxicities when used concomitantly. Currently, there is no standard of practice for adjusting CNI doses upon

azole antifungal initiation. Although the product information for fluconazole (FLC) and isavuconazole (ISA) indicate concomitant use with tacrolimus or

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cyclosporine can lead to increased CNI levels, they do not provide any recommendations for dose adjustments.^{4,5} The product information for posaconazole (POS) recommends reducing tacrolimus and cyclosporine doses by two-thirds and one-fourth, respectively, when initiating POS, but there is conflicting evidence supporting this practice.⁶ Furthermore, there are limited comparative data on the effects of azole antifungals on CNI levels in HSCT patients.⁷ The purpose of this study was to compare the effects of FLC, POS, and ISA on tacrolimus and cyclosporine levels and subsequent dose adjustments in allogeneic HSCT patients.

Methods

This single health system, retrospective study was conducted at Oregon Health & Science University and approved by the institutional review board. Patients admitted to the institution between April 2008 and December 2018 who received concomitant CNI (tacrolimus or cyclosporine) and antifungal (FLC, ISA, or POS) therapy were identified using electronic health records. Both oral and intravenous formulations of FLC and ISA were included, and POS formulations included oral tablets and suspension. We included patients who were 18–90 years old, admitted for an allogeneic HSCT, and initiated on CNI therapy during the admission. Patients were excluded if they had an active fungal infection, received other medications with significant interactions with tacrolimus or cyclosporine, or were switched to another antifungal or CNI during the data collection period. For included patients, two investigators performed electronic chart review to collect the following information: patient demographics, antifungal dose, initial CNI dose and dose adjustments through day +15, goal CNI level, and CNI levels through day +15.

The primary endpoint of this study was the median CNI dose ratio on day +10 to +15 of transplant compared to day 0 of transplant. This endpoint compares the initial product information recommended dose on a per kilogram basis to the final steady state dose the patient received after antifungal initiation. We used a range of day +10 to +15 of transplant as the point where steady state was achieved since not all patients have CNI levels checked on the same day due to patient care considerations. Secondary endpoints included the number of CNI levels within goal of the targeted level at steady state and the final CNI route of administration. Descriptive statistics were used to evaluate all endpoints using medians and ranges where appropriate.

At our institution, tacrolimus or cyclosporine is initiated on day -2 of transplant and antifungal therapy is started two days later on day 0, the day of stem cell infusion. Starting doses for tacrolimus and cyclosporine, respectively, are 0.015 mg/kg and 1.5–2 mg/kg

intravenously every twelve hours. CNI dosing is adjusted based on serum levels and is pharmacist managed utilizing an immunosuppressant therapy collaborative practice agreement, an institutionally supported protocol where the pharmacist is empowered to adjust doses and monitor medications within stated parameters without physician consultation. The first CNI trough serum level is typically checked on day 0, then twice weekly with additional levels ordered as needed. The target therapeutic levels are protocol dictated by type of HSCT, with tacrolimus commonly targeted to 5–10 ng/mL and cyclosporine to 200–300 ng/mL. Intravenous to oral dose conversions in this study were based on our institution protocol, which are 1:1.5 for tacrolimus and 1:1.8 for cyclosporine.

Results

A total of 139 patients were included in this study: 100 fluconazole (72%), 20 posaconazole (14%), and 19 isavuconazole (14%). Of the initial 228 patients who fit the inclusion criteria, 89 patients were excluded, primarily due to switching to another antifungal agent. Baseline characteristics of included patients are presented in Table 1. The overall median age was 59 years old and was similar across all groups except CSA/ISA, which had a median age of 23 years old. The most common malignancies were acute myeloid leukemia (44%), myelodysplastic syndrome (21%), and acute lymphoblastic leukemia (16%).

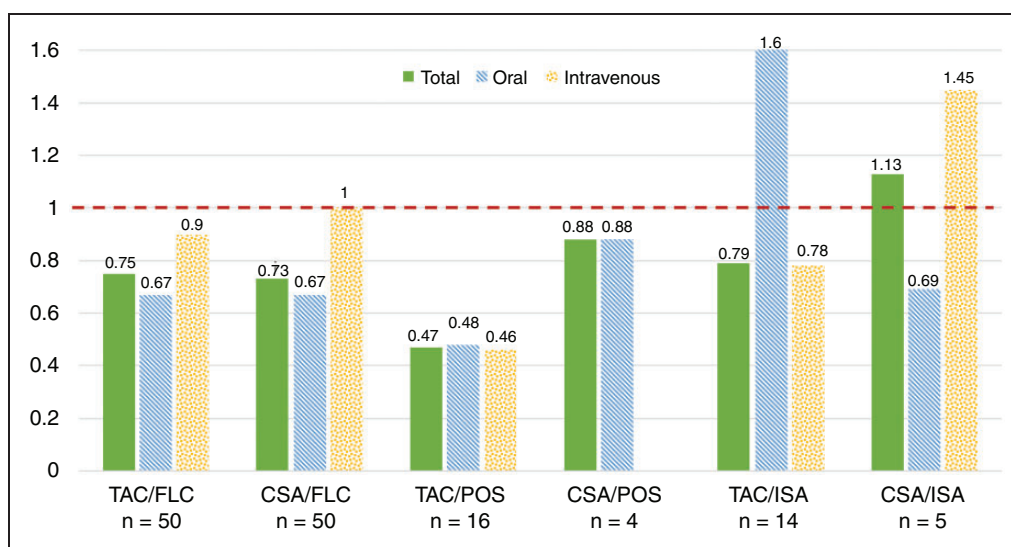
The median CNI dose ratio comparing steady state doses (between day +10 to +15 of transplant) to day 0 doses for each group, and when separated by route of CNI administration, is shown in Figure 1. The median CNI dose ratio for the TAC/FLC group was 0.75, indicating tacrolimus doses at steady state, after FLC was initiated, were overall 25% lower than the initial D0 doses. The median CNI dose ratio for the CSA/FLC group was 0.73, indicating a 27% decrease in cyclosporine doses at steady state. In the POS groups, the median TAC and CSA dose ratios, respectively, were 0.47 and 0.88, demonstrating a 53% and 12% decrease in TAC and CSA doses. For ISA the median CNI dose ratio was 0.79 for TAC, indicating a 21% decrease in TAC doses and 1.13 for CSA, indicating a 13% increase in CSA doses at steady state.

The median CNI dose ratios in the FLC groups when separated by oral and intravenous CNI route of administration, respectively, were 0.67 and 0.9 for TAC and 0.67 and 1 for CSA. In the TAC/POS group, the median CNI dose ratio was 0.48 for oral route and 0.46 for intravenous route. All patients in the CSA/POS group were receiving CSA intravenously. In the ISA groups, the median CNI dose ratios by oral versus

Table 1. Baseline patient characteristics.

Patient characteristics	Total (n = 139)	TAC/FLC (n = 50)	CSA/FLC (n = 50)	TAC/POS (n = 16)	CSA/POS (n = 4)	TAC/ISA (n = 14)	CSA/ISA (n = 5)
Gender, n (%)							
Male	75 (54)	27 (54)	30 (60)	9 (56)	2 (50)	5 (36)	2 (40)
Female	64 (46)	23 (46)	20 (40)	7 (44)	2 (50)	9 (64)	3 (60)
Age, median years (range)	59 (18–77)	60 (18–71)	59 (22–77)	59 (20–72)	65 (57–67)	58 (24–68)	23 (18–64)
BMI, median kg/m ² (range)	26 (13–47)	26 (13–44)	26 (18–47)	27.5 (18–36)	26 (24–29)	25 (18–36)	23 (17–38)
Diagnosis, n (%)							
AML	61 (44)	23 (46)	14 (28)	12 (75)	2 (50)	9 (64)	1 (20)
MDS	29 (21)	10 (20)	13 (26)	4 (25)	–	1 (7)	1 (20)
ALL	22 (16)	8 (16)	12 (24)	–	–	–	2 (40)
Myelofibrosis	7 (5)	4 (8)	1 (2)	–	–	2 (14)	–
CML	5 (4)	3 (6)	2 (4)	–	–	–	–
Aplastic anemia	5 (4)	–	1 (2)	–	2 (50)	2 (14)	–
CMML	2 (1)	1 (2)	1 (2)	–	–	–	–
Other	8 (6)	1 (2)	6 (12)	–	–	–	1 (20)

TAC: tacrolimus; CSA: cyclosporine; FLC: fluconazole; POS: posaconazole; ISA: isavuconazole; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia.

**Figure 1.** Median CNI dose ratio comparing steady state to day 0 by route of CNI administration.

intravenous route of administration were 1.6 versus 0.78 for TAC and 0.69 versus 1.45 for CSA.

Table 2 shows the final route of CNI administration at steady state and the percentage of CNI within goal, indicating if the CNI serum concentration at steady state was within the targeted goal. Overall, 65% of patients were receiving CNI orally at the time of steady state, and 67% of CNI levels at steady state were within goal.

Discussion

Our retrospective study adds to the limited data on the effects of FLC, ISA, and POS on CNI doses in clinical

practice and to our knowledge, is the largest of its kind. In addition to characterizing dose adjustments, we compared CYP3A4 effects among three azole antifungals.

Based on our results in the FLC groups, initiation of FLC likely requires a 25% reduction in both tacrolimus and cyclosporine doses. To our knowledge, this is the largest study to assess the effects of FLC on TAC and CSA levels in clinical practice, and the high sample size increases the reliability of this recommendation. A previous study by Osowski et al. in 21 HSCT patients found FLC initiation results in a 21% and 16% increase in CSA and TAC concentrations, respectively.⁸ While these results were not deemed to be clinically

Table 2. CNI results at steady state.

	Total (n = 139)	TAC/FLC (n = 50)	CSA/FLC (n = 50)	TAC/POS (n = 16)	CSA/POS (n = 4)	TAC/ISA (n = 14)	CSA/ISA (n = 5)
Final CNI route, n (%)							
Oral	90 (65)	37 (74)	33 (66)	10 (63)	4 (100)	3 (21)	3 (60)
Intravenous	49 (35)	13 (26)	17 (34)	6 (37)	0	11 (79)	2 (40)
CNI within goal, n (%)							
Yes	93 (67)	34 (68)	32 (64)	13 (81)	4 (100)	9 (64)	1 (20)
No	46 (33)	16 (32)	18 (36)	3 (19)	–	5 (36)	4 (80)

CNI: calcineurin inhibitor; TAC: tacrolimus; CSA: cyclosporine; FLC: fluconazole; POS: posaconazole; ISA: isavuconazole.

significant, this increase in CNI concentration correlates with our recommended dose adjustments. In a more recent study by Peska et al., the authors recommend a 50% decrease in initial TAC doses when FLC is used concomitantly.⁷ However, there were only 20 FLC patients in this study when combining the TAC and sirolimus patients, and the lower sample size may be the cause of the difference between our findings.

Results for POS varied between the TAC and CSA groups. TAC doses may need to be reduced by 50% when TAC is used concomitantly with POS. This reduction is smaller than manufacturer recommendations to reduce tacrolimus doses by two-thirds upon POS initiation but is consistent with two previous studies in HSCT patients that recommend an empiric 50% reduction in tacrolimus doses when POS is initiated.^{6,7,9} Greater TAC dose reductions were needed in our POS group compared to FLC, which is consistent with the fact that POS is a strong CYP3A4 inhibitor and FLC is a moderate CYP3A4 inhibitor.¹⁰ Contrarily, those in the CSA/POS group required smaller CSA dose reductions compared to patients receiving FLC. A previous study in 41 HSCT patients found POS initiation leads to a 50% reduction in CSA doses, which is a greater reduction than what we found in our study.¹¹ However, there were only four patients in our CSA/POS group and two were receiving POS oral suspension which has unpredictable bioavailability.¹²

Our results for ISA were also variable between the two CNI groups. We found initiation of ISA may require a 20% decrease in TAC doses. These results are similar to a study in 55 solid organ transplant patients that found TAC doses were 25% lower when patients were receiving ISA versus when off ISA.¹³ However, data in HSCT patients are limited and results vary. One case report by Kim et al. recommends a 50% decrease in TAC doses when ISA is initiated with possibly an additional 25–50% decrease, whereas another case report by Kuvel et al. found no TAC dose

reduction is needed.^{14,15} In another study in 22 HSCT patients, the authors found ISA initiation leads to a 42% increase in TAC concentration/dose ratio, but this result was not statistically significant.¹⁶ In our study, the reduction in TAC doses between our ISA and FLC groups was similar, which is consistent with the fact that both antifungals are moderate CYP3A4 inhibitors.¹⁷ On the other hand, patients in the CSA/ISA group required higher CSA doses after ISA initiation. The median age of the CSA/ISA group was much younger at 23 years old compared to all other groups in the study. Previous studies have found younger patients need higher CSA doses, suggesting younger patients in this group may have been underdosed, resulting in subsequent dose increases.¹⁸ A prospective study in 34 HSCT patients found there is no difference between ISA and FLC and their effect on CSA levels or average number of CSA dose adjustments.¹⁹ Patients in the ISA group needed on average 1.3 dose adjustments, but the specific dose adjustments were not quantified. As the newest azole, ISA is the least studied among the azole antifungals and there are limited published studies in regards to its effects on CNI doses.

When median CNI dose ratios were separated by route of CNI administration, we found in the TAC/FLC, CSA/FLC, and CSA/ISA groups, oral CNI administration required larger dose reductions compared to intravenous administration. This finding is likely due to azole inhibition of intestinal CYP3A4 enzymes which only effects orally administered medications that undergo first-pass metabolism.²⁰ The TAC/ISA group did not support this finding, but two of the three patients in the oral tacrolimus group were much younger at 27 and 24 years old and needed dose increases, which may have skewed the median CNI dose ratio.

Limitations of this study include the retrospective nature of the study and the small number of patients included in the POS and ISA groups. The small sample size in these groups limits our ability to draw

conclusions regarding the effects of POS and ISA on CNI doses. In addition, pharmacogenomic data were not available for patients included in this study and polymorphisms in CYP3A4 can affect the CNI dose needed for an individual.²¹ Finally, one-third of patients did not have a CNI level within goal, causing our primary endpoint to potentially misrepresent doses needed for these patients after antifungal initiation.

Conclusion

We found close monitoring of CNI levels after azole antifungal initiation is needed to make appropriate CNI dose adjustments and ensure CNI levels remain within goal serum concentrations. These data suggest initiation of FLC, POS, or ISA requires a reduction in TAC doses and initiation of FLC requires a reduction in CSA doses. The larger sample size of the FLC group makes the conclusion for this group more reliable than the data for the POS and ISA groups. Our results require validation in future studies of HSCT patients, and larger sample sizes are required to provide recommendations for the percentage of reduction in CNI doses and to fully characterize differences among these antifungals.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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