Received: 3 March 2021 | Revised: 19 May 2021 | Accepted: 30 May 2021

DOI: 10.1111/tid.13675

ORIGINAL ARTICLE

WILEY

Comparing posaconazole and itraconazole for antifungal prophylaxis in critically ill lung transplant recipients: Efficacy and plasma concentrations

Simon Kallee[1] | Christina Scharf[1] | Ines Schroeder[1] | Michael Paal[2] | Michael Vogeser[2] | Michael Irlbeck[1] | Johannes Zander[3] | Michael Zoller[1] | Jette Jung[4] | Nikolaus Kneidinger[5] | Christian Schneider[6] | Sebastian Michel[7] | Uwe Liebchen[1]

[1]Department of Anesthesiology, University Hospital, LMU Munich, Munich, Germany

[2]Institute of Laboratory Medicine, University Hospital, LMU Munich, Munich, Germany

[3]Laboratory Dr. Brunner, Konstanz, Germany

[4]Max-von-Pettenkofer-Institute Munich, Ludwig Maximilian University, Munich, Germany

[5]Department of Internal Medicine V, University Hospital, LMU Munich, Comprehensive Pneumology Center (CPC-M), Member of the German Center for Lung Research (DZL), Munich, Germany

[6]Department of Thoracic Surgery, University Hospital, LMU Munich, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Munich, Germany

[7]Department of Cardiac Surgery, University Hospital LMU Munich, Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Munich, Germany

Correspondence
Uwe Liebchen, Department of Anesthesiology, University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany.
Email: uwe.liebchen@med.uni-muenchen.de

Funding information
This work was funded by institutional sources. UL acknowledges research funding

Abstract

Background: Posaconazole and itraconazole are commonly used for systemic antifungal prophylaxis after lung transplantation. The aim of this study on critically ill lung transplant recipients was to assess the rate of adequate plasma concentrations and the frequency of fungal-induced transitions from antifungal prophylaxis to therapy after the administration of either posaconazole or itraconazole for systemic prophylaxis.

Methods: Critically ill lung transplant recipients with postoperative posaconazole or itraconazole prophylaxis and therapeutic drug monitoring from February 2016 to November 2019 were retrospectively included in the study. Positive fungal cultures or *Aspergillus* antigen tests resulting in a transition from antifungal prophylaxis to therapy were analyzed from the first day of prophylaxis until 7 days after the last sample for each patient. Adequate plasma concentrations were defined as ≥500 μg/L for itraconazole and ≥700 μg/L for posaconazole.

Results: Two hundred seventy-five samples from 73 patients were included in the analysis. Overall, 60% of the posaconazole and 55% of the itraconazole concentrations were subtherapeutic. Administration of posaconazole suspension resulted significantly ($P < .01$) more often in subtherapeutic concentrations than tablets (68% vs 10%). Patients treated with posaconazole showed less positive fungal records resulting in a transition from prophylaxis to therapy than patients treated with itraconazole (10% vs 33%, *P*-value: .029). The detection of a fungal pathogen was not associated with the measured plasma concentrations or the achievement of the target concentrations.

Conclusion: Our findings suggest that posaconazole should be used instead of itraconazole for systemic prophylaxis in critically ill lung transplant recipients.

Simon Kallee and Christina Scharf contributed equally to this work.

from the Munich Clinician-Scientist Program (Ludwig-Maximilians-Universität München).

KEYWORDS
antifungal prophylaxis, critically ill, itraconazole, lung transplant, posaconazole, therapeutic drug monitoring

1 | INTRODUCTION

Fungal infections remain a challenge in immunocompromised patients, such as lung transplant recipients. Approximately 8%-19% of the lung transplant recipients develop a fungal infection, and the mortality rate is up to 60%.[1–4]

Lung transplant recipients receive immunosuppressants to reduce the risk of an allograft rejection. However, immunosuppression increases the risk of a fungal infection, with *Aspergillus* spp. and *Candida* spp. being the most frequently observed pathogens.[1] Consequently, lung transplant recipients need an effective antifungal prophylaxis. The Infectious Diseases Society of America recommended the use of triazoles or inhalative amphotericin B as prophylaxis for 3 to 4 months after lung transplantation.[5] A recent survey in 62 transplant centers in the United States identified the two triazoles posaconazole and itraconazole as the most commonly used drugs administered for systemic prophylaxis in lung transplant recipients.[6] The antifungal activity of posaconazole and itraconazole includes yeasts (eg, *Candida* spp.) and *Aspergillus* spp.[1]

Critically ill patients are, in general, due to pharmacokinetic alterations (eg, an increased volume of distribution), at risk of suboptimal drug exposure with standard dosing.[7] Previous studies showed indeed a high variability and subtherapeutic concentrations of itraconazole and posaconazole in this population.[8,9] In addition, there have been several drug–drug interactions reported in previous studies for azoles. For example, proton pump inhibitors (PPI), metoclopramide, and rifampicin lower drug concentrations, whereas macrolide antibiotics, amiodaron, ciprofloxacin, and some antiviral drugs raise the azole plasma concentration.[3,10,11] However, critically ill lung transplant recipients depend on an effective prophylaxis, as they have a high risk to develop a fungal infection, because the allograft is exposed to the environment and high steroid doses are administered; catheters further increase the risk of a fungal infection.[1,12,13] As a result, therapeutic drug monitoring (TDM) is recommended for both drugs.[8,14-16] The British Society of Mycology recommended a target concentration in steady state of ≥500 µg/L for itraconazole and ≥700 µg/L for posaconazole as prophylaxis. Lower azole plasma levels were associated with a higher mortality.[2,15,17]

In our intensive care unit (ICU) at the LMU hospital in Munich, either itraconazole or posaconazole is administered at the discretion of the responsible physician as antifungal prophylaxis in the postoperative period of lung transplant recipients. TDM is regularly performed.

Previous studies investigated antifungal prophylaxis mainly in patients with hematologic malignancies, neutropenic patients, or non-critically ill lung transplant recipients in general wards.[2,3,18–20] This retrospective study in critically ill lung transplant patients aimed to compare the rate of adequate plasma concentrations after posaconazole or itraconazole administration as systemic prophylaxis in critically ill lung transplant recipients and the frequency of fungal-induced transitions from prophylaxis to targeted therapy (FITPTs).

2 | MATERIAL AND METHODS

2.1 | Study setting

This was a monocentric, retrospective study evaluating antifungal prophylaxis with itraconazole tablet (Itraconazol 100 mg, ratiopharm®), posaconazole suspension (Noxafil® 40 mg/mL suspension, MSD), and posaconazole tablet (Noxafil® 100 mg tablets, MSD) at the anesthesiologic ICU of the LMU hospital in Munich, from February 2016 to November 2019. The local institutional review board approved the study (registration number 20-168).

2.2 | Laboratory measurements and data collection

All clinical-chemical parameters were extracted from electronic patient records. The azole plasma concentrations were measured with an isotope-dilution liquid chromatography tandem mass spectrometry method using a commercially available IVD kit (Chromsystems, Gräfelfing, Germany). All measured values of antimycotic plasma concentrations, corresponding doses, and additional laboratory measurements including albumin, aspartate-aminotransferase, alanine-aminotransferase, bilirubin, creatinine, the glomerular filtration rate (GFR) calculated according to the Chronic Kidney Disease Epidemiology Collaboration, C-reactive protein (CRP), and Interleukin 6 (IL-6) were collected.[21] The Simplified Acute Physiology Score II was assessed at the first day of the azole use.[22]

2.3 | Study population

All itraconazole and posaconazole plasma concentrations of lung transplant recipients in the immediate postoperative period measured between February 2016 and November 2019 were screened for inclusion. Inclusion criteria of the study were as follows:

- itraconazole treatment for at least seven consecutive days prior to measurement

or

- posaconazole treatment for at least five consecutive days prior to measurement.

After this time, a steady state was assumed as described in the literature.[3,15,23] Multiple samples per patient were included when available. The patients with posaconazole treatment were divided into two groups (Group 1: suspension; Group 2: tablets). If patients received suspension or tablet formulations, the sample was assigned to one of the groups if the patient received the same formulation more than 90% of the time within the 5 days prior to the sample. Samples with less than 90% of the same formulation 5 days prior to the sample were excluded from the analysis. The standard procedure of our ICU allows the responsible physician to choose between posaconazole and itraconazole as prophylaxis and to adapt the dosage regimen. Therapeutic drug monitoring of plasma concentrations is performed once a week, screening for fungal infections (swabs, endotracheal aspirate/sputum analysis) twice a week.

2.4 | Fungal-induced transition from prophylaxis to therapy

Positive fungal cultures (*Candida* spp. or *Aspergillus* spp.) or *Aspergillus* antigen tests resulting in a transition from prophylaxis to antifungal therapy within 7 days after the positive record were defined as an FITPT. The decision to switch from prophylaxis to therapy is reached at our center as a team approach including the attending intensive care physician, an infectiologist, a microbiologist, and a radiologist. Fungal cultures and *Aspergillus* antigen tests were analyzed from the day of the first azole dose until 7 days after the last sample for each patient.[24,25] Galactomannan antigen testing from the patient's serum was performed twice a week using the Bio-Rad Laboratories Platelia Aspergillus EIA (Bio-Rad Laboratories, Feldkirchen, Germany) according to the manufacturer's instructions. Positive and negative cut-off controls were included in each run. Threshold for positivity was an optical density (OD) index of >0.5. For all positive samples, the test was repeated with a second aliquot and considered positive only if both tests showed an OD index of >0.5. BAL/endotracheal aspirate fluid samples were tested analogously, and OD indices >1/4.5 were defined positive. Fungal cultures were performed weekly on Sabouraud-Dextrose-Agar incubated at 35°C for 7 days. Any growing molds were identified by MALDI-TOF mass spectrometry. Patients with a prior antifungal treatment were excluded from the analysis.

2.5 | Covariates

The existing literature was screened for potential influencing co-medications. We identified PPI, immunosuppressants (tacrolimus and ciclosporin), cytochrome P450 inhibitors (ciprofloxacin, isoniazid, clarithromycin, and erythromycin), cytochrome P450 inductors (glucocorticoids, rifampicin, carbamazepine, and barbiturate), norepinephrine, and amiodaron as potential influencing co-medication for itraconazole. For posaconazole, we included PPI, norepinephrine, H2 antagonists (ranitidine and cimetidine), and phase-2 enzyme inhibitors and inductors including ciclosporin, erythromycin, carbamazepine, phenytoin, and rifampicin. All co-medications that might influence the antimycotic plasma concentrations were collected from our hospital's electronic patient records. The norepinephrine dose was evaluated at each timepoint when the patients received the azole.[3,11,20,26,27] The type of food intake was divided in four categories: no food (1), tube feeding (2), normal food (3), and tube feeding + normal food (4). Protein drinks were included in the tube feeding group.

2.6 | Definition of target attainment

Target attainment was defined as recommended by the British Society of Mycology and in accordance with the previously published literature. Trough concentrations of ≥500 μg/L for itraconazole[15,17,28,29] and of ≥700 μg/L for posaconazole were defined as target concentrations.[3,15,20]

2.7 | Statistical analysis

Statistical analysis was performed using R (R version 4.02, CRAN.R-project.org). To analyze the effects of the covariates on the azole plasma concentrations, a linear mixed effect model was used. Effects were considered significant with a *P*-value ≤ .05. To decrease the risk of a Type I error, the *P*-value was corrected using the false discovery rate method.[30]

Age, height, weight, and body mass index were evaluated on ID level, whereas CRP, GFR, IL-6 bilirubin, albumin, norepinephrine, PPI, cytochrome p450 inhibitors and inductors, H2 antagonists, phase 2 inhibitors, and nutrition were evaluated on a sample level. A linear mixed effect model was used to compare the plasma concentration difference between posaconazole suspension and posaconazole tablet. To compare the probability of an FITPT between itraconazole and posaconazole, Fisher's exact test was used.

3 | RESULTS

A total of 275 samples from 73 patients were included in the analysis. Forty-nine patients were treated with itraconazole (median: two samples per patient, range 1-14), and 31 patients were treated with posaconazole (median: three samples per patient, range 1-28). Seven patients received itraconazole and posaconazole one after the other during the observed period and were therefore included twice in the analysis. Table 1 shows the patient characteristics. The most frequent underlying disease leading to lung transplantation

TABLE 1 Patient characteristics

	Overall n (%)	Itraconazole n (%)	Posaconazole tablets n (%)	Posaconazole suspensions n (%)
No. of patients	73[a]	49[a]	5[a]	27[a]
No. of samples	275	117	21	137
Gender (male/female)	44 (60)/29 (40)	32 (61)/19 (39)	3 (60)/2 (40)	16 (59)/11 (41)
Cystic fibrosis	13 (18)	3 (6)	4 (80)	6 (22)
COPD	16 (22)	12 (24)	1 (10)	4 (15)
Pulmonary fibrosis	33 (45)	26 (53)	0 (0)	12 (44)
Other underlying disease	11 (15)	8 (16)	0 (0)	5 (19)
Single lung transplantations	9 (12)	7 (14)	0 (0)	2 (7)
Re-transplantations	2 (3)	1 (2)	1 (20)	0 (0)
Mortality	6 (8)	3 (6)	0 (0)	4 (15)
	Median (range)	**Median (range)**	**Median (range)**	**Median (range)**
Age (y)	56 (16-68)	56 (25-68)	30 (26-52)	55 (16-67)
BMI (kg/m^2)	23.0 (13.0-31)	22 (16-31)	20 (15-25)	24 (13-31)
SAPS II[b]	41 (14-91)	42 (21-91)	29 (25-44)	44 (14-91)
IL-6 (pg/mL)	16.9 (1.5-5307)	14 (2.2-5307)	12.1 (3.7-331)	24.2 (1.5-429)
CRP (mg/dL)	0.1 (0.1-33.4)	1.3 (0.1-20.8)	1.0 (0.1-33.4)	3.3 (0.1-27)
Creatinine (mg/dL)	0.9 (0.2-2.9)	0.85 (0.2-2.8)	1.2 (0.8-2.9)	0.9 (0.3-2.5)
GFR-CKD-Epi (mL/min)	97 (24-160)	101 (25-159)	100 (24-126)	90 (28-160)
Bilirubin (mg/dL)	0.5 (0.1-12.8)	0.6 (0.2-3.1)	0.3 (0.2-0.7)	0.5 (0.1-12.8)
Albumin (mg/dL)	2.7 (1.5-4.5)	2.5 (1.9-3.5)	2.9 (2.0-3.4)	2.9 (1.5-4.5)
Norepinephrine (mg/h)[c]	0.04 (0-1.39)	0.08 (0-0.87)	0 (0-0.45)	0.02 (0-1.39)
Azole plasma level (μg/L)	—	454 (20-1973)	1437 (300-3566)	426 (50-4538)
Daily azole dose (mg)	—	350 (300-700)	300 (300-400)	800 (200-1800)
PPI (mg/d)[c]	50 (0-205)	85 (0-205)	33 (0-40)	33 (0-120)
PPI (% of d observed)	90 (0-100)	100 (0-100)	83 (0-100)	83 (0-100)
CYP inductors (% of d observed)	—	0 (0-100)	—	—
CYP inhibitors (% of d observed)	—	25 (0-100)	—	—
H2 antagonists (% of d observed)	—	—	0 (0-16)	0 (0-100)
Phase 2 inhibitors (% of d observed)	—	—	0 (0)	0 (0-100)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CYP, cytochrome P; GFR-CKD-EPI, glomerular filtration rate according to 21; IL-6, Interleukin 6; PPI, proton pump inhibitors; SAPS, Simplified Acute Physiology Score 22.

[a]Eight patients received several azole forms in different time intervals and were therefore included twice in the analysis.

[b]First day of azole use.

[c]Mean amount in mg/day (PPI) or mg/h (norepinephrine) per day.

was pulmonary fibrosis (45%), followed by COPD (22%) and cystic fibrosis (18%). Patients received PPIs 90% of the days observed and predominantly received tube feeding (42% of days observed), followed by normal food intake (20%) or normal food intake supported by tube feeding (27%). The median daily dose was 800, 300, and 350 mg for posaconazole suspensions, posaconazole tablets, and itraconazole, respectively. Dose adjustments were made by the responsible physician in 0, 11, and 5 patients in the posaconazole tablet group, the posaconazole suspension group, and the itraconazole group, respectively.

3.1 | Plasma concentrations of posaconazole and itraconazole

Overall, 60% of the measured posaconazole plasma concentrations were subtherapeutic, and the median concentration was 496 μg/L. The median posaconazole plasma concentration after administration of the tablets was 1437 μg/L, whereby 10% of the samples were subtherapeutic in this subgroup. The median posaconazole plasma concentration after administration of the suspension was 426 μg/L, and in this subgroup, 68% of the samples were subtherapeutic. The

administration of tablets led to significantly ($P < .01$) less subtherapeutic concentrations, compared with the suspensions. Fifty-five percent of the measured itraconazole plasma concentrations were below the defined target of 500 μg/L. The median itraconazole plasma concentration was 454 μg/L. Target attainment was not significantly more often achieved in the posaconazole group than in the itraconazole group ($P = .39$). Two (40%), 20 (74%), and 37 (75%) patients receiving posaconazole tablets, posaconazole suspension, or itraconazole showed at least one sample below the target attainment. There was no significant correlation between the administered median daily amount of the azole and the plasma concentration (itraconazole *P*-value: .26; posaconazole *P*-value: .62). In Figures 1 and 2, the measured plasma concentrations are displayed related to the median daily dose.

3.2 | Covariates

All patients were immunosuppressed with a calcineurin-inhibitor (tacrolimus or ciclosporin) and corticosteroid therapy. Ninety percent, 80%, and 74% ($P = .14$) of the patients received mycophenolate mofetil additionally in the itraconazole, posaconazole tablet, and posaconazole suspension group, respectively. In 64% of the samples, the patient received less than 0.1 mg/h norepinephrine when the azole was administered. None of the investigated covariates showed a significant effect on the plasma concentrations of itraconazole or posaconazole.

3.3 | Fungal-induced transition from prophylaxis to therapy

In total, 19 patients (26%) showed an FITPT in our study with a median time from transplantation to fungal detection of 18 days (range: 2-162). Of these 19 patients, 16 patients received itraconazole and 3 patients received posaconazole as prophylaxis. In the itraconazole group, 13 patients showed positive fungal cultures, and 3 showed positive antigen findings, while the 3 patients in the posaconazole group (all patients received suspension) showed only positive antigen tests. Seven of the observed FITPTs in the itraconazole group occurred before the defined steady state but none in the posaconazole group. The positive fungal cultures included *Candida albicans* (5), *Aspergillus fumigatus* (1), *Candida species* (6), and *Candida glabrata* (1). The sites of the positive cultures were bronchoalveolar lavage (2), urine (1), endotracheal aspirate (5), thoracic drainage swab (2), and sputum (3). The aspergillus antigen tests were performed on serum (4), bronchoalveolar lavage (1), and endotracheal aspirate (1). There was a significant difference in the number of FITPTs between the posaconazole and itraconazole group detectable ($P = .029$), with an odds ratio 4.4 times higher for itraconazole patients showing an FITPT. Table 2 shows the characteristics of patients with an FITPT. The median length of ICU stay of patients with FITPT was 48 vs 37 days in patients without FITPT ($P = .14$). A CMV replication was found in 39 patients (53%); 8 of them developed an FITPT. There was no significant association between CMV replication and FITPT ($P = .30$).

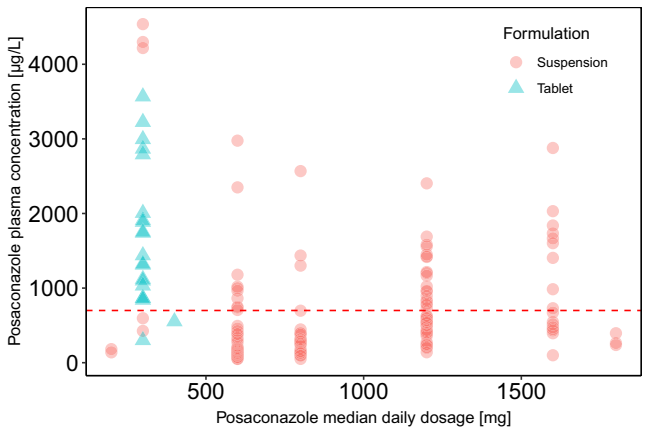

FIGURE 1 Posaconazole plasma concentrations related to the median daily dose in μg/L for suspensions (red dots) and tablets (blue triangle). Ten percent of the posaconazole plasma concentrations after intake of tablets and 68% of the posaconazole plasma concentrations after intake of suspension were subtherapeutic. Dotted line: defined target of 700 μg/L for posaconazole according to Ashbee et al[15]

There was no influence of target attainment on the development of an FITPT for itraconazole ($P = .97$) and posaconazole ($P = .98$). Furthermore, the plasma concentrations did not show a significant influence on the development of an FITPT (posaconazole $P = .48$, itraconazole $P = .96$). The median posaconazole plasma concentration was slightly lower for patients with (436 μg/L) than without (523 μg/L) an FITPT. The median itraconazole concentration was even higher for patients with an FITPT (601 μg/L) than without an FITPT (441 μg/L). Figure 3 compares the plasma concentrations for patients with FITPT to patients without an FITPT.

4 | DISCUSSION

To the best of our knowledge, this is the first study investigating antifungal prophylaxis with the triazoles posaconazole and itraconazole in lung transplant recipients postoperatively during their stay at the ICU. In our population, posaconazole was found to be significantly ($P = .029$) more effective in the prevention of FITPTs than itraconazole.

Our results are in line with previous studies in neutropenic patients and hematologic patients undergoing chemotherapy or hematopoietic stem cell transplantation.[19] Cornely et al studied a group of neutropenic patients receiving either fluconazole/itraconazole or posaconazole.[18] In this study, posaconazole prevented invasive fungal infections more effectively than either fluconazole or itraconazole and improved overall survival.[18] Similar results were found by Copley et al in patients with acute myeloid leukemia undergoing intensive chemotherapy: posaconazole was associated with fewer fungal infections and a lower need for continued antifungal prophylaxis compared with itraconazole.[31] Based on the available evidence,

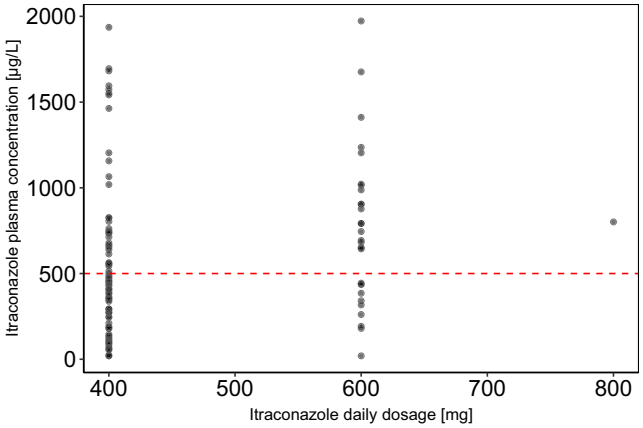

FIGURE 2 Itraconazole plasma concentrations related to the median daily dose. Fifty-five percent of the itraconazole plasma concentrations were subtherapeutic. Dotted line: defined target of 500 µg/L for itraconazole according to Ashbee et al[15]

TABLE 2 Characteristics of patients with a fungal-induced transition from prophylaxis to therapy after the administration of posaconazole or itraconazole as prophylaxis

	Itraconazole Median (range) or median (%)	Posaconazole Median (range) or median (%)
Number of patients	16	3
Positive antigen records	3	3
Positive fungal cultures	13	0
Mortality	0	0
Single lung transplantations	3 (19)	0
Re-transplantations	0	0
Gender (male/female)	10 (63)/6 (37)	2 (67)/1 (33)
Age (y)	48 (33-68)	62 (33-64)
BMI (kg/m^2)	22.1 (17.93-30.49)	21.5 (13.1-25.1)
SAPS II	45 (22-91)	57 (52-63)
Azole plasma concentration (µg/L)	601 (20-1936)	436 (98-1436)
IL-6 (pg/mL)	15.4 (5.3-5307)	37.1 (8.3-169)
CRP (mg/dL)	1.4 (0.3-19.2)	4.8 (0.4-25.2)
Norepinephrine (mg/h)	0.14 (0-0.9)	0.02 (0-0.79)
Average amount per day (mg)	350 (300-525)	800 (300-1200)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, Interleukin 6; SAPS, Simplified Acute Physiology Score.[22]

the German Society of Hematology and Medical Oncology recommended posaconazole as prophylaxis for patients at high risk of invasive fungal infections.[16] Our data support the use of posaconazole in lung transplant recipients in the immediate postoperative period.

The initiation of an antifungal therapy in the itraconazole group seemed to be independent of the achieved plasma concentrations. Even attaining the target concentrations (>500 ng/L) provided by the British Society of Mycology did not appear to be protective against an FITPT.[15] It has been previously reported that the defined target might be too low.[15,32] On the other hand, patients treated with posaconazole did not show a high number of FITPTs, although 60% of the patients showed subtherapeutic concentrations according to the definition provided by the British Society of Mycology.[15] Future studies should investigate and reevaluate whether the defined targets are linked with therapeutic efficacy in critically ill patients, and the target thresholds should be adapted if necessary.

The number of FITPTs in our population (26%) appears to be high but has been similarly described in previous studies.[13] None of the patients with an FITPT deceased during their stay at the ICU in comparison with an up to 60% mortality described in other studies for lung transplant recipients with invasive fungal infections.[13] This might be explained by the few FITPTs caused by *Aspergillus* spp. and a limited surveillance period. In addition, it can be suspected that the indication for therapy was presumably applied generously because of the immunosuppressed and critically ill condition of the patients. ICU stay was slightly, non-significantly longer in patients with FITPT than in patients without FITPT (48 vs 37 days). Both mortality and length of ICU stay are multifactorially influenced and based on the limited number of patients in our study; interpretation of these parameters should be cautious. Overall, we found more FITPTs caused by *Candida* spp. (n = 12) than by *Aspergillus* spp. (culture = 1, antigen = 6) in our study population. Even though *Candida* spp. is in general the more frequently observed pathogen in lung transplant recipients, the observed ratio seems to be high.[33] Our findings could be related to the early observation period of the study (patients were excluded from the study when transferred to a general ward). Infections by *Candida* spp. regularly occur within the first month after transplantation, whereas infections by *Aspergillus* spp. tend to occur after 3-12 months.[34] Therefore, the extent to which itraconazole and posaconazole protect against infections by *Aspergillus* spp. can only be interpreted to a limited extent. However, posaconazole seems to be more effective in prophylaxis against *Candida* spp. infections, which usually dominate in the postoperative period. Seven FITPTs occurred before the steady state was reached in the itraconazole group. Therefore, it can be concluded that especially in the first period of prophylaxis, administration of itraconazole tablets does not provide adequate protection against fungal detection. Other routes of administration (inhalative, IV) may offer advantages by reaching adequate exposure more quickly.

Patients receiving posaconazole suspension showed significantly ($P < .01$) more concentrations below the target than patients receiving prophylaxis with posaconazole tablets. This has also been reported by Stelzer et al in a group of lung transplant recipients during a routine follow-up and was mainly associated with the use of PPI and the diagnosis of cystic fibrosis.[3,35] We did not find any significant covariates influencing the plasma concentrations of posaconazole or

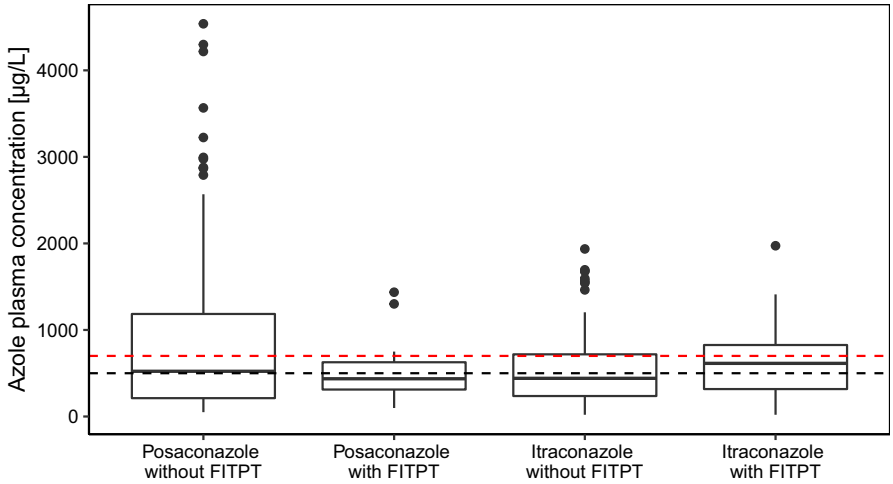

FIGURE 3 Azole plasma concentrations for posaconazole and itraconazole with and without fungal induced transition from prophylaxis to therapy (FITPT). Measured concentrations were not significantly different between patients with and without FITPT. Red dotted line: defined target attainment of 700 µg/L for posaconazole according to Ashbee et al[15] Black dotted line: defined target attainment of 500 µg/L for itraconazole according to Ashbee et al[15]

itraconazole. This might be explained by the fact that several factors (simultaneously) alter the pharmacokinetics of azoles and critically ill patients are subject to diverse influences. In this context, our study population might have been too small to identify influencing factors. Many lung transplant recipients suffer from dysphagia caused by long-term ventilation, especially in the postoperative period, and have problems swallowing the tablets. In principle, unpredictable bioavailability/pharmacokinetics could be circumvented by intravenous or inhalative administration. Mellinghoff et al recommended the use of an intravenous formulation of posaconazole if the administration of posaconazole tablets is prevented.[16] Sime et al investigated the pharmacokinetics of posaconazole in critically ill patients after the administration of 300 mg of an intravenous formulation and observed higher rates of target attainment.[36] Although we did not investigate intravenous administration of posaconazole, the studies described earlier in combination with the high rate of subtherapeutic concentrations after posaconazole suspension in our analysis support the administration of an intravenous formulation of posaconazole instead of a suspension to lung transplant recipients with dysphagia (or patients with other inability to swallow tablets) in the postoperative setting. Similarly, the use of an alternative formulation with better bioavailability of itraconazole (SUBA-itraconazole) could lead to a higher rate of target attainment and a higher efficacy in prophylaxis using itraconazole.

Our study has several limitations. It cannot be assumed that all FITPTs represented probable/proven invasive fungal infections according to ISHLT or EOTRC/MSG guidelines.[37,38] Thus, comparison of our data with prevalence rates of infections in other studies is not possible without limitations. However, the reliability of diagnostic criteria of invasive fungal infections in the context of critically ill patients is questionable. Guidelines for critically ill patients are currently in progress.[39] The subjective primary endpoint chosen in our study (definition of FITPT = clinical decision to initiate a targeted therapy) included all information available to an experienced intensive care specialized team at the time of the positive fungal record. However, although the same definition was applied to patients receiving itraconazole and posaconazole, a bias (ie, clinicians were less "comfortable" when cultures were positive in patients they knew were on itraconazole) cannot be completely excluded because of the retrospective, unblinded study design.

The structured evaluation of radiologic, bronchoscopic, and histologic results would have been desirable for our study. Unfortunately, no uniform diagnostics were carried out for patients with positive microbiological results making a meaningful evaluation not feasible in this study.

Finally, due to the retrospective study design, a bias due to unobserved confounders cannot be excluded. Therefore, future prospective studies are needed to confirm our results.

5 | CONCLUSIONS

Itraconazole and posaconazole prophylaxis led to a high rate of subtherapeutic plasma concentrations. The plasma concentrations achieved were not linked with efficacy. However, posaconazole, compared with itraconazole, showed a greater efficacy in preventing FITPTs in critically ill lung transplant recipients and should therefore be used preferentially in this context. Future studies should reevaluate the existing target concentrations of posaconazole and itraconazole in critically ill patients. Because the administration of the suspension of posaconazole resulted more often in insufficient plasma concentrations, preference should be given to tablets.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The local institutional review board approved the study (registration number 20-168).

CONFLICT OF INTEREST

All authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

UL, CS, and MZ designed the study. JJ collected the microbiological dataset. SK collected the clinical dataset. MP performed LC-HRMS-analysis. SK and UL designed the data analysis. SK and UL analyzed the data. All authors discussed results. SK, UL, and CS drafted the manuscript. All authors commented on and

approved the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Simon Kallee https://orcid.org/0000-0002-8364-2986
Christina Scharf https://orcid.org/0000-0002-5310-4116
Ines Schroeder https://orcid.org/0000-0002-7060-3785
Michael Paal https://orcid.org/0000-0001-8831-0238
Michael Vogeser https://orcid.org/0000-0002-2745-2475
Johannes Zander https://orcid.org/0000-0003-4539-0703
Nikolaus Kneidinger https://orcid.org/0000-0001-7583-0453
Uwe Liebchen https://orcid.org/0000-0002-4375-0923

REFERENCES

1. Kennedy CC, Razonable RR. Fungal infections after lung transplantation. *Clin Chest Med*. 2017;38(3):511-520. https://doi.org/10.1016/j.ccm.2017.04.011
2. Brett J, Chong O, Graham GG, et al. Antifungal use and therapeutic monitoring of plasma concentrations of itraconazole in heart and lung transplantation patients. *Ther Drug Monit*. 2013;35(1):133-136. https://doi.org/10.1097/FTD.0b013e318275fe69
3. Stelzer D, Weber A, Ihle F, et al. Comparing azole plasma trough levels in lung transplant recipients: percentage of therapeutic levels and intrapatient variability. *Ther Drug Monit*. 2017;39(2):93-101.
4. Arthurs SK, Eid AJ, Deziel PJ, et al. The impact of invasive fungal diseases on survival after lung transplantation: mycoses and lung transplant survival. *Clin Transplant*. 2009;24(3):341-348. https://doi.org/10.1111/j.1399-0012.2009.01076.x
5. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;63(4):e1-e60. https://doi.org/10.1093/cid/ciw326
6. Pennington KM, Yost KJ, Escalante P, Razonable RR, Kennedy CC. Antifungal prophylaxis in lung transplant: a survey of United States' transplant centers. *Clin Transplant*. 2019;33(7):e13630. https://doi.org/10.1111/ctr.13630
7. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Med*. 2013;39(12):2070-2082. https://doi.org/10.1007/s00134-013-3088-4
8. Vandewoude K, Vogelaers D, Decruyenaere J, et al. Concentrations in plasma and safety of 7 days of intravenous itraconazole followed by 2 weeks of oral itraconazole solution in patients in intensive care units. *Antimicrob Agents Chemother*. 1997;41(12):2714-2718.
9. Störzinger D, Borghorst S, Hofer S, et al. Plasma Concentrations of posaconazole administered via nasogastric tube in patients in a surgical intensive care unit. *Antimicrob Agents Chemother*. 2012;56(8):4468-4470. https://doi.org/10.1128/AAC.06167-11
10. Dolton MJ, Brüggemann RJM, Burger DM, McLachlan AJ. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. *Antimicrob Agents Chemother*. 2014;58(11):6879-6885. https://doi.org/10.1128/AAC.03777-14
11. Noxafil® 40 mg/ml Suspension zum Einnehmen. Published online 2020:9. https://www.msd.de/fileadmin/files/fachinformationen/noxafil.pdf
12. Gadre SK, Koval C, Budev M. Candida blood stream infections post lung transplant. *J Heart Lung Transplant*. 2017;36(4):S241. https://doi.org/10.1016/j.healun.2017.01.637
13. Solé A, Salavert M. Fungal infections after lung transplantation. *Transplant Rev*. 2008;22(2):89-104. https://doi.org/10.1016/j.trre.2007.12.007
14. Heykants J, Van Peer A, Van de Velde V, et al. The clinical pharmacokinetics of itraconazole: an overview. *Mycoses*. 1989;32:67-87. https://doi.org/10.1111/j.1439-0507.1989.tb02296.x
15. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British society for medical mycology. *J Antimicrob Chemother*. 2014;69(5):1162-1176. https://doi.org/10.1093/jac/dkt508
16. Mellinghoff SC, Panse J, Alakel N, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the infectious diseases working party (AGIHO) of the German society for haematology and medical oncology (DGHO). *Ann Hematol*. 2018;97(2):197-207. https://doi.org/10.1007/s00277-017-3196-2
17. Glasmacher A, Hahn C, Leutner C, et al. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. *Mycoses*. 1999;42(7-8):443-451. https://doi.org/10.1046/j.1439-0507.1999.00505.x
18. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348-359. https://doi.org/10.1056/NEJMoa061094
19. Zhao YJ, Khoo AL, Tan G, et al. Network meta-analysis and pharmacoeconomic evaluation of fluconazole, itraconazole, posaconazole, and voriconazole in invasive fungal infection prophylaxis. *Antimicrob Agents Chemother*. 2015;60(1):376-386. https://doi.org/10.1128/AAC.01985-15
20. Ray J, Campbell L, Rudham S, Nguyen Q, Marriott D. Posaconazole plasma concentrations in critically ill patients. *Ther Drug Monit*. 2011;33(4):387-392. https://doi.org/10.1097/FTD.0b013e31821fb197
21. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
22. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957-2963.
23. Gubbins PO, Krishna G, Sansone-Parsons A, et al. Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. *Antimicrob Agents Chemother*. 2006;50(6):1993-1999. https://doi.org/10.1128/AAC.00157-06
24. Hites M, Goicoechea Turcott EW, Taccone FS. The role of galactomannan testing to diagnose invasive pulmonary aspergillosis in critically ill patients. *Ann Transl Med*. 2016;4(18):353. https://doi.org/10.21037/atm.2016.08.32
25. Chumpitazi BFF, Lebeau B, Faure-Cognet O, et al. Characteristic and clinical relevance of candida mannan test in the diagnosis of probable invasive candidiasis. *Med Mycol*. 2014;52(5):462-471. https://doi.org/10.1093/mmy/myu018
26. Zimmermann T, Yeates RA, Laufen H, Pfaff G, Wildfeuer A. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. *Eur J Clin Pharmacol*. 1994;46(2): https://doi.org/10.1007/BF00199879
27. Itraconazol Heumann 100 mg Hartkapseln. Published online 2020:8. https://www.heumann.de/fileadmin/user_upload/produkte/infos/Fachinformation-Itraconazol-Heumann-100-mg-Hartkapseln.pdf
28. Zhang J, Liu Y, Nie X, Yu Y, Gu J, Zhao L. Trough concentration of itraconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *Infect Drug Resist*. 2018;11:1283-1297. https://doi.org/10.2147/IDR.S170706

29. Nakamura Y, Matsumoto K, Sato A, Morita K. Effective plasma concentrations of itraconazole and its active metabolite for the treatment of pulmonary aspergillosis. *J Infect Chemother*. 2020;26(2):170-174. https://doi.org/10.1016/j.jiac.2019.08.002
30. Noble WS. How does multiple testing correction work? *Nat Biotechnol*. 2009;27(12):1135-1137. https://doi.org/10.1038/nbt1209-1135
31. Copley MS, Waldron M, Athans V, et al. Itraconazole vs. posaconazole for antifungal prophylaxis in patients with acute myeloid leukemia undergoing intensive chemotherapy: a retrospective study. *Int J Antimicrob Agents*. 2020;55(3):105886. https://doi.org/10.1016/j.ijantimicag.2020.105886
32. Stott KE, Hope WW. Therapeutic drug monitoring for invasive mould infections and disease: pharmacokinetic and pharmacodynamic considerations. *J Antimicrob Chemother*. 2017;72(suppl 1):i12-i18. https://doi.org/10.1093/jac/dkx029
33. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the transplant-associated infection surveillance network (TRANSNET). *Clin Infect Dis*. 2010;50(8):1101-1111. https://doi.org/10.1086/651262
34. Villalobos AP-C, Husain S. Infection prophylaxis and management of fungal infections in lung transplant. *Ann Transl Med*. 2020;8(6):414. https://doi.org/10.21037/atm.2020.03.102
35. Thompson GR, Rinaldi MG, Pennick G, Dorsey SA, Patterson TF, Lewis JS. Posaconazole Therapeutic drug monitoring: a reference laboratory experience. *Antimicrob Agents Chemother*. 2009;53(5):2223-2224. https://doi.org/10.1128/AAC.00240-09
36. Sime FB, Stuart J, Butler J, et al. Pharmacokinetics of intravenous posaconazole in critically ill patients. *Antimicrob Agents Chemother*. 2018;62(6). https://doi.org/10.1128/AAC.00242-18
37. Husain S, Sole A, Alexander BD, et al. The 2015 international society for heart and lung transplantation guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: executive summary. *J Heart Lung Transplant*. 2016;35(3):261-282. https://doi.org/10.1016/j.healun.2016.01.007
38. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. *Clin Infect Dis*. 2020;71(6):1367-1376. https://doi.org/10.1093/cid/ciz1008
39. Bassetti M, Scudeller L, Giacobbe DR, et al. Developing definitions for invasive fungal diseases in critically ill adult patients in intensive care units. Protocol of the FUNgal infections definitions in ICU patients (FUNDICU) project. *Mycoses*. 2019;62(4):310-319. https://doi.org/10.1111/myc.12869

How to cite this article: Kallee S, Scharf C, Schroeder I, et al. Comparing posaconazole and itraconazole for antifungal prophylaxis in critically ill lung transplant recipients: Efficacy and plasma concentrations. *Transpl Infect Dis*. 2021;23:e13675. https://doi.org/10.1111/tid.13675