

Management of Drug Interaction between Posaconazole and Sirolimus in Patients Who Undergo Hematopoietic Stem Cell Transplant

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ABSTRACT STUDY OBJECTIVE To determine an appropriate empiric oral sirolimus dose adjustment when given concurrently with posaconazole oral suspension in patients who undergo hematopoietic stem cell transplant (HSCT).

DESIGN Retrospective cohort study.

SETTING Comprehensive cancer center in the United States.

SUBJECTS Seventy five allogeneic HSCT patients who received posaconazole oral suspension and oral sirolimus concurrently between 2009 and 2011.

MEASUREMENTS AND MAIN RESULTS Sirolimus concentrations were recorded at baseline and for up to 28 days after posaconazole initiation. The sirolimus concentration/dose (C/D) ratio was determined for each sirolimus concentration obtained. Following analysis of patient data and based on the initial empiric sirolimus dose reduction, patients were stratified into two groups: $\geq 50\%$ sirolimus dose reduction (Group 1) and $< 50\%$ sirolimus dose reduction (Group 2). The mean sirolimus C/D ratio was 2.29 ng/mL/mg prior to posaconazole initiation. Coadministration of posaconazole and sirolimus resulted in an increase in the steady state sirolimus C/D ratio to 6.24 ng/mL/mg, which occurred approximately 17–20 days after initiation of posaconazole. The mean maximum sirolimus concentration was significantly higher in Group 2 compared to Group 1 (12.64 ng/mL vs. 9.24 ng/mL, $p=0.001$). Significantly more patients in Group 2 than Group 1 experienced at least one sirolimus concentration > 15 ng/mL (27% vs. 2.6%, $p=0.003$).

CONCLUSION Coadministration of posaconazole oral suspension with oral sirolimus increases the sirolimus C/D ratio by approximately 2.7-fold in HSCT patients. An initial empiric oral sirolimus dose reduction between 50% and 65% may be recommended for most clinically stable patients with close sirolimus concentration monitoring for at least 3 weeks following posaconazole initiation.

KEY WORDS sirolimus, posaconazole, drug interaction, cytochrome P450, p-glycoprotein, hematopoietic stem cell transplant.

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Introduction

Patients undergoing allogeneic hematopoietic stem cell transplant (HSCT) for life-threatening hematologic disorders, including leukemia and lymphoma, require complex pharmacotherapy to treat and prevent graft-versus-host-disease (GVHD) and infectious complications. These patients may need to receive both GVHD prophylaxis with sirolimus—a substrate of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)—and fungal prophylaxis with posaconazole, an inhibitor of CYP3A4 and P-gp.

Posaconazole, an azole antifungal agent that is approved by the U.S. Food and Drug Administration (FDA) for the prophylaxis of invasive fungal infections caused by *Aspergillus* and *Candida* in HSCT patients, has unique pharmacokinetics.¹ It is metabolized by uridine diphosphate-glucuronosyltransferase (UGT) enzyme pathways and is a substrate and inhibitor of the P-gp efflux transporter.^{2, 3} Although posaconazole does not have major cytochrome P450 oxidative metabolites, it is a strong inhibitor of CYP3A4 metabolizing enzymes.^{2, 3} As such, plasma concentrations of drugs that are substrates of CYP3A4 may be increased when given with posaconazole. Posaconazole oral suspension absorption is also affected by gastric acidity and motility, with absorption increased in the presence of high-fat meals and decreased in the presence of medications that reduce gastric acidity, such as proton-pump inhibitors.²

Posaconazole is primarily eliminated in the feces as unchanged drug, with a mean terminal elimination half-life for the oral suspension of 35 hours.² Steady-state posaconazole concentrations are expected to be achieved after 7 days of continuous therapy.⁴ Although routine monitoring of posaconazole serum concentrations currently may vary among practitioners, the British Society for Medical Mycology recently recommended targeting posaconazole serum trough concentrations >0.7 mg/L when using posaconazole for *Aspergillus* prophylaxis, although the evidence for improved clinical response was weak.⁴

Sirolimus is an inhibitor of mammalian target of rapamycin (mTOR), which leads to an inhibition of activation of proliferation of T-lymphocytes in response to cytokine stimulation. Although not FDA-approved for the prevention of GVHD, sirolimus has been used for this indication in combination with other immunosuppressants such as tacrolimus in patients

undergoing allogeneic HSCT.^{5, 6} Sirolimus is extensively metabolized to primarily inactive metabolites by CYP3A4 and is a substrate for P-gp efflux.⁶ Therefore, drugs that inhibit or induce CYP3A4 or P-gp would be expected to affect sirolimus serum concentrations. Sirolimus metabolites are primarily excreted in the feces with a mean terminal half-life of approximately 62 hours in renal transplant recipients.^{6, 7} Sirolimus steady state concentrations, therefore, would be expected to be reached after more than 5–7 days of continuous therapy.⁸ Previous studies have shown an association between sirolimus serum concentrations >10–15 ng/mL and the development of sirolimus-related adverse effects, such as hypertriglyceridemia, thrombocytopenia, thrombotic microangiopathy, and sinusoidal obstructive syndrome of the liver.^{9–11} Because of the large interpatient variability in sirolimus pharmacokinetics, routine monitoring of sirolimus serum concentrations is recommended, especially during coadministration with strong CYP3A4 inhibitors.⁸

At our institution, posaconazole is usually initiated as fungal prophylaxis in allogeneic HSCT patients who are receiving systemic corticosteroids for GVHD treatment and who are able to tolerate oral medications. According to the manufacturer, however, posaconazole is contraindicated with sirolimus because of a pharmacokinetic drug interaction that results in substantial increases in the sirolimus plasma concentration and increased risk for sirolimus-related toxicities.¹ An empiric dose reduction of sirolimus may allow for safe coadministration with posaconazole, but the magnitude of the sirolimus dose reduction has not been well established. The objectives of this study are to (i) determine an appropriate empiric oral sirolimus dose adjustment when given concurrently with posaconazole oral suspension in HSCT patients and (ii) determine if an association between the initial empiric oral sirolimus dose adjustment and frequency of sirolimus concentrations above the target range exists.

Methods

Study Population

We conducted a retrospective cohort study of allogeneic HSCT patients who received concomitant posaconazole and sirolimus at a 217-bed comprehensive cancer center between March 4, 2009, and December 19, 2011. Patients who had

undergone HSCT were identified from an internal HSCT patient database. Patients who had received both posaconazole and sirolimus were identified from the computerized pharmacy medication database. Patients were included if they were at least 18 years of age, had received at least 26 projected days of concomitant posaconazole and sirolimus, had at least two consecutive sirolimus concentration measurements with no change in sirolimus dose prior to the initiation of posaconazole, and had at least two documented sirolimus concentrations after initiation of posaconazole. Patients were excluded if they had a serum creatinine ≥ 2.5 mg/dL or total bilirubin ≥ 3.0 mg/dL during administration of posaconazole and sirolimus, if they did not receive concomitant sirolimus and posaconazole for more than 5 consecutive days at any time during the study period (e.g., drug being held due to toxicity), or if they were on an azole antifungal (e.g., fluconazole, itraconazole, posaconazole, or voriconazole) prior to admission for HSCT. Information regarding patient age, gender, conditioning regimen, underlying hematologic disorder, transplant type, doses of posaconazole and sirolimus, concomitant drugs that might interact pharmacokinetically with sirolimus, serum creatinine, and serum bilirubin were recorded. The study was reviewed and approved by the institutional review board of the study site.

Exposure

Sirolimus tablets or oral solution were administered by mouth at 12 noon on each scheduled day. Sirolimus whole blood concentrations were generally measured every Monday and Thursday between 1 AM and 6 AM using the liquid chromatography with mass spectroscopy (LCMS) method. According to institutional clinical practice, sirolimus doses were adjusted to target sirolimus serum concentrations between 5 and 10 ng/mL. Posaconazole oral suspension was administered with meals at a dose of either 400 mg by mouth twice daily (preemptive treatment) or 200 mg by mouth 3 times daily (prophylaxis). When available, posaconazole serum or plasma concentrations were measured using LCMS.

Determination of Sirolimus Concentrations and Concentration/Dose Ratios

The baseline sirolimus concentration (C_0) was defined as the most recently measured concentration prior to or on the same day as posa-

conazole initiation. Sirolimus concentrations were measured every 3 to 4 days over a 28-day period after posaconazole initiation. The sirolimus concentration/dose (C/D) ratio was determined by dividing the observed sirolimus concentration by the calculated average daily dose of sirolimus the patient had received since the previous sirolimus concentration was determined. The sirolimus C/D ratio before and after posaconazole initiation was determined to evaluate the magnitude of the interaction between the two drugs on sirolimus concentrations. Mean sirolimus C/D ratios were determined at baseline and for up to 28 days after posaconazole initiation.

The effect of an initial empiric sirolimus dose reduction on sirolimus concentrations after posaconazole initiation was evaluated by stratifying patients into two groups based on the median dose reduction of 50% for the entire cohort: $\geq 50\%$ empiric sirolimus dose reduction (Group 1) or $<50\%$ empiric sirolimus dose reduction (Group 2). Mean minimum and maximum sirolimus concentrations observed and number of patients with sirolimus concentrations >15 ng/mL were determined for each group.

Statistical Analysis

Statistical analysis was performed using GraphPad InStat version 3.10 (GraphPad Software, Inc., La Jolla, CA, USA). Categorical variables were compared using the Fisher exact test and continuous variables were compared using the Student t test or Mann-Whitney U test. Two-tailed tests were used and a p value <0.05 was considered statistically significant.

Results

Patient Demographics

A total of 75 patients were identified as eligible for this study. The percent dose modification of sirolimus in the entire cohort (N=75) ranged from 6% to 250% (median 50%). For analyses, we grouped the cohort into Group 1 (N=38) and Group 2 (N=37) based on the median percentage dose modification of 50%. The characteristics of the study population are detailed in Table 1. Overall, 63% of patients received reduced intensity transplant conditioning regimens (based on fludarabine plus melphalan) and the remaining patients received full intensity regimens (based on total body irradiation or intensity modulated radiation therapy in combination with busulfan,

Table 1. Patient Demographics and Clinical Characteristics: Group 1 ($\geq 50\%$ empiric sirolimus dose reduction), Group 2 ($< 50\%$ empiric sirolimus dose reduction)

	Group 1 Patients (%) (n=38)	Group 2 Patients (%) (n=37)	p Value
Age in years			
Median	52	53	0.38
Range	23-71	18-89	
Gender			
Male	24 (63%)	24 (65%)	1.00
Female	14 (37%)	13 (35%)	
Transplant donor type			
Matched	13 (34%)	8 (22%)	0.35
related			
Matched	22 (58%)	23 (62%)	
unrelated			
Mismatched	3 (8%)	6 (16%)	
Diagnosis			
AML	17 (45%)	15 (40%)	0.24
ALL	6 (16%)	7 (19%)	
NHL	0 (0%)	4 (11%)	
CML	3 (8%)	1 (3%)	
CLL	1 (2%)	3 (8%)	
Other	11 (29%)	7 (19%)	
Conditioning regimen			
Full intensity	16 (42%)	12 (32%)	0.48
Reduced intensity	22 (58%)	25 (68%)	
Posaconazole dose			
400 mg PO BID	6 (16%)	4 (11%)	0.74
200 mg PO TID	32 (84%)	33 (89%)	
Median no. of sirolimus levels analyzed per patient (range)	7 (4-7)	7 (4-7)	0.28
Other interacting drugs			
Tacrolimus	38 (100%)	37 (100%)	1.00
CYP3A4 inducers	0 (0%)	1 (3%)	
CYP3A4 inhibitors	1 (3%)	1 (3%)	
Mean baseline serum creatinine (mg/dL)	0.69	0.73	0.43
Mean baseline serum bilirubin (mg/dL)	0.29	0.34	0.36

cyclophosphamide, and/or etoposide). Baseline characteristics were similar between the two groups. The majority of patients were receiving posaconazole for prophylaxis. All patients received tacrolimus targeted to a serum concentration between 5 and 10 ng/mL throughout the study period. Concomitant use of other drugs with the potential to affect sirolimus concentrations was infrequent and limited to one patient in each group. One patient in Group 1 was on verap-

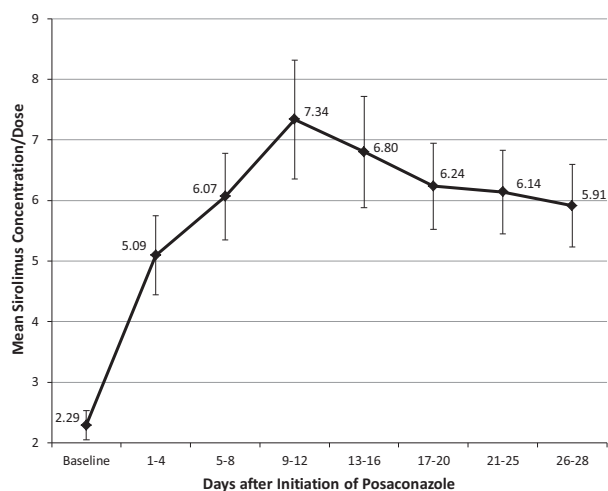


Figure 1. Mean Sirolimus Concentration/Dose Ratio Changes after Posaconazole Initiation for the Overall Group (N=75) ($\pm 95\%$ Confidence Interval).

amil, an inhibitor of CYP3A4 and P-gp, and one patient in Group 2 was on diltiazem, an inhibitor of CYP3A4, and phenytoin, an inducer of CYP3A4. In both cases, these interacting drugs were started prior to the initiation of posaconazole.

Sirolimus Concentration/Dose Ratio Changes after Posaconazole Initiation

The mean (\pm SD) sirolimus C/D ratio prior to posaconazole initiation was 2.29 ± 1.06 ng/mL/mg. After posaconazole initiation, the mean C/D ratios ranged from 5.09 to 7.34 ng/mL/mg, with the highest C/D ratio observed 9–12 days after posaconazole initiation. A new steady state C/D ratio of approximately 6.24 ng/mL/mg appeared to occur about 17–20 days after posaconazole initiation (Figure 1). The mean (\pm SD) sirolimus C/D ratio over the entire 28-day period was 6.21 ± 3.46 ng/mL/mg (range of means for individual patients: 2.06-14.64 ng/mL/mg; Table 2). The mean magnitude increase in the sirolimus C/D ratio after posaconazole initiation was calculated by dividing the steady state C/D ratio by the baseline C/D ratio for all patients and was found to be approximately 2.7.

Initial Empiric Sirolimus Dose Adjustments and Observed Sirolimus Concentrations

Patients were stratified into two groups based on their initial empiric sirolimus dose adjustment upon posaconazole initiation. The mean sirolimus dose adjustment in Group 1 ($\geq 50\%$

Table 2. Sirolimus Dose and Serum Concentrations before and after Posaconazole Initiation for the Overall Group (N=75)

	Baseline	After Posaconazole	p-Value
Sirolimus dose per day (mg), mean \pm SD (range [*])	3.02 \pm 1.24 (1.0–6.0)	1.16 \pm 0.64 (0.25–2.0)	
Sirolimus concentration (ng/mL), mean \pm SD (range [*])	6.04 \pm 2.25 (2.2–12.3)	5.81 \pm 2.32 (2.0–11.6)	
Sirolimus C/D ratio (ng/mL/mg), mean \pm SD (range [*])	2.29 \pm 1.06 (0.73–5.40)	6.21 \pm 3.46 (2.06–14.64)	<0.001

*Range of means for individual patients.

dose reduction) was $-60\% \pm 12\%$ (-94% to -50%) and in Group 2 ($<50\%$ dose reduction) was $-1\% \pm 40\%$. (-43% to $+250\%$; Table 3). The mean sirolimus C_0 was significantly lower in Group 2 than Group 1 (5.24 ± 2.31 ng/mL vs. 6.82 ± 1.96 ng/mL, $p=0.0008$), but mean sirolimus C/D ratios at baseline and steady state did not differ significantly between the groups (Table 3). However, after posaconazole initiation, mean sirolimus concentrations for Group 2 were higher at almost all time intervals compared to Group 1, and statistically significantly higher on days 5–8 and 9–12 (Figure 2).

Initial Empiric Sirolimus Dose Adjustments and Risks for Sirolimus Toxicity

The mean maximum sirolimus concentration observed over the 28-day study period in Group

2 was significantly higher than that observed in Group 1 (12.64 ng/mL vs. 9.46 ng/mL, $p=0.001$) (Table 3). Significantly more patients in Group 2 experienced at least one sirolimus concentration greater than 15 ng/mL compared to Group 1 (27% vs. 2.6%, $p=0.003$; Table 4). However, there was no significant difference between Group 1 and Group 2 in the percentage of patients experiencing tacrolimus levels greater than 15 ng/mL (10.5% vs. 8.1%, $p=1.0$) and there was no significant difference between groups in the mean maximum serum creatinine or bilirubin, change in serum creatinine or bilirubin from baseline, or mean minimum sirolimus concentration (Table 4, Figure 3).

Posaconazole Concentrations

During the study period, posaconazole concentrations were available for 31 patients (41.3%). The mean posaconazole concentration was 0.75 mg/L (range: 0.13–2.37 mg/L).

Discussion

In a sample of 75 HSCT patients receiving both sirolimus and posaconazole, a new steady state sirolimus C/D ratio is reached in about 17–20 days after posaconazole initiation that is approximately 2.7-times higher than the baseline sirolimus C/D ratio. This suggests that empirically reducing the sirolimus dose by approximately 50–65% upon initiation of posaconazole can be used to maintain sirolimus concentrations within the target range.

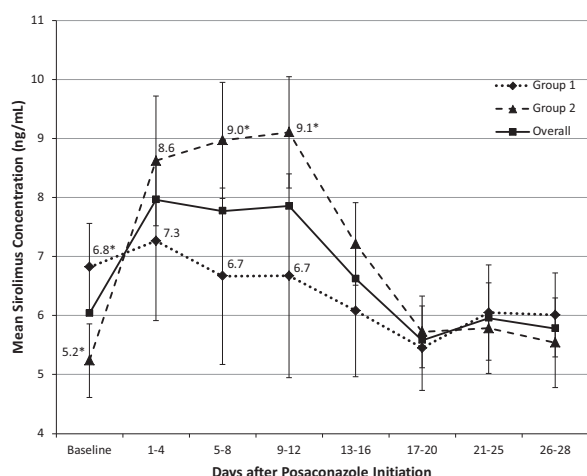
In contrast, one pharmacokinetic study reported a 6.7-fold increase in the maximum observed serum sirolimus concentration and an

Table 3. Sirolimus Concentrations for Group 1 and Group 2

	Group 1 (N=38)	Group 2 (N=37)	p Value
Baseline sirolimus concentration (ng/mL), mean \pm SD (range)	6.82 \pm 1.96 (3.3–11.6)	5.24 \pm 2.31 (2.2–12.3)	0.0008
Baseline sirolimus C/D ratio (ng/mL/mg), mean \pm SD (range)	2.32 \pm 1.02 (0.93–5.40)	2.26 \pm 1.13 (0.73–5.40)	0.83
Steady state sirolimus C/D ratio (ng/mL/mg), mean \pm SD (range)	6.36 \pm 3.22* (2.00–16.43)	6.10 \pm 3.07** (1.63–15.46)	0.73
Percent sirolimus dose adjustment, mean \pm SD (range)	$-60\% \pm 12\%$ (-94% to -50%)	$-1\% \pm 40\%$ (-43% to $+250\%$)	
Minimum sirolimus concentration (ng/mL), mean \pm SD (range)	3.90 \pm 1.39 (2.0–6.9)	4.00 \pm 1.47 (2.0–6.9)	0.77
Maximum sirolimus concentration (ng/mL), mean \pm SD (range)	9.46 \pm 2.81 (4.6–15.4)	12.64 \pm 4.81 (6.0–22.2)	0.001

*N=37.

**N=34.



*P<0.05

Figure 2. Mean Sirolimus Concentrations after Posaconazole Initiation for Group 1, Group 2 and Overall (\pm 95% Confidence Interval).

Table 4. Toxicity Measures for Group 1 and Group 2

	Group 1 (N=38)	Group 2 (N=37)	p Value
No. of patients with sirolimus concentrations > 15 ng/mL	1 (2.6%)	10 (27.0%)	0.003
Maximum serum creatinine (mg/dL), mean \pm SD (range)	0.97 \pm 0.29 (0.43–1.74)	1.08 \pm 0.34 (0.49–2.29)	0.14
Maximum change in serum creatinine (mg/dL), mean \pm SD (range)	0.28 \pm 0.21 (–0.09–0.88)	0.35 \pm 0.22 (–0.07–0.97)	0.16
Maximum total bilirubin (mg/dL), mean \pm SD (range)	0.56 \pm 0.21 (0.20–1.10)	0.72 \pm 0.46 (0.30–2.90)	0.06
Maximum change in total bilirubin (mg/dL), mean \pm SD (range)	0.29 \pm 0.18 (0.0–0.8)	0.39 \pm 0.32 (0.0–1.4)	0.11

8.9-fold increase in sirolimus area under the curve when given concomitantly with posaconazole.¹² However, the sample included only 12 healthy volunteer subjects, and sirolimus was coadministered with posaconazole for only one dose.

Two studies recently have reported on the effects of posaconazole on sirolimus concentra-

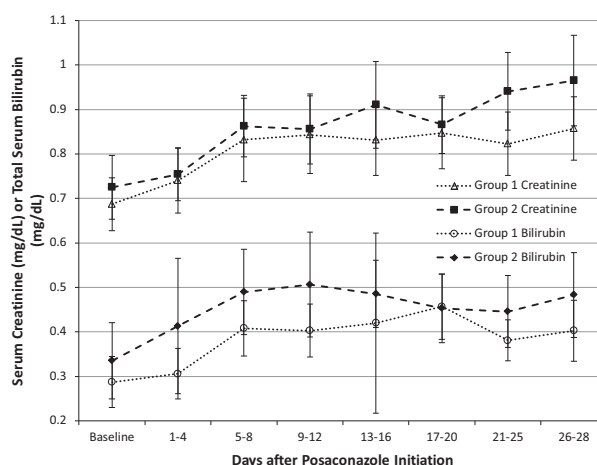


Figure 3. Mean Serum Creatinine Concentrations and Total Serum Bilirubin Concentrations for Group 1 and Group 2 (\pm 95% Confidence Interval).

tions in allogeneic HSCT patients.^{13, 14} The first report, a retrospective study of 15 patients receiving concurrent posaconazole oral suspension and sirolimus, recommended a 33–50% empiric sirolimus dose reduction upon posaconazole initiation.¹³ The median empiric sirolimus dose reduction upon posaconazole initiation was 50% and the median daily sirolimus dose after 7 days of coadministration was 1 mg–33% less than the baseline dose before coadministration.¹³ The median sirolimus concentrations were 5.5 ng/mL at baseline and 5.3 ng/mL after coadministration.¹³ One patient with a maximum sirolimus concentration of 19.5 ng/mL developed a suspected case of thrombotic microangiopathy.¹³ Because sirolimus has a mean terminal elimination half-life of 62 hours,^{6, 7} it is possible that not all patients in this study had reached a new steady state sirolimus concentration by day 7, thus potentially underestimating the magnitude of the interaction with posaconazole on sirolimus concentrations.

The second report was a retrospective analysis of patients receiving concomitant sirolimus, tacrolimus, and various azole antifungals. The authors suggested an empiric sirolimus starting dose of 1.3 mg/day upon posaconazole initiation in order to achieve a target sirolimus concentration of 3–12 ng/mL.¹⁴ Although this recommendation was based on data from four patients and may not be applicable to those patients who are on a sirolimus dose <1.3 mg/day at the time of posaconazole initiation, the recommended empiric adjusted sirolimus dose of 1.3 mg/day is similar to the mean sirolimus dose of 1.16 mg/day observed in our patient population over a 28-day period (Table 2).

While the goal of the previous studies was to determine an appropriate sirolimus dose reduction upon posaconazole initiation, our study also attempted to retrospectively evaluate the differences in target sirolimus concentrations and serum creatinine and bilirubin concentrations in two cohorts of patients. Retrospective analysis of patients based on their initial empiric sirolimus dose reduction revealed that the mean sirolimus C_0 in Group 2 was significantly lower than in Group 1 (5.24 ± 2.31 ng/mL vs. 6.82 ± 1.96 ng/mL, $p=0.0008$). This was most likely due to a calculated attempt by clinicians to increase the sirolimus concentrations of patients with lower baseline sirolimus concentrations by not making major reductions to the sirolimus dose upon posaconazole initiation. When sirolimus doses were decreased by $\geq 50\%$ upon posaconazole initiation (Group 1, mean 60% dose reduction), the mean maximum sirolimus concentration was <10 ng/mL (9.46 ± 2.81 ng/mL). When sirolimus doses were decreased by $<50\%$ (Group 2, mean 1% dose reduction), the mean maximum sirolimus concentration was >10 ng/mL (12.64 ± 4.81 ng/mL) and significantly more patients experienced sirolimus concentrations greater than 15 ng/mL compared to Group 1 (27% vs. 2.6%, $p=0.003$). The mean minimum sirolimus concentrations, however, were not significantly different between groups (Table 3). Based on these observations, empiric sirolimus dose reductions generally should be recommended upon posaconazole initiation, even in patients with baseline sirolimus concentrations at the lower end of the target range.

Various sirolimus-related adverse effects have been associated with sirolimus serum concentrations >10 – 15 ng/mL.^{9–11} Trends toward higher serum creatinine and total bilirubin concentrations among patients in Group 2 compared to Group 1 were observed, although the differences were not statistically significantly different. In addition, patients with unstable renal or hepatic function or who had doses held due to clinical instability or drug toxicity were specifically excluded from the present study. Therefore, we lacked sufficient clinical data on all patients to allow for analysis of any correlations between sirolimus serum concentrations or empiric dose adjustments on the development of sirolimus-related adverse effects.

At the time of our study, the only published study of the magnitude of the pharmacokinetic interaction between sirolimus and posaconazole

in healthy volunteers suggested that concurrent administration should be avoided. Therefore, we chose a retrospective analysis to investigate the feasibility of empiric sirolimus dose reductions in HSCT patients receiving concurrent posaconazole. Although our study results may be limited by several confounders, such as the contribution of variables that could decrease the oral absorption of medications (e.g. intestinal GVHD), or decrease the absorption of posaconazole, (e.g. administration in a fasted state or with acid-reducing medications), our study reports the effects of posaconazole on sirolimus concentrations in the largest series of HSCT patients to date. Because sirolimus pharmacokinetics are subject to significant and well-documented interpatient variabilities,^{3, 8, 15} a relatively large patient sample size may be required to improve the generalizability of results across larger populations. In addition, patients were followed for up to 28 days after posaconazole initiation with a median of seven sirolimus levels analyzed for each one, thus potentially lessening the contribution of non-steady state conditions and inpatient variability on our observations. With the availability of posaconazole tablets that have more consistent bioavailability than the oral suspension, future studies should focus on prospective analyses of patients randomized to different sirolimus dose reduction cohorts when given concurrently with posaconazole tablets.

Although our study provides a rationale for an empiric sirolimus dose reduction upon posaconazole initiation, the following points need to be considered: (i) the validity and safety of this approach remains to be verified prospectively, (ii) the magnitude of the interaction with other formulations of posaconazole, such as the intravenous injection and delayed-release tablet, may be different from what we determined for the oral suspension, and (iii) because of the inherent unpredictability of sirolimus pharmacokinetics, empiric sirolimus dose reduction recommendations are not intended to replace clinical judgment and vigilant monitoring of sirolimus concentrations.

Conclusion

Coadministration of posaconazole oral suspension and oral sirolimus increases the sirolimus C/D ratio by a factor of 2.7 in HSCT patients who are also receiving tacrolimus. In general, an initial empiric sirolimus dose reduction between 50%

and 65% may be recommended in clinically stable patients upon posaconazole initiation to maintain the sirolimus concentration within the target range. This empiric dose reduction should not supersede clinical judgment, and close monitoring of sirolimus concentrations is recommended for at least 3 weeks after posaconazole initiation, with further sirolimus dose adjustments as needed.

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