ORIGINAL RESEARCH

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Dose adjustment of immunosuppressants during co-administration of posaconazole: a systematic review

Abstract

Purpose: The purpose of this retrospective study was to analyze the dose adjustment of immunosuppressants (cyclosporine, tacrolimus and sirolimus) for the patients with allogeneic hematopoietic stem cell and solid-organ (heart/lung) transplantation during co-administration of posaconazole.

Methods: MEDLINE, EMBASE and Cochrane Library were searched from January 1, 2000 to June 30, 2017 for clinical reports of patients who received allogeneic hematopoietic stem cell and organ transplantation and were co-administered posaconazole and immunosuppressants (cyclosporine, tacrolimus or sirolimus).

Results: Seven studies were included in the systematic review with a total of 215 patients. Five studies involved hematopoietic stem cell transplant, one heart transplant and one lung transplant. In general, the co-administration of posaconazole with sirolimus, tacrolimus or cyclosporine necessitated immunosuppressant dose reductions to maintain the levels of the drug in the optimal therapeutic range. Reported dose reductions were 50%–68% for sirolimus, 75% for tacrolimus and 14%–49% for cyclosporine. The findings were similar for hematopoietic stem cell, heart or lung transplantation studies.

Conclusion: Our findings indicate that, when posaconazole is co-administered, the dosage of sirolimus and tacrolimus should be reduced by 60%–70% and for cyclosporine and by 30%–40% following allogeneic hematopoietic stem cell and solid-organ transplantation.

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A complex pharmacotherapy is required to treat and prevent graft-versus-host disease (GVHD) and infectious complication in patients undergoing allogeneic hematopoietic stem cell transplant for hematologic disorders, such as leukemia and lymphoma. Such patients may require administration of a prophylaxis for GVHD, such as sirolimus, tacrolimus or cyclosporine [1,2]. Similarly, immunosuppressive therapy, with drugs such as cyclosporine A or tacrolimus, is necessary to prevent acute rejection episodes in patients after solid-organ transplantation [3,4].

A leading cause of morbidity and infection-related mortality in hematopoietic stem transplantation is fungal infection [5]. Previous studies have reported that over 60% of hematopoietic stem cell recipients acquired invasive fungal infection [5] and that invasive fungal infection also occurred after heart and lung transplant [6]. Antifungal prophylaxis has been reported to decrease the incidence and mortality of fungal infections following lung transplant [6]. International guidelines recommend prophylaxis for fungal infections using mould-active antifungals such as voriconazole in high-risk patients [7,8].

Posaconazole is a triazole with broad-spectrum antifungal activity [9,10]. A large, randomized trial showed that posaconazole was effective in preventing all invasive fungal diseases in recipients of hematopoietic stem-cell transplants with severe GVHD who were receiving immunosuppressive agents during a 16-week period [11]. Guidelines for primary antifungal prophylaxis suggest the use of posaconazole for patients ≥ 18 years of age undergoing allogeneic hematopoietic stem cell transplantation with acute Grade II–IV or chronic extensive GVHD [12]. Posaconazole is also an alternative to voriconazole in solid organ transplant recipients with suspected invasive fungal infections [8].

Although co-administration of posaconazole and immunosuppressants are recommended, drug interactions can occur [13,14]. Cyclosporine, tacrolimus and sirolimus are substrates of cytochrome P450-3A4 (CYP3A4) [13] and posaconazole is a CYP3A4 inhibitor. In the presence of posaconazole, plasma concentrations of these immunosuppressants are substantially increased [15,16,17] and this increase is associated with adverse events [15,18]. The increase in exposure of immunosuppressants in the presence of posaconazole requires adjustment of the dose of the immunosuppressant to sustain the therapeutic levels of the drug and reduce adverse events associated with increased immunosuppressant concentrations [13,20,21]. The prescribing information for posaconazole recommends reducing the dose of cyclosporine by approximately 75% and

the dose of tacrolimus approximately one-third of the original dose upon initiation of posaconazole treatment [19]. Due to adverse events resulting from the interaction of sirolimus with posaconazole (e.g., nephrotoxicity, hematotoxicity and hyperlipidemia), the posaconazole prescribing instructions does not recommended the co-administration of these two drugs [19].

The magnitude of the immunosuppressant dose reduction during co-administration of posaconazole depends on the selected immunosuppressant [21,22]. The management of drug-drug interactions between posaconazole and immunosuppressants in transplant patients remains challenging, and strategies for optimal management in clinical practice are currently lacking. The present systematic review aims to investigate and summarize the strategies of dose reduction of immunosuppressants during co-administration with a fixed dose of posaconazole in patients who received hematopoietic and solid-organ transplantation.

Materials and Methods

Search strategy

MEDLINE, EMBASE and Cochrane Library databases were search from January 1, 2000 to June 30, 2017 using the following keywords: posaconazole AND (cyclosporine OR sirolimus OR tacrolimus) AND (transplant OR transplantation). Additional papers and book chapters were identified by a manual search of the references from the key articles. Prospective, retrospective and cohort studies were included without restriction of language. Included studies had to have assessed patients who received allogeneic hematopoietic stem cell, heart or lung transplantation, and were co-administered posaconazole and immunosuppressants (cyclosporine, tacrolimus or sirolimus). Studies had to be designed to investigate the interaction between posaconazole and an immunosuppressant, and had to have reported the adjustment of cyclosporine, tacrolimus or sirolimus dosages. Letters, comments, editorials, case report and personal communication were excluded. Since this review was specifically focused on posaconazole, studies were also excluded if patients received other types of azole antifungals (e.g., voriconazole).

Data collection

Review for study inclusion and data extraction was performed by two independent reviewers, and third reviewer was consulted, if necessary, to resolve any disagreements. Data extracted included demographic and clinical characteristics,

TABLE 1. Demographic data and clinical characteristics

Author (year)	Study design	No. of patients	Age (years)*	Male (%)	Underlying diseases	Dose of posaconazole	Duration of co-administration or follow-up
Peksa (2015) [24]	Retrospective	4	50 (32-61)	50%	ALL: 0; AML: 2 (50%); CML: 1 (25%); myelofibrosis: 1 (25%)	600 mg/d orally	17 days
Cho (2015) [25]	Retrospective	≥50% sirolimus dose reduction: 38	52 (23-71)	63%	AML 17 (45%); ALL 6 (16%); CML 3 (8%); CLL 1 (2%); other 11 (29%)	400 mg PO BID 6 (16%); 200 mg PO TID 32 (84%)	28 days
		<50% sirolimus dose reduction: 37	53 (18-89)	65%	AML 15 (40%); ALL 7 (19%); NHL 4 (11%); CML 1 (3%); CLL 3 (8%); other 7 (19%)	400 mg PO BID 4 (11%); 200 mg PO TID 33 (89%)	28 days
Sánchez-Ortega (2012) [20]	Retrospective	41	50 (18-68)	61%	AML/MDS 29 (71%); CLPD 9 (22%); other 3 (7%)	600 mg/d PO	30 days
Kubiak (2012) [15]	Retrospective	15	50 (23-63)	60%	AML 5 (33); Myelodysplastic syndrome 2 (13); CLL 2 (13); CML 2 (13); ALL 2 (13); Aplastic anemia 1 (6); TLL 1 (6)	600 mg: 13 (87%) PO 800 mg: 2 (13%) PO	78 (25-177) days
Berge (2009) [27]	Retrospective	14 (2 were excluded from analysis)	25 ± 8 [†]	50%	Lung transplant patients with cystic fibrosis	800 mg/day, orally	n/a
Sansone-Parsons (2007) [16]	Retrospective	Cyclosporine group: 4	54 (41-62)	100%	Heart transplant recipients (no data for underlying diseases)	100 mg Tablet BID	3 weeks
		Tacrolimus group: 36	25.8 (20.0-40.0)	50%		400 mg PO BID	3 weeks
Langston (2007) (Abstract) [26]	Randomized	Cyclosporine group: 19	n/a	n/a	n/a	200 mg PO TID	2 weeks
		Tacrolimus group: 7	n/a	n/a	n/a	200 mg PO TID	2 weeks

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BID, twice daily; CLL, chronic lymphocyte leukemia; CLPD, chronic lymphoproliferative disorder; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; n/a, not available; NHL, non-Hodgkin lymphoma; PO, oral suspension; TID, 3 times daily, TLL, T-cell acute lymphoblastic leukemia.

* Median (range); [†] mean ± SD.

TABLE 2. Adverse reactions and conclusion/recommendation of the included studies

Author (publication year)	Adverse reactions	Conclusion/recommendation
Peksa (2015)	This study excluded 8 of 36 patients who developed acute renal failure and/or hemolysis. Four of eight excluded patients did have dose reductions of their initial immunosuppressive regimen and still experienced toxicity.	Dose reductions of 50–75% for both sirolimus and tacrolimus, in combination with standard dosing of azole antifungal agents, were necessary to achieve therapeutic drug concentrations for immunosuppressants and potentially avoid toxicities.
Cho (2015)	This study 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.	Co-administration 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.
Sánchez-Ortega (2012)	The strategy of this study was safe and well tolerated from a clinical perspective. Only seven patients (17%) had CsA-related toxicities, including renal dysfunction (n=4), hypertension (n=1), essential tremor (n=1), and mild thrombotic microangiopathy (n=1), all of which resolved with dose adjustment, as planned.	Our recommendation is to maintain CsA at the initiation of combined treatment with posaconazole and to subsequently adjust the CsA dose on the basis of individualized patient results of close monitoring of blood CsA levels a minimum of three times weekly and clinical toxicity (Day 30: -48.9%).
Kubiak (2012)	The majority of patients with initial empiric sirolimus or tacrolimus dosage reductions tolerated the co-administration of posaconazole well and did not experience any drug-related adverse events or elevations in serum creatinine from baseline values. Only one patient with an elevation of sirolimus level experienced an adverse event during the first month of co-administration.	In conclusion, an empiric sirolimus dose reduction of at least 33% to 50% is warranted when initiating posaconazole therapy, followed by close serum trough concentration monitoring.
Berge (2009)	This study did not report safety or side effects of either co-administration of posaconazole with TRL or reducing the initial dose of TRL.	By closely managing azole–tacrolimus (TRL) drug interactions in lung transplant patients with CF, we were able to adapt TRL dose schedules, decreasing the dose of TRL by a factor of 3 with PSZ. Careful therapeutic drug monitoring made it possible to prevent the high levels of nephrotoxicity generally observed in cases of uncontrolled TRL overdose.
Sansone-Parsons (2007)	Three of four subjects receiving concurrent administration of posaconazole and cyclosporine had at least one adverse event, and required 14–29% reductions in their established cyclosporine dosages. An increased frequency of adverse events (30/36; 83%) was found in patients receiving concurrent administration of posaconazole and tacrolimus. No adverse reaction was reported in patients with initial cyclosporine dosage reductions.	When either cyclosporine or tacrolimus is co-administered with posaconazole, the dosage of the immunosuppressant should be reduced at the start of posaconazole therapy. Monitoring of blood levels of cyclosporine or tacrolimus is recommended during its administration with posaconazole (14–29% reductions in their established cyclosporine dosages were found).
Langston (2007)	This study did not report safety or side effects of either co-administration of posaconazole with TRL or reducing the initial dose of TRL.	CsA dose reductions of approximately 30% to 45% upon initiation of prophylaxis are recommended in order to maintain effective drug levels within the therapeutic range.

Abbreviations: CF, cystic fibrosis ;CsA, Cyclosporine ; HSCT, hematopoietic stem cell transplant; TRL, tacrolimus.

TABLE 3. Dosage and pharmacokinetics of immunosuppressants

Author (publication year)	Immuno-suppressant	Time point of measurement	Dose	Plasma level	Plasma level/dose ratio	% Dose reduction
Peksa (2015)	Sirolimus	Baseline*	12 mg oral loading dose followed by 4 mg/day	Target trough level: 3-12 ng/mL	n/a	—
		After discontinuation	Maintenance oral dose at discharge: 1.3 ± 0.5 mg/day	Trough level on discharge: 5.7 ± 2.8 ng/mL	n/a	-67.5%
	Tacrolimus	Baseline*	0.02 mg/kg/day i.v. by continuous infusion	Target trough level: 5–10 ng/mL	n/a	—
		After discontinuation	Maintenance oral dose at discharge: 0.038 ± 0.020 mg/kg/day	Trough level on discharge: 6.1 ± 2.0 ng/mL	n/a	—
Cho (2015)	Sirolimus ≥50% sirolimus dose reduction	Baseline*	3.02±1.24 mg/day	6.82±1.96 ng/ml	2.32±1.02	—
		During co-administration	1.16±0.64 mg/day†	9.46±2.81 ng/ml (maximum)	6.36±3.22	-60% ± 12% (-94% to -50%)
	<50% sirolimus dose reduction	Baseline*	3.02±1.24 mg/day	5.24±2.31 ng/ml	2.26 ± 1.13	—
		During co-administration	1.16±0.64 mg/day†	12.64±4.81 ng/ml (maximum)	6.10±3.07	-1% ± 40% (-43% to +250%)
Sánchez-Ortega (2012)	cyclosporine	Baseline*	3.09 ± 0.1.01 mg/kg/day	225.8 ± 119.3 ng/ml	82.1 ± 72.2	—
		During co-administration	Day 7: 3.06 ± 1.10 mg/kg/day Day 14: 2.61 ± 1.15 mg/kg/day Day 30: 1.58 ± 0.82 mg/kg/day	Day 7: 293.1± 150.9 ng/ml Day 14: 304.9± 132.9 ng/ml Day 30: 245.8± 121.8 ng/ml	Day 7: 113.1 ± 90.5 Day 14: 138.0 ± 80.3 Day 30: 172.6± 76.2	Day 7: -1% Day 14: -15.5% Day 30: -48.9%
Kubiak (2012)	Sirolimus	Baseline*	2 (1-3) mg/day†	Trough level: 5.5 (2.8-28.3) ng/ml‡	n/a	-50 (0 to -90)%
		During co-administration	1 (0.3-3) mg/day†	Trough level: 5.3 (2.8-12.1) ng/ml‡	n/a	-33 (-50 to -83)%
Berge (2009)	Tacrolimus	Baseline*	8.0 ± 2.4 mg/day	Trough level: 10.0 ± 2.0 ng/ml	1.4 ± 0.3	—
		During co-administration	2.0 ± 0.8 mg/day	Trough level: 7.8 ± 2.0 ng/ml	4.6 ± 0.8	-75%
Sansone-Parsons (2007)	Cyclosporine	Baseline*	BID at their established doses (175 mg or 150 mg)	4.1 (2.7-6.2) ng/ml/mg§	n/a	Three of four subjects required 14–29% reductions in cyclosporine dosages.
		During co-administration	n/a	4.3 (2.9-7.7) ng/ml/mg§	n/a	
	Tacrolimus	Baseline*	0.05 mg/kg	24.2 (31) ng/ml	n/a	—
		During co-administration	0.05 mg/kg	51.7 (18) ng/ml	n/a	
Langston (2007)	Cyclosporine	Baseline*	570.9 mg/day	351 ng/ml	0.93	—
		During co-administration	307.8 mg/day	314.2 ng/ml	1.09	-46%
	Tacrolimus	Baseline†	15.3 mg/day	10.6 ng/ml	3.43	—
		During co-administration	4.0 mg/day	12.2 ng/ml	4.39	-74%

Abbreviations: BID, twice daily; n/a, not available

*Prior or at posaconazole initiation; †according to institutional clinical practice, sirolimus doses were adjusted to target sirolimus serum concentrations between 5 and 10 ng/mL;

‡median dose, trough level or dose reduction (range); § mean (coefficient variation, %).

FIGURE 1. Flow chart for study selection

such as study design, number of participants, participants' age, underlying disease and type of transplantation. Also extracted were cyclosporine, tacrolimus or sirolimus dosages, plasma levels of cyclosporine, tacrolimus or sirolimus and the ratio of plasma level/dose (C/D ratio) before, during and after discontinuation of posaconazole. Other information extracted included percentage dosage reductions of cyclosporine, tacrolimus or sirolimus.

Reporting quality and risk of bias

Since the majority of included studies were retrospective in design, the methodological quality of each study was assessed using a Cochrane risk of bias assessment tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) by two reviewers [23]. Briefly, seven domains of bias (due to confounding, bias in selection of participants, bias in measurement of interventions, bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in reported result) were

evaluated. Risks of bias figures were generated using Cochrane Review Manager Software v. 5.3.

Results

Sixty-six studies were initially identified (Figure 1), of which 56 were excluded following initial review of the titles and abstracts because they were duplicates and/or irrelevant. Ten studies underwent full-text review; three of which were eliminated because they were letters to the editor, were unrelated to the objective of the study or because they assessed everolimus (another type of immunosuppressants) [21]. Seven studies were included in the systematic review, with a total of 215 patients [15,16,20,24-27].

Demographic data and clinical characteristics of the participants are shown in Table 1. Six of the studies [15,16,20,24,25,27] were retrospective in design and one [25] was an abstract of a randomized study (Table 1). Across the seven studies, the age of patients ranged from 25 to 54 years

A.

B.

FIGURE 2. Results of quality assessment for (A) individual studies and (B) the summary of bias for all seven included studies.

and the percentage of males in the study populations ranged from 50% to 100%. The patient population was heterogeneous and included patients with different types of leukemia [15,20,25-26], as well as lung transplant [27] and heart transplant [16] recipients. The adverse reactions and conclusion/ recommendation of the included studies are summarized in Table 2.

The dosages and pharmacokinetics of the various immunosuppressants are summarized in Table 3. The dose of posaconazole used among the seven studies ranged from 200 to 800 mg per day. Three studies evaluated dose reduction of sirolimus when posaconazole was co-administered (Table 3). In the studies by Peksa *et al.* (2015) [24] and Kubiak *et al.*

(2012) [15], addition of posaconazole resulted in a 33% to 67.5% reduction in the dose of sirolimus. Following reduction, the trough serum levels of sirolimus (ranged, 5.3 to 5.7 ng/mL) were similar to the trough levels prior to concomitant administration of posaconazole (range, 3 to 6.8 ng/mL). In the study by Cho *et al.* (2015) [25], subgroup analysis evaluated the dose reduction of sirolimus in patients with <50% reduction ($-1\% \pm 40\%$) and those with $\geq 50\%$ reduction ($-60\% \pm 12\%$) of the drug. They found that the C/D ratio increased from 2.26 ± 1.13 to 6.10 ± 3.07 in <50% reduction group, and from 2.32 ± 1.02 and 6.36 ± 3.22 in $\geq 50\%$ reduction group. The maximum sirolimus levels were higher in the <50% sirolimus reduction group (9.46 ± 2.81 ng/mL) compared with the group with $\geq 50\%$ reduction in the dose of sirolimus (9.46 ± 2.81 ng/mL) ($P=0.001$).

Of the four studies that assessed tacrolimus dose reduction [16,24,26,27], two reported reducing the levels of tacrolimus (range, 74% to 75%) when co-administered with posaconazole. The plasma trough levels for tacrolimus plus posaconazole in the two studies (ranged, 6.1 to 7.8 ng/mL) were similar to levels prior to addition of posaconazole to tacrolimus therapy (range, 5.0 to 10 ng/mL). Berge *et al.* (2009) [27] found that the C/D ratio increased from 1.4 ± 0.3 in baseline to 4.6 ± 0.8 during co-administration. In contrast, no major change in C/D ratio before and after the addition of posaconazole was found in study by Langston *et al.* (2007) [26].

Three studies investigated the dose reduction of cyclosporine, when administered concurrently with posaconazole [16,20,26]. Across these studies, dose reductions of cyclosporine were reported in two studies [20,26]. Sánchez-Ortega *et al.* (2012) reduced the dose of cyclosporine by 15.5% at day 14, and 48.9% at day 30 [20]. The C/D ratio of cyclosporine increased from 82.1 ± 72.2 at baseline to 138.0 ± 80.3 at day 14 during co-administration with posaconazole [20]. Langston *et al.* (2007) reduced the dose of cyclosporine by 46.0% at day 14 [26]. No major change in C/D ratio before and after the addition of posaconazole was found in study by Langston *et al.* (2007) [26]. In the study by Sansone-Parsons *et al.* (2007), three of the four subjects required 14% to 29% reduction in cyclosporine dosage following the addition of posaconazole, resulting in similar dose normalized maximum cyclosporine plasma concentration before and after the addition of posaconazole (4.1 and 4.3 ng/mL/mg, respectively) [16].

Data quality assessment

Quality and risk of bias were assessed using ACROBAT-NRSI [23]. The results of quality assessment are shown in Figure 2.

The major bias was due to confounders not being properly controlled in most of the studies. The bias also came from measurement of interventions because of the lack of detail description in methodology and incomparable in outcome assessment across intervention groups.

Discussion

The current literature has investigated the dose adjustments for the use of azoles with immunosuppressants as individual agents in transplant recipients [13,28]. The purpose of this systematic review was to assess the dose adjustment of the immunosuppressants cyclosporine, tacrolimus and sirolimus for the patients with allogeneic hematopoietic stem cell transplant or solid-organ transplant (lung or heart) during co-administration of these immunosuppressants with posaconazole.

In general, the co-administration of posaconazole with sirolimus, tacrolimus or cyclosporine necessitated dose reductions to maintain the levels of the immunosuppressant in the optimal therapeutic range. Depending upon the immunosuppressant used, dose reduction ranged from 50% to 68% for sirolimus, approximately 75% for tacrolimus and 14% to 49% for cyclosporine. The need for dose reduction of immunosuppressant therapy was apparent in studies with hematopoietic stem cell transplants as well as studies with heart and lung transplants. This is consistent with the posaconazole prescribing information, which recommends that, at initiation of posaconazole therapy, tacrolimus should be reduced to one third of the original dose and cyclosporine should be reduced to approximately 75% of the original dosage [19].

Given the long half-lives of azoles, a maximal effect of the addition of posaconazole may not be seen until steady-state concentrations are reached after 5 to 7 days [24]. Sanchez-Ortega *et al.* found that within one week of addition of posaconazole therapy, a significant increase in blood cyclosporine levels in allo-BMT recipients was observed [20]. In the study by Cho *et al.*, the highest C/D ratio was observed 9 to 12 days after posaconazole initiation [25].

The impact of posaconazole on the pharmacokinetics of immunosuppressants is supported the study by Sansone-Parsons *et al.* (2007) [16]. The addition of posaconazole 400 mg twice/day for eight days to patients undergoing tacrolimus therapy significantly increased systemic exposure to tacrolimus (C_{max} and AUC_T) over a 14-day period. In addition, the mean elimination terminal phase half-life of tacrolimus was prolonged from 29.0 to 35.9 hours, which resulted in reduction in total body clearance from 21.4 to 4.31

L/hour. Similarly, concomitant administration of posaconazole with sirolimus was found to increase the sirolimus blood concentration by approximately nine-fold and can result in sirolimus toxicity [19].

Our findings indicate that the dosage of sirolimus, cyclosporine or tacrolimus should be reduced when posaconazole therapy is started and that plasma levels of the immunosuppressant should be monitored during and at the discontinuation of posaconazole therapy so that dosages are adjusted accordingly. These findings are consistent with guideline recommendations that therapeutic drug monitoring should be used to guide the dose adaptations of immunosuppressants [12]. In addition, the results indicated that dosing of the immunosuppressant should be individualized, based on the measurement and interpretation of drug concentrations [21].

An important reason for dose reduction of immunosuppressants when posaconazole is added to treatment is the potential for an increase in adverse events (toxicity). Indeed, in a study for patients following heart transplantation, co-administration of posaconazole with immunosuppressants was associated with an increased frequency of adverse events, with 30 of 36 subjects (83%) reporting at least one treatment emergent adverse event compared with 14 (39%) or 24 (67%) during treatment with single-dose tacrolimus alone or posaconazole alone, respectively [16]. In the study by Cho *et al.*, a greater percentage of patients in the subgroup of patients with <50% sirolimus dose reduction compared with those with ≥50% dose reduction had sirolimus plasma levels >15 ng/mL, a dose level associated with adverse events (e.g., hypertriglyceridemia, thrombocytopenia, thrombotic microangiopathy and sinusoidal obstructive syndrome of the liver) [25]. Most patients with initial dosage reductions of immunosuppressants tolerated the co-administration of posaconazole well and did not experience any drug-related adverse events [15,16,20,25]; however, the seven studies in this retrospective review might lack sufficient clinical data to allow for analysis of any correlations between dose reduction of immunosuppressant and adverse effects.

The need to reduce immunosuppressants when co-administered with azoles has also been observed in other solid organ transplants. A case report describes a 55-year-old female who developed rhinocerebral mucormycosis 108 days after liver transplantation [31]. The patient received posaconazole therapy for 3 months with co-administration with immunosuppressants. The patient was initially treated with tacrolimus, followed by cyclosporine; however, she was

switched to sirolimus therapy due to adverse effects. The initial dose of sirolimus was 3 mg daily with a goal trough 6 to 8 ng/mL, which was reduced to 0.5 mg orally daily after co-administration with posaconazole. The author suggested that the sirolimus goal concentration was <10 ng/mL, hence the sirolimus dose should be decrease by 60% to 75% at the initiation of posaconazole therapy [31].

Another case report described a 54-year-old male renal transplant patient who received co-administration of everolimus, a derivative of sirolimus, with oral voriconazole, another triazole antifungal medication, over the first 40 days following transplantation [21]. Because the risk of aspergillosis was still present, posaconazole was introduced approximate one month later at 400 mg twice daily. A change was found in everolimus trough concentrations from 20 to 25 ng/mL (overdose stage), and following dose reduction was 4 to 10 ng/mL. Subsequently, everolimus dosage was modified, based on therapeutic drug monitoring, from 2.0 mg to 0.5 mg twice daily so as to maintain the 10 ng/mL trough concentration range. The strength of the drug-drug interaction was quantitatively evaluated using a normalized-to-dose ratio of everolimus concentration. This ratio was 12.5 ± 3.0 during the overdose stage, and 3.3 ± 1.1 after the dose reduction ($P < 0.001$).

Posaconazole is metabolized by uridine diphosphate-glucuronosyltransferase enzyme pathways [25], and oxidative metabolism by CYP enzymes plays only a minor role in the elimination of posaconazole. Cyclosporine, tacrolimus and sirolimus are predominantly metabolized by CYP3A4 but these immunosuppressants are also competitive inhibitors of CYP3A4 [13,32]. Cyclosporine, tacrolimus, and sirolimus are also both substrates and inhibitors of P-glycoprotein (P-gp) membrane transporter [13,25]. Cytochrome P450-mediated drug interactions of the immunosuppressants should have a limited impact posaconazole pharmacokinetics [32]. For most of the included studies, the daily dose of posaconazole was either 600 mg or 800 mg, and the dose was not reduced during the study.

The number of studies with pediatric patients was limited. One recent study evaluated the need for dose reduction of cyclosporine in pediatric patients receiving cyclosporine and posaconazole following hematopoietic stem cell transplantation [29]. In this pediatric population, a mild increase of cyclosporine levels was found in eight patients on day 3 to day 8 after the first cyclosporine dose. Among those patients, cyclosporine dosage was reduced by up to 24% in five patients.

Several limitations of this analysis should be considered when interpreting the results. The number of studies and the total population were small, since both a case report and a letter to the editor were excluded. Most of the studies were retrospective single-arm studies, which had low evidence levels and are less generalizable. In addition, of the seven studies included, three had treatment arms of ≤ 7 patients. Significant heterogeneity was present across the studies in dosing, duration of therapy and underlying disease. The strategy of tapering the dose of a given immunosuppressant was also diverse among the included studies, which makes it difficult to recommend a particular treatment algorithm for the dosing of immunosuppressant when co-administered with posaconazole.

In summary, due to the posaconazole-related inhibition of CYP3A4 activity, the plasma level of the immunosuppressants sirolimus, tacrolimus and cyclosporine are elevated when co-administered with posaconazole; therefore, at initiation of posaconazole therapy, the dosage of these immunosuppressants should be reduced. Based on the findings of the included studies, sirolimus and tacrolimus should have dose reductions of at least 60% to 70%, and cyclosporine dose should be reduced by at least 30% to 40%. Our findings indicate that plasma levels of the immunosuppressant should be monitored during administration and continually at discontinuation of posaconazole therapy so that dosages of the immunosuppressant are adjusted accordingly. Due to the sparse number of articles in literature, more well-designed clinical studies should be needed to delineate the drug-drug interaction between immunosuppressants and azole antifungals in solid-organ transplantation.

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