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CLINICAL THERAPEUTICS

Antifungal Prophylaxis with Posaconazole Delayed-Release Tablet and Oral Suspension in a Real-Life Setting: Plasma Levels, Efficacy, and Tolerability

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ABSTRACT We continuously determined posaconazole plasma concentrations (PPCs) in 61 patients with hematological malignancies receiving posaconazole (PCZ) delayed-release tablets (DRT; 48 patients; median duration of intake, 92 days) and PCZ oral solution (OS; 13 patients; median duration of intake, 124 days). PCZ DRT and OS antifungal prophylaxis was efficient and well tolerated. Thirty-four of 48 patients (71%) receiving DRT always had PPCs of >0.7 mg/liter, while 14 of 48 patients (29%) had at least one PPC of ≤0.7 mg/liter. In patients receiving OS, 4 of 13 patients (31%) always had PPCs of >0.7 mg/liter, 6 of 13 patients (46%) had at least one PPC of ≤0.7 mg/liter, and 3 (23%) patients never reached a PPC of 0.7 mg/liter. In patients with at least one determined PPC, the mean proportion of all PPCs of >0.7 mg/liter was 91% for PCZ DRT, whereas it was 52% for PCZ OS ($P = 0.001$). In the per sample analysis, PPCs were significantly more likely to be >0.7 mg/liter in patients receiving DRT than in patients receiving OS (PPCs were >0.7 mg/liter in 91.4% [297/325] of patients receiving DRT versus 70.3% [85/121] of patients receiving OS; $P < 0.001$). Patients receiving PCZ DRT had higher proportions of PPCs of >0.7 mg/liter than patients receiving OS both in the per patient and in the per sample analyses. Two patients (3%) had side effects during PCZ prophylaxis, and one (2%) had fungal breakthrough infection. Therapeutic drug monitoring enables detection of extended periods of PPCs of ≤0.7 mg/liter (e.g., due to nonadherence or graft-versus-host disease), which may also be associated with the loss of protective intracellular PCZ concentrations, regardless of the PCZ formulation.

KEYWORDS plasma concentration, posaconazole

Posaconazole (PCZ) has broad-spectrum antifungal activity against most *Aspergillus* and *Candida* spp. and is currently approved for use for antifungal prophylaxis in patients with prolonged neutropenia and in patients with acute graft-versus-host diseases (GVHD) after hematopoietic stem cell transplantation (HSCT) (1–5). PCZ is nowadays administered as a delayed-release tablet (DRT) formulation due to its better bioavailability than that of posaconazole oral solution (OS) (6, 7). Whereas therapeutic drug monitoring (TDM) of PCZ plasma levels is recommended in patients receiving PCZ OS, the need for TDM in patients receiving PCZ DRT is uncertain (7–10). In contrast to

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TABLE 1 Characteristics of patients receiving PCZ DRT or OS[a]

Characteristic	Value(s) for patients receiving:		*P* value
	DRT ($n = 48$)	OS ($n = 13$)	
No. (%) men/no. (%) women	24 (50)/24 (50)	7 (54)/6 (46)	
Mean (IQR) age (yr)	55 (47.0–64.0)	49 (29.5–66.0)	NS[a]
Mean (IQR) BMI	25.2 (21.6–28.0)	23.7 (21.7–26.0)	NS
No. (%) of patients with:			
AML	31 (65)	3 (23)	<0.001
ALL	1 (2)	4 (31)	NS
CLL	0	1 (8)	NS
Myelofibrosis	3 (6)	0	NS
Diffuse large B-cell lymphoma	3 (6)	1 (8)	NS
Aplastic anemia	2 (4)	0	NS
Others	8 (17)	4 (31)	NS
HSCT allogeneic	34 (71)	8 (62)	0.039
GVHD present[b]	25 (74)	5 (63)	<0.001
PPI treatment	34 (71)	8 (62)	<0.001
Diarrhea	12 (25)	1 (8)	0.002

[a]BMI, body mass index; NS, not significant; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia.

[b]The percentages indicate the percentages of patients with GVHD among patients with allogeneic HSCT. Sixty percent of patients receiving DRT and 40% of patients receiving OS had GVHD grade 3 or 4; the rest had GVHD grade 1 or 2.

PCZ OS, limited data showing an association between breakthrough infections and PCZ trough levels below the recommended cutoff of 0.7 mg/liter exist for PCZ DRT (9, 11, 12). However, studies have shown that although overall PCZ levels are higher among those receiving PCZ DRT, approximately 10 to 29% of posaconazole plasma concentrations (PPCs) in these patients do not reach this target (10, 13–15). In addition, inadequate exposures cannot be predicted by observable clinical conditions (e.g., mucositis) (9). TDM therefore remains the direct approach for identifying patients with suboptimal PCZ plasma levels and may also be an important measure of patient adherence.

Most previous studies of PPCs in patients receiving PCZ DRT either used historical cohorts for comparison of DRT and OS or were solely descriptive in nature with no comparator cohort at all. In others, PPCs were determined only once within a given time frame (e.g., days 7 to 14 after initiation), and some lacked data on efficacy and/or tolerability (10, 15–17). Additionally, in most studies, PPCs considered adequate (i.e., >0.7 mg/liter) were shown as the proportions of levels reaching this target from all measured PPCs, which increases the numbers and statistical power but does not reflect the course of PPCs in individual patients during their full course of PCZ antifungal prophylaxis.

The purpose of this analysis was to assess continuously determined PPCs in patients with hematological malignancies receiving PCZ DRT or OS and also to correlate PPCs with the efficacy and tolerability of PCZ prophylaxis.

RESULTS

Per patient analyses. Demographic data and the underlying diseases of 61 patients receiving PCZ prophylaxis are shown in Table 1. Overall, 48 patients received PCZ DRT and 13 received PCZ OS. The median duration of PCZ prophylaxis was 92 days (minimum, 8 days; maximum, 341 days; interquartile range [IQR], 38 to 121 days) in patients receiving DRT and 124 days (minimum, 4 days; maximum, 294 days; IQR, 41 to 211 days) in patients receiving OS. Patients receiving DRT had a median of 4 PPCs (minimum, 1; maximum, 30; IQR, 2 to 8), whereas patients receiving OS had a median of 7 PPCs (minimum, 1; maximum, 17; IQR, 3 to 15). PPCs of ≤0.7 mg/liter were observed in 29% (14/48) of patients receiving DRT and 69% (9/13) of patients receiving OS ($P = 0.008$). Thirty-four of 48 patients (71%) receiving DRT always had PPCs of >0.7 mg/liter, while 14 of 48 patients (29%) had at least one PPC of ≤0.7 mg/liter (1 patient

TABLE 2 Factors associated with having one or more PPCs of ≤0.7 mg/liter in the logistic regression model

Factor	Univariate analysis			Multivariate analysis[a]		
	OR	95% CI	*P* value[b]	OR	95% CI	*P* value
Age (per year)	0.98	0.95–1.02	0.335			
Female sex	0.35	0.12–1.02	0.055	0.28	0.08–1.01	0.052
Allogeneic stem cell transplantation	1.47	0.47–4.64	0.508			
GVHD[c]	3.92	1.30–11.84	**0.016**	7.00	1.67–29.42	0.008
Concomitant PPI	0.76	0.25–2.31	0.634			
Diarrhea	1.51	0.44–5.24	0.514			
Posaconazole DRT	0.15	0.04–0.58	**0.005**	0.07	0.01–0.39	0.002

[a]Hosmer-Lemeshow goodness-of-fit chi-square value, 5.284 ($P = 0.382$); ROC area under the curve of the model, 0.84 (95% CI, 0.74 to 0.94).
[b]*P* values of <0.2, the cutoff for inclusion of the respective variables in the multivariable model, are in bold.
[c]Sixty percent of patients receiving DRT and 40% of patients receiving OS had GVHD grade 3 or 4; the rest had GVHD grade 1 or 2.

had only a single PPC which was below the target). In patients receiving OS, 4 of 13 (31%) always had PPCs of >0.7 mg/liter, 6 of 13 patients (46%) had at least one PPC of ≤0.7 mg/liter, and 3 (23%) patients never reached a PPC of 0.7 mg/liter (1, 2, and 4 measured PPCs, respectively). In patients with at least one determined PPC, the mean proportion of all PPCs of >0.7 mg/liter was 91% for patients receiving PCZ DRT, whereas it was 52% for patients receiving PCZ OS ($P = 0.001$). None of our patients had rifampin, phenytoin, metoclopramide, or ranitidine comedication.

Table 2 shows the results of the logistic regression model. Among the variables included in univariate analysis, the presence of graft-versus-host disease (GVHD) was predictive of having at least one PCZ concentration below the target, while receiving the posaconazole DRT was protective against having PCZs below the target (Table 2). These three variables were entered in the multivariate model, where GVHD remained a risk factor (odds ratio [OR], 7.00; 95% confidence interval [CI], 1.67 to 29.42; $P = 0.008$) and receiving the posaconazole DRT formulation remained a protective factor (OR, 0.07; 95% CI, 0.01 to 0.39; $P = 0.002$) against having one or more PCZ concentrations below the target. In the stepwise approach, receiving the posaconazole DRT remained the sole predictor in step 1.

Per sample analyses. In total, 446 PPCs were measured: 325 in patients receiving DRT and 121 in patients receiving OS. Table 3 compares the PPCs between those receiving posaconazole DRT and those receiving posaconazole OS. The PPCs were significantly more likely to be >0.7 mg/liter in patients receiving DRT than in patients receiving OS (91.4% [297/325] of PPCs of >0.7 mg/liter in patients receiving DRT versus 70.3% [85/121] in patients receiving OS; $P < 0.001$).

Table 4 shows the results of the univariate and multivariable linear mixed-effects models. Receipt of posaconazole DRT was significantly associated with higher PPCs in the univariate analysis (increase of 1.25 mg/liter [95% CI, 0.58 to 1.92 mg/liter] in those receiving DRT versus those receiving OS), as was the duration of PCZ administration (increase of 0.014 mg/liter [95% CI, 0.001 to 0.028 mg/liter] per 10 days of administration); none of the other variables showed a significant effect ($P > 0.2$ for all variables).

TABLE 3 Pre-steady-state and early-steady-state PPCs in patients receiving PSC as DRT or OS

Regimen	Days 1–6		Days 7–14	
	No. (%) of patients with PPCs[a]	Median (IQR) PPC (mg/liter)	No. of patients with PPCs[b]	Median (IQR) PPC (mg/liter)
DRT ($n = 48$ cases)	12 (25)	1.49 (0.83–2.10)	14 (29)	1.61 (1.04–2.05)
OS ($n = 13$)	4 (31)	0.71 (0.47–1.13)	5 (38)	0.45 (0.29–0.80)
P value		0.008		<0.001

[a]Twenty-two (patients receiving DRT) and 11 (patients receiving OS) PPCs were measured.
[b]Twenty-eight (patients receiving DRT) and 12 (patients receiving OS) PPCs were measured.

TABLE 4 Mixed-effects model on impact of formulation, time, age, and other factors on PPCs[a]

Variables included in mixed-effects model	Univariate model			Multivariate model		
	Mean (SE) increase in PPC (mg/liter)	*t* value	*P* value	Mean (SE) increase in PPC (mg/liter)	*t* value	*P* value
PSC DRT	1.253 (0.342)	3.67	<0.001	1.275 (0.340)	3.754	<0.001
Days since PSC initiation (10-day intervals)	0.014 (0.007)	2.07	0.039	0.015 (0.007)	2.196	0.029
Age (1-yr increase)	0.006 (0.011)	0.57	>0.200			
Wt (1-kg increase)	0.005 (0.010)	0.49	>0.200			
Female sex	0.217 (0.313)	0.69	>0.200			
GVHD	0.356 (0.312)	1.14	>0.200			
Concomitant PPI	0.225 (0.341)	0.66	>0.200			

[a]Data are for 446 observations from 61 patients.

In the multivariable model (intercept, 0.72 mg/liter; 95% CI, 0.12 to 1.32 mg/liter; $P = 0.021$), posaconazole DRT remained the strongest factor, with an estimated increase of 1.28 mg/liter in PPCs in those receiving DRT (Table 4).

Correlation of pre-steady-state with steady-state PPCs. PPCs measured from days 1 to 6 (pre-steady state) and from days 7 to 14 (early steady state) are shown in Table 3. A total of 10 patients (7 receiving DRT, 3 receiving OS) had PPCs measured as pre-steady-state concentrations and early steady-state concentrations, and Spearman rho correlation analysis showed a highly significant correlation between the earliest pre-steady-state and the earliest steady-state concentrations ($r = 0.867$; $P = 0.001$). No significant difference between pre-steady-state and early steady-state concentrations was observed by the Wilcoxon signed-rank sum test ($P = 0.878$). There was also no significant increase of PPCs overall between pre-steady-state and steady-state PPCs in those receiving DRT ($P = 0.398$) or OS ($P = 0.144$).

Tolerability and efficacy. Two patients had side effects possibly associated with PCZ prophylaxis: one receiving DRT (loss of appetite, vomiting, and blurred vision) and one receiving OS (nausea and loss of appetite). In the first patient, PCZ DRT had to be discontinued due to increased concentrations of bilirubin (2.8 mg/dl; normal range, 0.10 to 1.20 mg/dl), alanine aminotransferase (ALT; 66 U/liter; normal range, 0 to 45 U/liter), gamma-glutamyltransferase (1,046 U/liter; normal range, 0 to 55 U/liter), and alkaline phosphatase (AP; 145 U/liter; normal range, 40 to 130 U/liter) after 1 month of intake. The PPC was 2.13 mg/liter 4 days prior to discontinuation. No mold-active antifungal prophylaxis was administered thereafter (photopheresis led to a reduction of immunosuppressants for GVHD). The second patient was switched from OS to DRT after 2 months of OS administration due to nausea and a loss of appetite, with a cessation of side effects after the introduction of DRT. Hepatic side effects were not observed in this patient. The PPC at 27 days prior to the switch to PCZ DRT was 0.73 mg/liter.

Thirty-three of 61 (54%) patients receiving PCZ prophylaxis (27 receiving DRT, 6 receiving OS) were admitted due to febrile illness. In 19 of these 33 (58%) patients, PCZ prophylaxis (16/27 [59%] receiving DRT, 3 [50%] receiving OS) was terminated and other antifungal agents were administered at the discretion of the treating physicians. The alternative intravenous agents used after PCZ antifungal prophylaxis were caspofungin, micafungin, voriconazole, and liposomal amphotericin B. Fungal breakthrough infection was diagnosed in 1 of 61 (2%) patients. This patient received PCZ DRT after allogeneic hematopoietic stem cell transplantation and suffered from meningoencephalitis, pansinusitis, and right-sided orbital abscess involving the medial bone of the orbital cavity (lamina papyracea), which were subsequently treated with meropenem, trimethoprim-sulfamethoxazole, doxycycline, linezolid, and liposomal amphotericin B. Culture of pus surgically obtained from the orbital cavity revealed *Candida glabrata* (the MIC was not determined by the routine laboratory) but no other fungi or bacteria. Histological examination of polypoid material from surgically removed tissue of the right-sided paranasal sinuses revealed chronic sinusitis with hints of molds within this tissue. Internal transcribed spacer-based sequencing of this material revealed fungal DNA with 99.7% homology to *Rhizopus microsporus* DNA. Unfortunately, the patient

died due to ischemic stroke. The PPC was 3 mg/liter 10 days prior to the diagnosis of the breakthrough infection. Previous PPCs were 3.61 mg/liter (day −15, related to diagnosis of breakthrough infection), 2.23 mg/liter (day −28), 1.29 mg/liter (day −38), and 0.72 mg/liter (day −46).

DISCUSSION

In our study, conducted in a real-life setting, concurrent PCZ prophylaxis with DRT and OS in patients with hematological malignancies was analyzed. We observed that PCZ DRT and OS antifungal prophylaxis was efficient and well tolerated. PCZ DRT showed higher rates of PPCs above the desired threshold of 0.7 mg/liter than PCZ OS and was associated with a mean increase of 1.28 mg/liter in the multivariate linear mixed-effects model. In contrast, PCZ OS was the most important predictor that patients would have at least one PPC below the target. The better performance of PCZ DRT than PCZ OS related to PPCs has also been shown in previous studies (7, 15, 18–22). In our study, the PPC was >0.7 mg/liter for 91.4% of 325 PPCs measured in patients receiving PCZ DRT and 70.3% of 121 PPCs determined in patients receiving PCZ OS. This rate is between the rates found in other studies, which showed that 71% to 100% of PPCs were >0.7 mg/liter in patients receiving PCZ DRT (13, 18).

However, these rates do not truly reflect PPCs in given patient groups, as one individual with many PPCs of ≤0.7 mg/liter might lower the rate of PPCs of >0.7 mg/liter in the whole cohort. Additionally, patients might temporarily have PPCs of ≤0.7 mg/liter during their whole course of PCZ antifungal prophylaxis and would subsequently be at risk for fungal infection in this time frame, even though the vast majority of other PPCs in such patients may be above the target. Therefore, analyses of the PPCs per patient followed for the period of PCZ antifungal prophylaxis may provide more clinical relevance and may allow for a correlation of PPCs with efficacy, tolerability, and breakthrough infection. In our cohort, 13 of 48 (27%) patients receiving PCZ DRT and 6 of 13 (46%) patients receiving PCZ OS had at least one PPC below 0.7 mg/liter. Theoretically, patients were at risk for fungal infection during time frames with insufficient PPCs. Although 23 of 61 (38%) patients (patients receiving DRT and patients receiving OS combined) always had or had at least one PPC of ≤0.7 mg/liter, we observed only one fungal infection considered a breakthrough infection. A fungal orbital abscess involving the medial bone of the orbital cavity, determined to be caused by *Candida glabrata* by culture of surgically removed pus, occurred during PCZ DRT prophylaxis. Blood cultures were negative. *Rhizopus microsporus* DNA was detected in material surgically removed from the right-sided paranasal sinuses showing chronic sinusitis, and molds were detected by histological examination. In this particular patient, the PPC measured 10 days prior to the presence of clinical signs and symptoms of meningoencephalitis, sinusitis, and orbital abscess was 3 mg/liter, suggesting an adequate PPC. Unfortunately, lumbar puncture with investigation of cerebrospinal fluid (CSF) could not be performed due to thrombocytopenia. Previously, PCZ concentrations in CSF have been reported to be low compared to the PPCs (23–25). Although the PPCs were sufficient 10 days prior to the development of signs and symptoms in our patient, it may be hypothesized that central nervous system and bone tissue PCZ concentrations were too low to prevent the *Candida glabrata* orbital abscess involving the orbital bone, the *Rhizopus microsporus* infection involving the paranasal sinuses, and the possibly related meningoencephalitis. As the MIC of *Candida glabrata* was not determined in the routine laboratory, we cannot exclude the possibility that the *Candida glabrata* strain was PCZ resistant.

Regarding the timing of the measurement of the first PPC, a previous study found that pre-steady-state trough PPCs may predict steady-state PPCs in patients receiving OS (26). PPCs measured early after the initiation of PCZ may therefore have clinical value. Our study findings indicate that the same may be true for the DRT formulation. Whether it is necessary to perform TDM in all patients receiving PCZ antifungal prophylaxis remains unknown. Recently, posaconazole TDM has been recommended for patients receiving PCZ DRT or the intravenous formulation for prophylaxis, for

patients receiving PCZ for the treatment of fungal infections (especially infections caused by pathogens with reduced susceptibility), or for patients experiencing breakthrough infection, a progressive infection unresponsive to PCZ treatment, and possible drug-drug interactions (9). Although up to 38% of patients showed at least one PPC below 0.7 mg/liter, the rate of fungal infections in patients receiving PCZ antifungal prophylaxis was low (e.g., 2% in our cohort, which is consistent with the 1.9% to 3.9% reported in previous larger studies [1–3, 10, 27, 28]). Previously, the posaconazole concentrations in pulmonary alveolar cells have been found to be over 40-fold higher than those in serum (29). Despite low PPCs at given time points, it has been speculated that a high intracellular posaconazole concentration might protect the patient from pulmonary fungal infection even in cases with a low plasma concentration of PCZ (8). *In vitro*, the protective effect of cell-associated PCZ to resist infection with *Aspergillus fumigatus* persisted for at least 48 h after removal of the free drug. However, in one study, all of three patients with invasive fungal infection had PPCs below 0.5 mg/liter measured prior to the development of infection (12). This finding was confirmed in a larger study, where the median posaconazole concentrations were significantly lower in those who developed breakthrough fungal infections than in those who did not develop fungal infections (11). Determination of PPCs might further help to identify patients with low/no adherence to the prescribed PCZ. Previously, onsite education on optimal PCZ OS intake had some success, leading to satisfactory PPCs in 43% of patients (30). Importantly, despite the detailed education, PPCs remained undetectable in 35% of the patients in that study, indicating that nonadherence may be a relevant issue, at least in some of those patients.

In our cohort, the incidence of hepatic side effects of PCZ antifungal prophylaxis was low (2% in the PCZ DRT group), whereas it was 20% in another study (10). Measurement of PPCs enables detection of potentially associated side effects of PCZ antifungal prophylaxis, as shown in a patient with PCZ-associated visual hallucinations (31). In another study, it was suggested that TDM of PCZ be used to identify patients who are potentially eligible for a dose reduction on the basis of PPC simulations (16). However, as intraindividual variability in PPCs reaches 29.3% in real life, such a dose reduction might lead to insufficient PPCs and a lack of efficacy of antifungal prophylaxis (10).

Based on our data and previous literature, we believe that TDM improves antifungal prophylaxis with PCZ. Whereas TDM is mandatory in patients receiving PCZ OS, measurement of PPCs could also ensure efficient antifungal prophylaxis in patients receiving PCZ DRT. In the latter group, TDM may be primarily intended to detect extended periods of insufficient PPCs (e.g., due to nonadherence or GVHD), which may also be associated with the loss of protective intracellular PCZ concentrations.

MATERIALS AND METHODS

This retrospective study included all patients receiving PCZ prophylaxis with routinely performed PCZ TDM from 1 July 2015 to 31 December 2016 at the Division of Hematology, Medical University Hospital Graz, Graz, Austria. All patients had PCZ prophylaxis according to recent recommendations (32). Although local guidelines have recommended PCZ DRT as the primary choice for PCZ prophylaxis since mid-2015, a proportion of patients continued PCZ OS prophylaxis for various reasons, e.g., difficulties with swallowing the tablets. The patients' medical records were reviewed individually by using a standardized data collection template in order to collect demographic information and clinical data; mycological laboratory test results, including PPCs; as well as the PCZ formulation used, dosing information, termination of PCZ prophylaxis, the introduction of antifungal therapy or a change of antifungal prophylaxis, and breakthrough infections. Breakthrough infections were defined as invasive fungal diseases diagnosed during PCZ prophylaxis according to European Organization for Research and Treatment of Cancer criteria (12, 33). Possible side effects, like QT prolongation, neutropenia, and hepatotoxicity, were observed by the use of electrocardiograms (ECG) and laboratory assessment of blood cell counts and the levels of liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP). Other possible adverse events, like headache, abdominal pain, nausea, or vomiting, were documented at outpatient visits or during the daily assessment during the hospitalization. Samples for PPC determination were obtained in the morning prior to the scheduled PCZ intake. The patients were assessed for acute and chronic GVHD, and the GVHD was graded according to recently published criteria (34–36). Trough PPCs were measured by an in-house laboratory employing a CE-IVD (Conformité Européene *in vitro* diagnostic medical device)-marked

Chromsystems PCZ reagent kit (Chromsystems GmbH, Munich, Germany), based on high-performance liquid chromatography, the results of which were analyzed by an UltiMate 3000 chromatography device (Dionex, Sunnyvale, CA, USA) and by a triple-quadrupole TSQ system (Thermo Fisher, Palo Alto, CA, USA) with an electrospray ionization (ESI) source as described previously (26). PPCs of ≤0.7 mg/liter were considered insufficient in the setting of prophylaxis, on the basis of previous recommendations (9).

The study adhered to the Declaration of Helsinki (1996) and good clinical practices, and the study protocol was approved by the local ethics committee at the Medical University Graz, Graz, Austria (protocol number 29-444 ex 16/17). The need to obtain written informed consent from the included patients was waived by the local ethics committee. All statistical analyses were performed using the Statistical Package for Social Sciences (version 23; SPSS Inc., Chicago, IL, USA) and using R (version 3.1.1) and the lme4 package. Continuous data (i.e., PPCs) are presented as medians and interquartile ranges (IQR), and categorical data are presented as proportions. The proportions of sufficient PPCs (i.e., PPCs of >0.7 mg/liter) were calculated for all measurements in all patients, as well as for patients with at least 2 measurements in both groups. The pre-steady-state PPCs in patients receiving DRT or OS obtained from days 1 to 6 were compared between the patients receiving the two formulations and to those at steady state (days 7 to 14). The targeted PCZ trough level was defined as a concentration of >0.7 mg/liter, according to a recent recommendation (9). Analyses of continuous independent data were performed by Student's *t* test, and categorical data were analyzed by the Mann-Whitney U test or Fisher's exact test, as appropriate.

Pre-steady-state PPCs, obtained between days 1 and 6, were compared to early-steady-state (day 7 to 21) PPCs using the Wilcoxon signed-rank test. Correlations were calculated using Spearman correlation analysis, due to the nonnormal distributions.

For each case, demographic variables, clinical risk factors, and the PCZ formulation were entered into a univariate logistic regression model, with one or more PCZ trough levels of ≤0.7 mg/liter versus all PCZ trough levels of >0.7 mg/liter being the outcome. Odds ratios (OR) including 95% confidence intervals (CI) were calculated. Each variable with a *P* value of <0.2 for PCZ trough levels of ≤0.7 mg/liter was entered into a multivariate logistic regression model. Model discrimination was assessed by use of the goodness-of-fit Hosmer-Lemeshow statistic, and its predictive performance was assessed using receiver operating characteristic (ROC) analysis. Also, univariate and multivariable linear mixed-effects models were performed for each sample by utilizing PCZ trough levels as the continuous outcome and including the following variables (fixed effects): the posaconazole formulation (DRT or OS), the time since posaconazole initiation (days), age, sex, GVHD, and concomitant use of a proton pump inhibitor (PPI). Estimated effects on PPCs, including standard errors (SE) and *t* values, were displayed. Each variable with a *P* value of <0.2 was included in the multivariable model. A *P* value of <0.05 was considered statistically significant.

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