



Original Article

Clinical considerations on posaconazole administration and therapeutic drug monitoring in allogeneic hematopoietic cell transplant recipients

Mateja Kraljevic¹, Nina Khanna ¹, Michael Medinger², Jakob Passweg², Stavroula Masouridi-Levrat³, Yves Chalandon³, Nicolas J. Mueller⁴, Urs Schanz⁵, Nathalie Vernaz ⁶, Christian Van Delden⁷, Dionysios Neofytos^{7,*} and for the Swiss Transplant Cohort Study[†]

¹Division of Infectious Diseases, University Hospital of Basel, Basel, Switzerland, ²Department of Hematology, Bone Marrow Transplant Unit, University Hospital of Basel, Basel, Switzerland, ³Hematology Division, Oncology Department, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland, ⁴Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Zurich, Switzerland, ⁵Department of Hematology, Bone Marrow Transplant Unit, University Hospital of Zurich, Zurich, Switzerland, ⁶Medical Directorate, Finance Directorate Geneva University Hospitals, University of Geneva, Geneva, Switzerland and ⁷Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland

*To whom correspondence should be addressed. Dionysios Neofytos, MD, MPH, Service des Maladies Infectieuses, Hôpitaux Universitaires de Genève Rue Gabrielle-Perret-Gentil 4, CH-1211 Genève 14, Switzerland. Tel: +41 (0)22 372 9839; Fax: +41 (0)79 553 5156; E-mail: dionysios.neofytos@hcuge.ch

[†]See Appendix 1

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Abstract

There is a paucity of data on posaconazole (PCZ) dosing and therapeutic-drug-monitoring (TDM) in allogeneic hematopoietic cell transplant recipients (allogeneic-HCTr). This was a 3-year retrospective multicenter study (January 1, 2016 to December 31, 2018) in adult allogeneic-HCTr who received PCZ (intravenously, IV and/or as delayed-release tablet, DRT) as prophylaxis or treatment for ≥ 7 consecutive days (D) with at least 1-PCZ-level available using data of the Swiss Transplant Cohort Study. The primary objective was to describe the distribution of PCZ-level and identify predictors of therapeutic PCZ-level and associations between PCZ-dosing and PCZ-level. A total of 288 patients were included: 194 (67.4%) and 94 (32.6%) received PCZ as prophylaxis and treatment, respectively, for a median of 90 days (interquartile range, IQR: 42–188.5). There were 1944 PCZ-level measurements performed, with a median PCZ level of 1.3 mg/L (IQR: 0.8–1.96). PCZ-level was < 0.7 mg/L in 383/1944 (19.7%) and < 1.0 mg/L in 656/1944 (33.7%) samples. PCZ-level was < 0.7 mg/L in 260/1317 (19.7%) and < 1.0 mg/L in 197/627 (31.4%) in patients who received PCZ-prophylaxis versus treatment, respectively. There were no significant differences in liver function tests between baseline and end-of-treatment. There were nine (3.1%) breakthrough invasive fungal infections (bIFI), with no difference in PCZ levels between patients with or without bIFI. Despite a very intensive PCZ-TDM, PCZ-levels remain below target levels in up to one-third of allogeneic-HCTr. Considering the low incidence of bIFI observed among patients with PCZ levels in the targeted range, our data challenge the clinical utility of routine universal PCZ-TDM.

Key words: posaconazole, therapeutic drug monitoring, allogeneic hematopoietic cell transplant recipients, antifungal prophylaxis, antifungal treatment.

Introduction

Posaconazole (PCZ) has been approved for the prophylaxis of invasive fungal infections (IFI) in allogeneic hematopoietic cell transplant (HCT) recipients with graft-versus-host disease (GvHD) requiring treatment with high-dose steroids and can be used as salvage therapy for patients with invasive mold infections (IMI).¹⁻⁴ Posaconazole is available as an intravenously (IV) administered formulation, an oral (PO) suspension, and more recently, as a delayed-release tablet (DRT). Target PCZ target concentrations of 0.7 and 1.0 mg/L for prophylaxis and treatment, respectively, have been proposed and endorsed by international societies.^{5,6} Data on therapeutic drug monitoring (TDM) of PCZ-DRT obtained from a phase-3 prospective prophylaxis clinical trial using a maintenance dose of 300 mg once daily demonstrated a steady-state $C_{min} \geq 0.7$ mg/L in 90% of subjects.⁷ Similarly, small retrospective studies have shown that >90% of patients on the DRT formulation achieve target blood levels.⁸⁻¹¹

However, there is a paucity of data on PCZ dosing, TDM, and possible associations with efficacy and toxicity from well-described real-life paradigms. Furthermore, there are no well-defined guidelines to inform clinicians on dose adjustments required to achieve therapeutic PCZ concentrations. In clinical practice, incremental dose adjustments by 100 mg are commonly used with successful outcomes, most of the times.¹² We conducted a retrospective multicenter cohort study in allogeneic HCT recipients using data of the Swiss Transplant Cohort Study (STCS) to describe the PCZ dosing and TDM.

Methods

Study design and inclusion/exclusion criteria

The STCS is a multicenter cohort study prospectively enrolling >95% of allogeneic HCT recipients in all Swiss HCT-centers between 2009 and 2018.¹³ We performed a 3-year retrospective observational cohort study of all patients, who received PCZ between January 1, 2016 and December 31, 2018. All adult (≥ 18 years) allogeneic HCT recipients were included if they received PCZ (IV and/or DRT) as prophylaxis or treatment for a minimum of 7 consecutive days (D) with at least one PCZ level available post-D3 of PCZ administration. For patients who received >1 HCT and/or >1 PCZ courses, data were recorded only for the first allogeneic HCT and/or PCZ-course. Patients were excluded if they received PCZ suspension or PCZ-administration for <7 days and had no PCZ-level available by D3 of PCZ administration. All patients had signed an informed consent form to participate in the STCS. The study was approved by the relevant Ethics Committees.

Data collection

Participants were identified through the STCS and hospital-pharmacy databases. The following data were directly retrieved

from the STCS-database: demographics and HCT variables: date of HCT, conditioning, HCT source, donor/recipient (D/R) matching, D/R cytomegalovirus (CMV) serology, engraftment-day, and GvHD \geq grade-2. The following data were retrieved by chart-review: PCZ administration variables (dose, mode of administration, start/stop dates), PCZ-level values, laboratory data at baseline and by D7, 14, 28, 42, 84, end-of-treatment (EOT), and EOT + D14, including C-reactive protein (CRP), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ -GT), alkaline phosphatase (ALP), and glomerular filtration rate (GFR).

Definitions

The indication of PCZ intake was either prophylaxis or treatment and was defined based on the indication suggested by the treating physician, as noted in patient charts. For patients with a proven/probable IFI before HCT treated with PCZ, PCZ was considered (secondary) prophylaxis if IFI was diagnosed >100 days pre-HCT and as treatment if the diagnosis was made within 3 months prior to HCT. Proven and probable IFI were diagnosed based on revised consensus guidelines.¹⁴ Breakthrough proven/probable IFI (bIFI) was defined as an IFI diagnosed after ≥ 7 days of PCZ administration.¹⁵

Posaconazole TDM

PCZ TDM was performed with high-performance liquid chromatography-mass spectrometry (HPLC/MS) by Chromsystems Instruments & Chemicals (Gräfelfing, Germany) in all centers. There were no established protocols of PCZ TDM and dose adjustment at any of the three centers. Posaconazole TDM and subsequent dose changes were performed as clinically indicated. All centers used the same cutoffs of 0.7 and 1.0 mg/L as PCZ targets for prophylaxis and treatment, respectively.

Objectives

The primary objective was to describe the distribution of PCZ-level in a large contemporary cohort of allogeneic HCT recipients. Secondary objectives included the identification of (a) predictors of therapeutic PCZ-levels, (b) associations between PCZ-dosing and PCZ-level, (c) liver function abnormalities, and (d) bIFI during PCZ-administration.

Statistical analysis

Categorical variables were presented as absolute counts and percentages. Continuous variables were described by median, mean, range of values, and interquartile range (IQR), as appropriate. Categorical and continuous variables were compared with the Fisher's exact and a two-tailed Student's *t*-test, respectively.

Intraindividual and interindividual variability of PCZ concentration was assessed by calculating the median of the coefficient of variation (CV) of all the PCZ-level measured in a single patient and the CV of the average PCZ-level of each patient, respectively. Backward logistic regression analysis was completed on different data points to evaluate variables associated with therapeutic PCZ-concentrations. Variables with a *P*-value < .1 in univariable analyses were included in the multivariable models using backwards stepwise logistic regression. A two-sided *P*-value < .05 was considered statistically significant for all tests. Statistical analysis was performed using STATA 16.0 (StataCorp, College Station, TX).

Results

Patient population and PCZ administration

A total of 288 patients were included in this study: 194 (67.4%) received PCZ as prophylaxis (prophylaxis-group) and 94 (32.6%) as treatment (treatment-group). The baseline patient characteristics are detailed in Table 1. PCZ administration data are presented in Table 2. PCZ was started before and after HCT in 46 (16%) and 242 (84%) patients, respectively. A loading dose was administered in 160 (55.6%) patients. Initial maintenance treatment was administered orally (234, 81.3%) at a dose of 300 mg once daily (268, 93.1%) in the vast majority of patients. Patients received PCZ for a median of 90 days (IQR: 42–188.5): 85 and 140 days, in the prophylaxis and treatment groups, respectively (*P*-value = .06).

Posaconazole TDM

Overall patient population

There were 1944 PCZ-level measurements performed during the study period. The median number of tests per patient was 5 (IQR: 3–8), with a median PCZ-level of 1.3 mg/L (IQR: 0.8–1.96; Figure 1A). Intraindividual and interindividual variability of PCZ concentration was 57.0% and 65.0%, respectively. PCZ-level was <0.7 mg/L in 383/1944 (19.7%) and <1.0 mg/L in 656/1944 (33.7%) of all samples (Table 3). PCZ levels significantly increased from a median of 0.73 mg/L by D5 and 0.91 mg/L by D7 to a median of 1.06 mg/L by D14 (*P*-value < .001) and 1.40 mg/L by D28 (*P*-value < .001; Figure 1B). After D28, the median PCZ level remained stable between 1.35 and 1.50 mg/L without significant changes.

By indication

There were 1317 (67.7%) and 627 (32.3%) PCZ level tests in the PCZ prophylaxis group and treatment group, respectively (Figure 2A). The median number of tests per patient was 5 (IQR: 3–8) and 6 (IQR: 3–9) in the prophylaxis group and treatment group, respectively (*P*-value = .87). PCZ level was <0.7 mg/L in 260/1317 (19.7%) and <1.0 mg/L in 197/627 (31.4%, *P*-value =

.10) in the prophylaxis-group and treatment-group, respectively. Overall, the median PCZ-level was lower in patients who received PCZ-prophylaxis (1.26 mg/L, IQR: 0.8–1.85) versus treatment (1.50 mg/L, IQR: 0.8–2.25; *P*-value < 0.001; Figure 2B). There were no significant differences in PCZ levels between the prophylaxis-group and treatment-group between D7 and D180 of PCZ administration (Table 3).

Predictors of PCZ level ≥ 0.7 mg/L

Baseline ALT >100 IU/L (OR: 5.75, *P*-value = .02) was a significant predictor of PCZ level ≥ 0.7 mg/L by D7 of PCZ administration, while baseline GFR <100 mL/min/1.73 m² (odds ratio, OR: 0.48, *P*-value = 0.02) was negatively associated with PCZ level ≥ 0.7 mg/L by D7 (Supplementary Table S1). PCZ level ≥ 0.7 mg/L by D7 was the only and strongest predictor of PCZ-level ≥ 0.7 mg/L by D14 (OR: 4.93, *P*-value = .001; Supplementary Table S2).

PCZ administration changes

Initial maintenance treatment was administered at 300 mg once daily in 268 (93.1%) patients, followed by 400 mg (17, 5.9%) and 200 mg (3, 1%). By EOT, PCZ was administered at 100, 200, 300, 400, 500, 600, 1000 mg daily in 15 (5.2%), 28 (9.7%), 199 (69.1%), 30 (10.4%), 9 (3.1%), 6 (2.1%), and 1 (0.4%) patients, respectively, when compared to initial treatment (*P*-value = .07; Supplementary Figure S1a). PCZ dose and formulation remained unchanged in 112/288 (38.9%) patients throughout their course, whereas 21 (7.3%) and 155 (53.8%) underwent formulation change only and dose \pm formulation change, respectively (Supplementary Figure S1b).

PCZ administration changes and PCZ-TDM

Additional analyses were performed in order to describe the relationship between dose and/or formulation changes and PCZ-level. For those analyses, patients were included if the following data were available: (a) PCZ dose and formulation during the first 365 days, (b) PCZ-level before (± 1 days) and 7 (± 1) days after change in PCZ dose and/or formulation. A total of 139 patients with 240 doses/formulation changes and available PCZ-level were identified (Supplementary Table S3). There were 43 (17.9%), 116 (48.3%), and 81 (33.8%) sets of data for administration formulation-only changes, increasing, and decreasing doses, respectively.

Administration formulation-only changes

In 43 cases of formulation-only changes, the median PCZ-level before and after PCZ change was 0.81 mg/L (IQR: 0.51, 1.42) and 0.96 mg/L (IQR: 0.66, 1.50; *P*-value = 0.68), respectively.

Table 1. Baseline patient characteristics

	All patients N = 288 (%)	PCZ Prophylaxis N = 194 (%)	PCZ Treatment N = 94 (%)	P-value ¹
Demographics				
Age, Mean Years (SD; Range)	51.5 (14.2; 18–76)	51.6 (14.2; 18–76)	50.2 (14.2; 18–73)	.45
Gender, Female	106 (36.8)	72 (37.1)	34 (36.2)	.90
HCT characteristics				
HCT Donor				
Matched related	82 (28.5)	50 (25.8)	32 (34.0)	.14
Matched unrelated	145 (50.3)	106 (54.6)	39 (41.5)	
Mismatched unrelated	23 (8.0)	16 (8.3)	7 (7.5)	
Haploidentical	38 (13.2)	22 (11.3)	16 (17.0)	
HCT source				
Bone marrow	55 (19.1)	31 (16.0)	24 (25.5)	.10
Peripheral blood stem cells	232 (80.6)	162 (83.5)	70 (74.5)	
Cord blood	1 (0.3)	1 (0.5)	0	
Conditioning regimen, Myeloablative	131 (45.4)	103 (53.1)	91 (46.9)	.49
GvHD prophylaxis				
Cyclosporine, MMF	115 (40.0)	72 (37.1)	43 (45.7)	.03
Cyclosporine, Methotrexate	122 (42.4)	83 (42.8)	39 (41.5)	
Tacrolimus, Methotrexate	13 (4.5)	13 (6.7)	0	
Tacrolimus, MMF, Cyclophosphamide	38 (13.1)	26 (13.4)	12 (12.8)	
GvHD ≥ grade 2	144 (50.0)	118 (60.8)	26 (27.7)	<.001
Gastro-intestinal GvHD ≥ grade 2	78 (27.1)	67 (34.5)	11 (11.7)	<.001
CMV donor/recipient serology status				
D-R-	89 (30.9)	57 (29.4)	32 (34.0)	.37
D-R+	65 (22.6)	47 (24.3)	18 (19.2)	
D + R+	106 (36.8)	68 (35.0)	38 (40.4)	
D + R-	28 (9.7)	22 (11.3)	6 (6.4)	
Proven/Probable IFI prior to HCT	59 (20.5)	19 (9.8)	40 (42.6)	<.001
IFI, Median Days before HCT (IQR)	65 (36, 124)	136 (124, 217)	42 (26.5, 66)	<.001
Laboratory values at PCZ initiation				
ANC (mm ³ /mL), Median (IQR) ²	1.95 (0.5, 4.2)	1.9 (0.6, 4)	2.0 (0.23, 4.5)	.53
ALC (mm ³ /mL), Median (IQR) ³	0.37 (0.1, 0.9)	0.36 (0.1, 0.8)	0.46 (0.15, 1.2)	.26
GFR (mL/min/1.73m ²), Median (IQR) ⁴	92 (68, 108)	88 (65, 108)	98 (78, 112)	.13
AST (IU/l), Median (IQR) ⁵	23 (17, 35)	23 (17, 37)	23 (16, 35)	.99
ALT (IU/l), Median (IQR) ⁶	28.5 (18, 57.5)	30 (19, 61)	26 (18, 49)	.62
g-GT (IU/l), Median (IQR) ⁷	72 (41, 159)	81.5 (40, 155)	62 (41, 162)	.64
ALP (IU/l), Median (IQR) ⁸	84 (57, 126)	81.5 (56, 116)	87.5 (61.5, 149)	.67
Center				
Center 1	122 (42.4)	86 (44.3)	36 (38.3)	.002
Center 2	96 (33.3)	73 (37.6)	23 (24.5)	
Center 3	70 (24.3)	35 (18.1)	35 (37.2)	

PCZ, Posaconazole; SD, standard deviation; IQR, interquartile range; HCT, hematopoietic cell transplant; GvHD, graft-versus-host disease; MMF, mycophenolate mofetil; CMV, Cytomegalovirus; D, donor; R, recipient; IFI, invasive fungal infection; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IU, international unit.

¹P-value was calculated by t-test and chi-square test for continuous and categorical variables, respectively.

²Data on ANC were available for 226 patients in total: 152 and 74 in the prophylaxis and treatment groups, respectively.

³Data on ALC were available for 258 patients in total: 173 and 85 in the prophylaxis and treatment groups, respectively.

⁴Data on GFR were available for 273 patients in total: 181 and 92 in the prophylaxis and treatment groups, respectively.

⁵Data on AST were available for 258 patients in total: 177 and 81 in the prophylaxis and treatment groups, respectively.

⁶Data on ALT were available for 272 patients in total: 182 and 90 in the prophylaxis and treatment groups, respectively.

⁷Data on gGT were available for 213 patients in total: 152 and 61 in the prophylaxis and treatment groups, respectively.

⁸Data on ALP were available for 266 patients in total: 178 and 88 in the prophylaxis and treatment groups, respectively.

Table 2. Posaconazole administration data

PCZ variables	All patients N = 288 (%)	PCZ Prophylaxis N = 194 (%)	PCZ Treatment N = 94 (%)	P-value ¹
PCZ started before HCT	46 (16)	36 (18.6)	10 (10.6)	
Median days PCZ initiation before HCT (IQR)	12.5 (4, 110)	12 (3, 110)	25 (8, 63)	.86
PCZ started after HCT	242 (84)	158 (81.4)	84 (89.4)	
Median days PCZ initiation after HCT (IQR)	31.5 (15, 135)	35.5 (15, 145)	28.5 (15, 128)	.94
PCZ loading dose	160 (55.6)	103 (53.1)	57 (60.6)	.26
Mode of loading dose, IV	42/160 (26.2)	30/103 (29.1)	12/57 (24.1)	.35
PCZ maintenance dose				
Initial dose, PO	234 (81.3)	152 (78.4)	82 (87.2)	.08
Initial dose mg/day				.20
Initial dose < 300 mg daily	3 (1.0)	3 (1.6)	0	
Initial dose 300 mg daily	268 (93.1)	183 (94.3)	85 (90.4)	
Initial dose 400 mg daily	17 (5.9)	8 (4.1)	9 (9.6)	
Number of dose changes during course				.30
No dose/no mode changes	112 (38.9)	69 (35.6)	43 (45.7)	
No dose/mode changes	21 (7.3)	16 (8.2)	5 (5.3)	
≥1 dose ± mode changes	155 (53.8)	109 (56.2)	46 (49.0)	
PCZ duration				
Median days (IQR)	90 (42, 188.5)	85 (39, 164)	140 (55, 230)	
≥7 days	288 (100)	194 (100)	94 (100)	1.00
≥14 days	278 (96.5)	187 (96.4)	91 (96.8)	1.00
≥28 days	238 (82.6)	158 (81.4)	80 (85.1)	.51
≥42 days	217 (75.4)	144 (74.2)	73 (77.7)	.56
≥84 days	158 (54.9)	99 (51.0)	59 (62.8)	.08
≥100 days	134 (46.5)	81 (41.7)	53 (56.4)	.02
≥180 days	83 (28.8)	47 (24.2)	36 (38.3)	.02
≥365 days	22 (7.6)	13 (6.7)	9 (9.6)	.48

PCZ, Posaconazole; HCT, hematopoietic cell transplant; IV, intravenous; PO, oral; IQR, interquartile range.

¹P-value was calculated by t-test and chi-square test for continuous and categorical variables, respectively.

Dose increase

In 116 sets of available data, the median PCZ-level before and after PCZ dose-increase was 0.53 mg/L (IQR: 0.35, 0.70) and 0.96 mg/L (IQR: 0.60, 1.50; *P*-value < .001), respectively (Figure 3A). PCZ-level decreased (N: 21) or did not change (N: 1) in 22/116 (19%) and increased in 94 (81%) cases. Dose increases led to higher median post-change PCZ-level between 0.91 and 1.16 mg/L, with the highest median PCZ-level attained with a dose-increase of 50–67% (Figure 3B).

Dose decrease

In 81 sets of data with dose decrease, the median PCZ-level before and after PCZ change was 2.33 mg/L (IQR: 1.50, 3.10) and 1.63 mg/L (IQR: 0.93, 2.29; *P*-value < .001), respectively (Figure 3C). PCZ-level increased in 23 of 81 (28.4%) and decreased in 58 of 81 (71.6%) cases. The baseline median PCZ level was significantly higher in those patients who had a dose-decrease by 33% (2.60 mg/L, *P*-value = 0.001) and 50–67% (2.61 mg/L, *P*-value = 0.04) as compared to 20–25% (1.46 mg/L), respectively (Supplementary Table S4). Dose

decreases led to lower median post-change PCZ-level between 1.23 and 1.96 mg/L, with the lowest median PCZ-level achieved with a dose-decrease of 50–67% (Figure 3D).

Liver function tests

To assess the effect of PCZ on liver function, ALT, ALP, and γ -GT for all patients between baseline, end-of-treatment (EOT), and 14 days after EOT (EOT + 14) were compared (Supplementary Figure S2a–c). There were no significant differences in the median (IQR) between baseline, EOT, and EOT + 14 for (a) ALT (baseline-median: 28 IU/L, IQR: 18, 56 versus EOT-median: 38 IU/L, IQR: 23, 64; *P*-value = .12 vs EOT + 14-median: 35 IU/L, IQR: 22, 61; *P*-value = .81), (b) ALP (baseline-median: 86 IU/L, IQR: 57, 126 vs EOT-median: 87 IU/L, IQR: 60, 134; *P*-value: 0.53 versus EOT + 14-median: 92 IU/L, IQR: 61, 129; *P*-value: 0.19), and (c) γ -GT (baseline-median: 72 IU/L, IQR: 41, 159 vs EOT-median: 78 IU/L, IQR: 38, 176; *P*-value = .70 vs EOT + 14-median: 66 IU/L, IQR: 31, 155; *P*-value = .10).

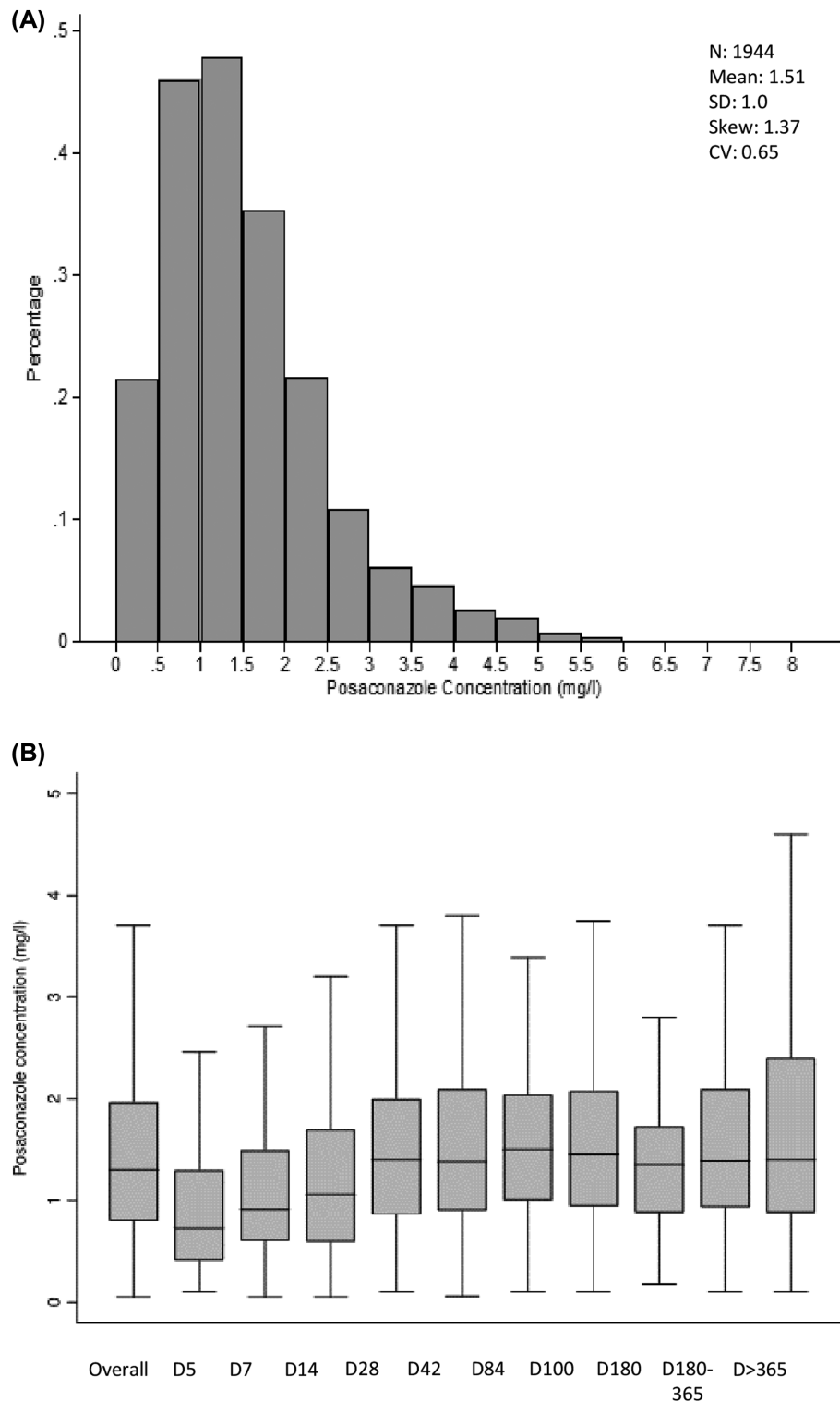


Figure 1. (A) Histogram demonstrating the distribution of posaconazole blood concentrations in the overall cohort. (B) Box-plots of posaconazole blood concentrations on predefined time points of posaconazole administration. Boxes represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within the interquartile range. Outliers are not shown. Significant *P*-values calculated by unpaired t-test for the mean values between different time-points for all patients are presented below: D5 to D14: .004, D5 to D28: <.001, D5 to D42: <.001, D5 to D84: <.001, D5 to D100: <.001, D5 to D180: .003, D5 to D180-365: <.001, D5 to D>365: <.001, D7 to D28: <.001, D7 to D42: <.001, D7 to D84: <.001, D7 to D100: <.001, D7 to D180-365: <.001, D7 to D > 365: <.001, D14 to D28: <.001, D14 to D42: <.001, D14 to D84: .002, D14 to D100: .003, D14 to D180-365: <.001, D14 to D > 365: <.001.

Table 3. Posaconazole mean/median values in the overall cohort and based on indication (prophylaxis versus treatment) of administration at predefined time-points

	Overall	D5	D7	D14	D28	D42	D84	D100	D180	D 180–365	D > 365
All patients¹											
Mean (SD) ²	1.50 (1.0)	0.92 (0.8)	1.12 (0.8)	1.23 (0.8)	1.59 (1.0)	1.59 (1.0)	1.58 (0.9)	1.61 (0.9)	1.39 (0.7)	1.63 (1.0)	1.83 (1.2)
Median	1.30	0.73	0.91	1.06	1.40	1.38	1.50	1.45	1.35	1.39	1.40
IQR	0.80, 1.97	0.40, 1.30	0.60, 1.50	0.59, 1.70	0.86, 2.00	0.90, 2.10	1.00, 2.04	0.90, 2.08	0.88, 1.73	0.93, 2.10	0.88, 2.40
Range	0.05, 8.28	0.10, 4.60	0.05, 4.10	0.05, 3.97	0.10, 5.49	0.06, 4.51	0.10, 4.20	0.10, 4.30	0.18, 3.15	0.10, 5.10	0.10, 5.00
Tests N	1944	86	125	186	155	122	82	62	31	285	83
Prophylaxis¹											
Mean (SD)	1.44 (0.9)	1.01 (0.8)	1.11 (0.8)	1.21 (0.8)	1.54 (0.9)	1.60 (1.0)	1.53 (0.9)	1.51 (0.9)	1.32 (0.6)	1.46 (0.9)	1.66 (1.1)
Median	1.26	0.90	0.90	1.06	1.40	1.38	1.40	1.40	1.35	1.30	1.40
IQR	0.80, 1.85	0.51, 1.30	0.60, 1.40	0.59, 1.70	0.90, 1.80	0.89, 2.11	0.93, 2.02	0.85, 2.00	0.90, 1.70	0.87, 1.90	0.73, 2.19
Range	0.05, 8.28	0.10, 4.60	0.05, 4.10	0.50, 3.97	0.20, 4.30	0.06, 4.32	0.10, 4.20	0.10, 4.39	0.18, 2.50	0.10, 4.90	0.10, 4.90
Tests N	1317	57	87	132	101	84	60	40	21	189	51
C < 0.7 N (%)	260 (19.7)	23 (40.4)	30 (34.5)	41 (31.1)	10 (9.10)	12 (14.3)	2 (9.10)	6 (15.0)	3 (14.3)	31 (16.4)	9 (17.7)
Treatment¹											
Mean (SD)	1.66 (1.1)	0.72 (0.7)	1.13 (0.7)	1.26 (0.9)	1.67 (1.2)	1.56 (0.8)	1.71 (0.9)	1.80 (1.0)	1.53 (0.9)	1.98 (1.2)	2.1 (1.4)
Median	1.5	0.72	1.04	1.04	1.46	1.35	1.65	1.80	1.32	1.62	1.68
IQR	0.8, 2.25	0.29, 1.00	0.54, 1.55	0.57, 1.70	0.70, 2.30	0.97, 1.92	1.14, 2.10	1.10, 2.20	0.72, 2.10	1.12, 2.86	1.08, 3.15
Range	0.05, 6.80	0.10, 2.66	0.10, 2.60	0.05, 3.80	0.10, 5.49	0.20, 4.51	0.29, 3.80	0.10, 4.30	0.51, 3.15	0.10, 5.10	0.10, 5.00
Tests N	627	29	38	54	54	38	22	22	10	96	32
C < 1.0 N (%)	197 (31.4)	21 (72.4)	19 (50.0)	26 (48.2)	20 (37.0)	10 (26.3)	3 (13.6)	4 (18.2)	3 (30.0)	18 (18.8)	7 (21.9)
P-value ³	<0.001	0.10	0.88	0.74	0.48	0.85	0.41	0.24	0.43	<0.001	0.11

D: Day, SD: Standard deviation, IQR: Interquartile Range, N: Number, C: Concentration.

D 5, 7, 14, 28, 42, 84, 100, 180, 180–365, and > 365: Posaconazole concentration by day 5, 7 + 2, 14 ± 2, 28 ± 2, 42 ± 2, 84 ± 2, 100 ± 5, 180 ± 5, 180–365, >365 of PCZ administration, respectively.

¹Values represent posaconazole concentration measured in mg/L.

²P-values were calculated by unpaired t-test for the mean values between different time-points for all patients are presented below: D5 to D7: .06, D5 to D14: .004, D5 to D28: <.001, D5 to D42: <.001, D5 to D84: <.001, D5 to D100: <.001, D5 to D180: .003, D5 to D180-365: <.001, D5 to D > 365: <.001, D7 to D14: .24, D7 to D28: <.001, D7 to D42: <.001, D7 to D84: <.001, D7 to D100: <.001, D7 to D180: .08, D7 to D180-365: <.001, D7 to D > 365: <.001, D14 to D28: <.001, D14 to D42: <.001, D14 to D84: .002, D14 to D100: .003, D14 to D180: .32, D14 to D180-365: <.001, D14 to D > 365: <.001, D28 to D42: .99, D28 to D84: .96, D28 to D100: .88, D28 to D180: .29, D28 to D180-365: .63, D28 to D > 365: .11, D42 to D84: .96, D42 to D100: .87, D42 to D180: .27, D42 to D180-365: .65, D42 to D > 365: .12, D84 to D100: .84, D84 to D180: .26, D84 to D180-365: .65, D84 to D > 365: .14, D100 to D180: .24, D100 to D180-365: .86, D100 to D > 365: .25, D180 to D180-365: .19, D180 to D > 365: .16.

³P-value were calculated by unpaired t-test for the mean values between Prophylaxis- and Treatment-groups at different timepoints.

Breakthrough IFI

There were nine proven/probable bIFIs in the cohort for an incidence of 3.1%, all diagnosed after at least 14 days of posaconazole administration. There were two cases of candidemia due to *C. glabrata* and one case of hepatosplenic candidiasis. Six cases of IMI were diagnosed: two proven (one mixed due to *Rhizomucor pusillus* and *Rhizopus* spp. and one due to *Aspergillus ustus*) and four probable (two due to *Aspergillus* spp., one due to *Rhizomucor pusillus* and one due to an unidentified mold). There was no significant difference in the number of bIFIs between the prophylaxis-group (7/194, 3.6%) and the treatment-group (2/94, 2.1%; *P*-value: 0.72). Duration of PCZ administration was similar between patients with bIFI (mean: 90.8 days, SD: 22.4, median: 86 days, range: 14–195) and no bIFI (mean: 147 days, SD: 152.5, median: 91 days, range: 8, 865; *P*-value: 0.27). There was no difference in the overall PCZ-level mean values between patients with (1.32 mg/L, SD: 0.48, range: 0.4, 1.9) and without (1.47 mg/L, SD: 0.74, range: 0.1, 4.2) bIFI (*P*-value = .55). Patients with bIFI had a median of 3 (range: 1, 13) PCZ-TDM performed prior to bIFI diagnosis. The median PCZ-level before bIFI for all nine patients was 1.31 mg/L (range: 0.4, 1.68). PCZ level was available for all nine

cases at a median of 4 days (range: 0–46) before the bIFI was diagnosed. The median of the most recent PCZ level before bIFI diagnosis was 1.1 mg/L (range: 0.4, 1.56). Except for one patient with a PCZ level at 0.4 mg/L measured 9 days prior to bIFI diagnosis, all other patients had a PCZ level between 0.97 and 1.56 mg/L.

Discussion

In this retrospective study with one of the largest contemporary collections of PCZ IV and DRT administration and associated blood concentrations, we observed PCZ levels below the target concentrations in 20–30% of cases, as previously reported.^{1,7,8,16–19} More than half of the patients required at least one dose-change, as a response to suboptimal PCZ-levels leading to dose adjustments. In contrast to baseline, when almost all patients received a maintenance dose of 300 mg daily, a large variability of PCZ dose, between 100 and 1000 mg daily, was observed in one-third of patients by EOT. These data suggest that although a universal maintenance dose of 300 mg daily may still be applicable in the large majority of allogeneic HCT recipients, there remains a substantial group of patients requiring dose adjustments in real life.

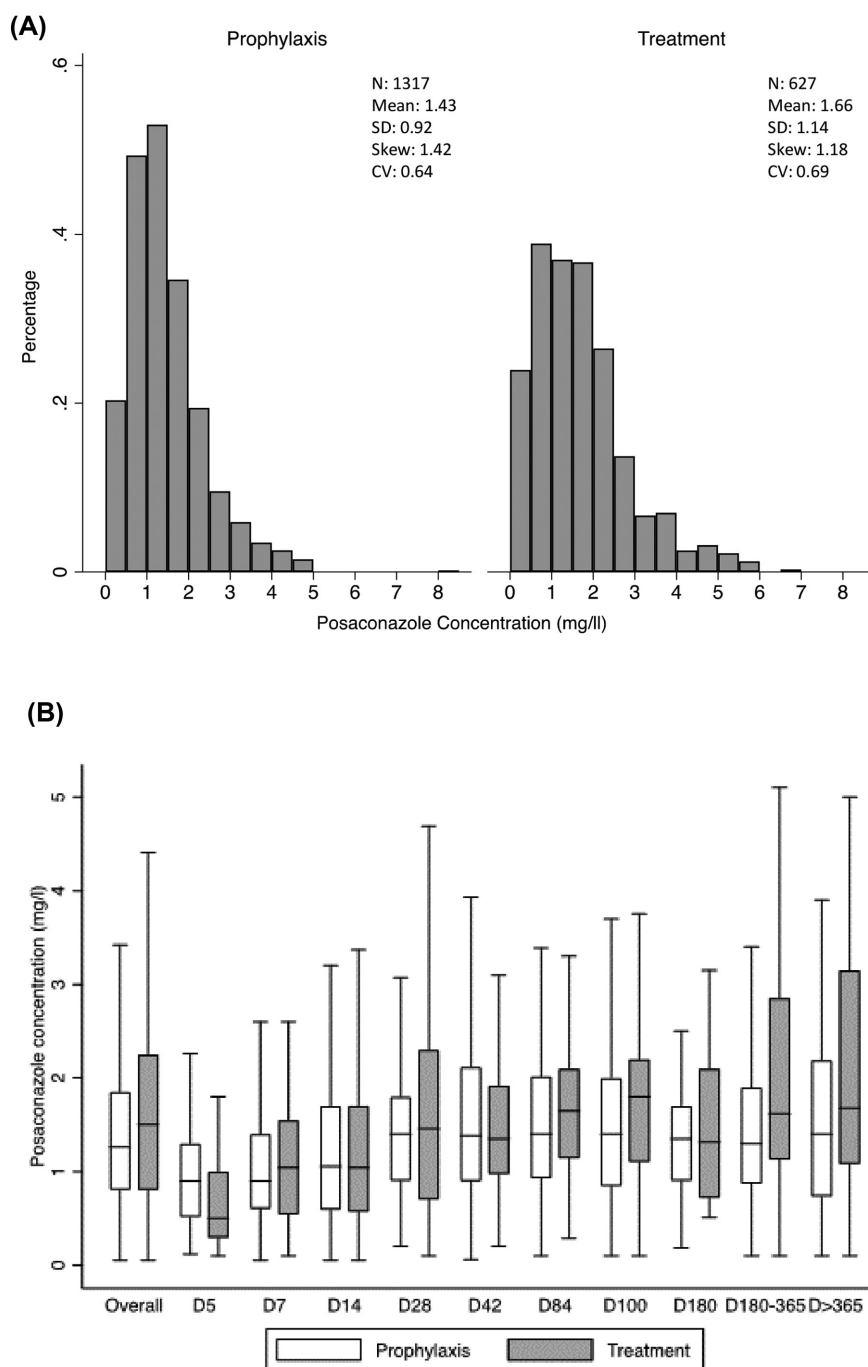


Figure 2. (A) Histogram demonstrating the distribution of posaconazole blood concentrations by indication: prophylaxis versus treatment. (B) Box-plots of posaconazole blood concentrations on predefined time points of posaconazole administration by indication: prophylaxis versus treatment. Boxes represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within the interquartile range. Outliers are not shown.

Dose-changes were associated with variable effects on PCZ-levels. In up to one-third of cases a dose change was followed by a counteractive effect, pointing out that dose changes do not always lead to the expected PCZ-level changes. Most dose changes observed in this study were in the range of 20–35%: for instance for a patient receiving 300 mg daily, an increase to 400 mg would be a dose-increase of 33%, while, for a patient receiving

400 mg daily, a decrease to 300 mg would be a dose-decrease of 25%. PCZ-dose increases by 100 mg-increments have been associated with satisfactory PCZ-level elevation.¹² While sufficient in a number of patients, more robust dose changes were frequently required to attain target PCZ levels in this study. Clearly, more data are needed to better appreciate the association and effect of PCZ-dose changes on PCZ levels.

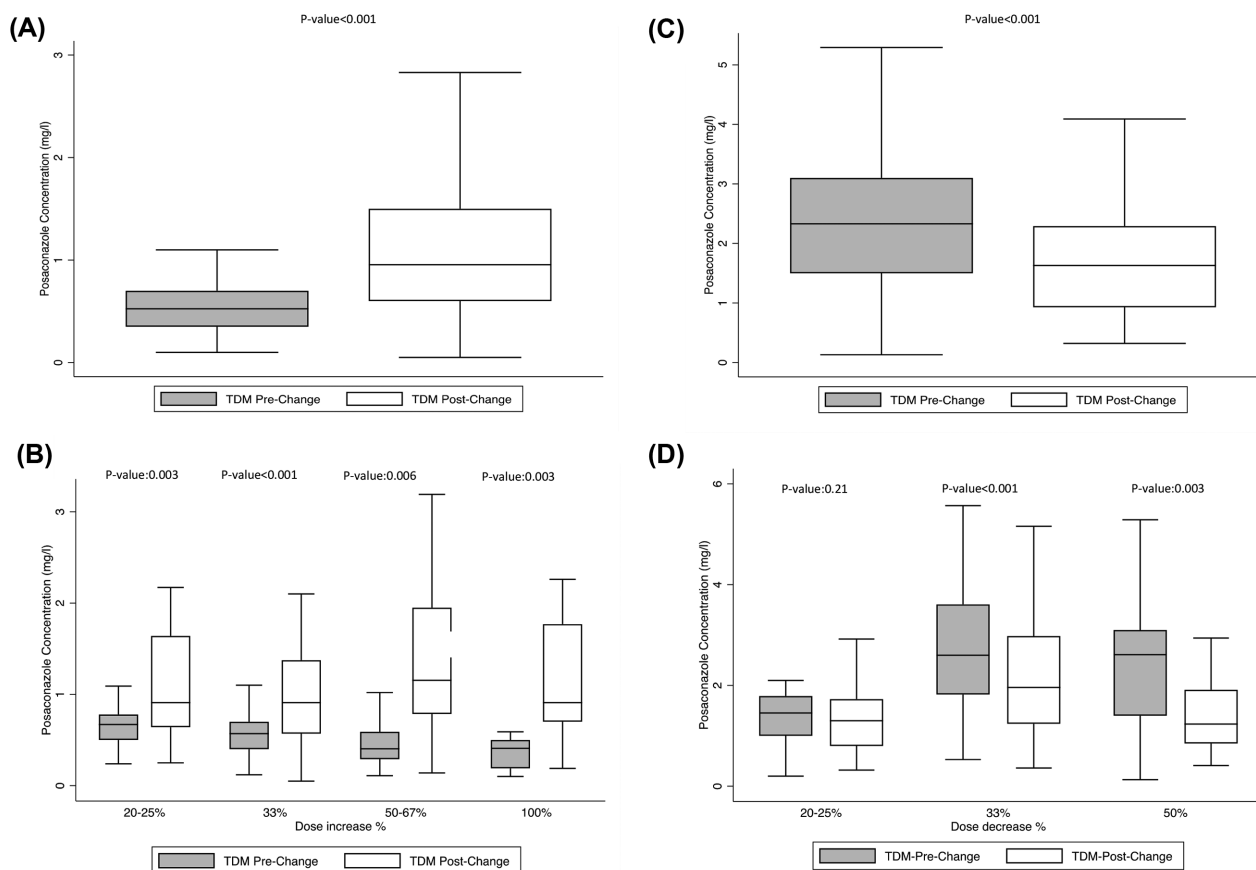


Figure 3. (A) Distribution of posaconazole blood concentrations in patients with dose increases. (B) Distribution of posaconazole blood concentrations in patients with dose increases by percentage of dose increase-categories. (C) Distribution of posaconazole blood concentrations in patients with dose decreases. (D) Distribution of posaconazole blood concentrations in patients with dose decreases by percentage of dose increase-categories. Boxes in Figures 3 a, b, c, and d represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within the interquartile range. Outliers are not shown.

More liberal dose increases may lead to higher rates of hepatotoxicity, frequently reported in patients treated with azoles.^{20–22} However, liver impairment was reported in only 3% of patients enrolled in the pivotal PCZ-prophylaxis clinical trials and no direct associations between PCZ dose and/or PCZ levels and hepatotoxicity have been demonstrated in pooled analyses.^{1,19,23} Similarly, our data did not show any significant differences in liver function between baseline, EOT, and even by 14 days post-EOT. This may reflect the rather normal baseline liver function in the vast majority of patients, modest effect of PCZ on liver function, or represent selection biases: patients with mild to modest liver function test changes during PCZ-administration might have been more likely to sustain PCZ dose changes or transition to another agent, before a significant change was noted.

A small number of bIFI was observed for an overall incidence of approximately 3%, consistent with prior reported rates.^{1,19,24} The low rate of bIFI may be explained by the overall higher PCZ concentrations observed in this study, with a median PCZ-level at 1.3 mg/L, higher than 0.49–0.91 mg/L observed in the PCZ-prophylaxis trials.^{1,19,25,26} Notably, all but one, patients with

bIFI had a PCZ level >0.7 mg/L shortly before the diagnosis of their breakthrough infection.

Target PCZ concentrations of 0.7 and 1.0 mg/L for prophylaxis and treatment, respectively, have been proposed based on post hoc analyses on the exposure-response relationship between PCZ levels and effective IFI prophylaxis, using a composite endpoint of clinical response, in which most cases represented patients who discontinued PCZ prophylaxis for empirical antifungal treatment initiation without confirmation of an IFI.⁵ Whether a certain PCZ blood concentration is associated with lower rates of IMI remains largely unknown.^{6,27,28} Similarly, the importance of plasma target PCZ concentrations to assure a clinical effect as opposed to adequate PCZ distribution in target tissues is unclear.²³ This is pertinent information for PCZ, a highly protein-bound compound, with multiple-fold higher concentrations in intracellular compartments, including alveolar cells, monocytes and polymorphonuclear cells, as compared to plasma.^{29–33} Furthermore, the optimal pharmacokinetic/pharmacodynamic parameters to measure antifungal treatment effect have not –as yet– been well defined.^{34,35} The above suggests that while plasma

PCZ-TDM is a useful tool, it may not necessarily be the best surrogate marker of PCZ clinical efficacy. This study was not designed neither powered to assess the clinical utility of PCZ-TDM or the efficacy of PCZ prophylaxis/treatment. However, considering the time, effort and costs invested on PCZ-TDM and dose adjustments based on our observations, low incidence of bIFI, and lack of relevant robust data the question on the utility and clinical significance of universal blood PCZ-TDM may need to be revisited with dedicated clinical trials in the future.³⁶ Notably, our findings contrast the results of a recently published modeling study, which suggested a potential benefit of routine PCZ-TDM in patient populations with a higher prevalence of subtherapeutic PCZ concentrations.³⁷ More data to better clarify the optimal PCZ-TDM and target levels are required.

This study has several limitations, including its retrospective observational nature, lack of data on gastrointestinal symptoms and concomitant medication administration, and unavailability of consistent PCZ-TDM, particularly associated with PCZ-dose changes. There were no standardized protocols in place in none of the three centers to perform PCZ TDM. Hence selection bias might have occurred, as patients with more frequent TDM could have been perceived at higher risk for subtherapeutic levels by the treating physician. However, the large number of patients and PCZ-TDM performed in this study have allowed for in-depth analyses of the PCZ-TDM distribution. In conclusion, our data suggest that despite appropriate dosing and close PCZ-TDM, PCZ-levels remain below target for a significant proportion of patients, requiring multiple dose adjustments with not always predictable outcomes. Future studies are required to assess the clinical utility of intensive PCZ-TDM and PCZ dose adjustments in select patient populations.

Supplementary material

Supplementary data are available at [MMYCOL](https://www.mycologyjournal.com) online.

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Declaration of interest

N.K. has received research support from MSD and Pfizer and consulting fees from MSD, Pfizer, Basilea, and Gilead.

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APPENDIX 1

The members of the Swiss Transplant Cohort Study are: Patrizia Amico, Andres Axel, John-David Aubert, Vanessa Banz, Beckmann Sonja, Guido Beldi, Christian Benden, Christoph Berger, Isabelle Binet, Pierre-Yves Bochud, Sanda Branca, Heiner Bucher, Thierry Carrel, Emmanuelle Catana, Yves Chalandon, Sabina de Geest, Olivier de Rougemont, Michael Dickenmann, Joëlle Lynn Dreifuss, Michel Duchosal, Thomas Fehr, Sylvie Ferrari-Lacraz, Alexander Leichtle, Christian Garzoni, Paola Gasche Soccac, Christophe Gaudet, Emiliano Giostra, Déla Golshayan, Karine Hadaya, Jörg Halter, Dimitri Hauri, Dominik Heim, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Michael Koller (Head of the data center), Bettina Laesser, Brian Lang, Roger Lehmann, Christian Lovis, Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Michele Martinelli, Katell Mellac, Pascal Meylan, Aurélie Merçay, Karin Mettler, Nicolas Mueller (Chairman Scientific Committee), Antonia Müller, Thomas Müller, Ulrike Müller-Arndt, Beat Müllhaupt, Mirjam Nägeli, Manuel Pascual (Executive office), Klara Posfay-Barbe, Juliane Rick, Anne Rossetlet, Simona Rossi, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Federico Simonetta, Katharina Staufer, Jürg Steiger (Head, Executive office), Guido Stirniman, Christian Toso, Christian Van Delden (Executive office), Jean-Pierre Venetz, Jean Villard, Madeleine Wick (STCS coordinator), Markus Wilhlem, Patrick Yerly.