Medical Mycology, 2022, **60**, myac041
https://doi.org/10.1093/mmy/myac041
Original Article
Advance access publication date: 29 August 2022

Antifungal prophylactic effectiveness and intrapulmonary concentrations of voriconazole versus posaconazole in lung transplant recipients

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Abstract

Invasive fungal diseases (IFDs) are one of the leading causes of death in lung transplant recipients. This study aimed to compare the antifungal prophylactic effectiveness, intrapulmonary and plasma levels of voriconazole with posaconazole in lung transplant recipients. This retrospective cohort study analyzed adult recipients who underwent lung transplantation between June 2017 and December 2020. Voriconazole oral tablets or posaconazole oral suspension was used for prophylaxis against posttransplant IFD. Drug concentrations in bronchoalveolar lavage fluid (BALF) and plasma were measured by using liquid chromatography-mass spectrometry. The 182 recipients included 142 in the voriconazole group and 40 in the posaconazole group. The trough plasma levels were comparable between voriconazole and posaconazole (1.65 ± 0.09 vs. 1.69 ± 0.03 μg/ml, $P = 0.55$). However, the BALF levels were significantly higher for posaconazole than voriconazole (17.47 ± 11.51 vs. 0.56 ± 0.49 μg/ml, $P < 0.001$). There was no significant difference in the total incidence of breakthrough IFDs between the voriconazole and posaconazole groups (10.6% vs. 7.5%, $P = 0.77$). The intrapulmonary concentrations of posaconazole were significantly higher than voriconazole. The two agents had comparable antifungal prophylactic effectiveness.

Keywords: invasive fungal disease, lung transplantation, prophylaxis, voriconazole, posaconazole

Introduction

Over the past 25 years, lung transplantation has become a viable treatment option for end-stage lung diseases. However, invasive fungal diseases (IFDs) are a major post-transplant complication and the second leading cause of death, affecting nearly 10% of lung transplant recipients.[1,2] Moreover, fungal airway colonization has also been associated with chronic lung allograft dysfunction.[3,4] Epidemiological studies showed that the majority of IFDs are caused by *Aspergillus* (44%), *Candida albicans* (23%), other moulds (19.8%), and Mucorales (3%).[5–7] Given the negative impact of IFDs on survival and clinical outcomes, pharmacologic antifungal prophylaxis is important because it decreases the incidence of fungal infections.[8,9] However, there is still no consensus on the choice of antifungal agents, route of administration, and duration of antifungal prophylaxis for lung transplantation.[8]

New azole-based antifungal agents have been recommended for IFD prophylaxis in lung transplantation.[9] Among them, voriconazole and posaconazole are the commonly used medications in most lung transplant centers, with the former being used more widely.[10,11] Although there is great heterogeneity in the choice of agents among lung transplant centers.[12]

A previous study reported the intrapulmonary concentrations of posaconazole in lung transplant recipients.[13] Other studies compared the safety and efficacy between voriconazole and posaconazole in preventing IFDs in high-risk patients with hematological malignancies, but the BALF concentrations were not compared in these studies.[14–16] However, their prophylactic effectiveness against IFDs in lung transplant recipients is not fully known. Moreover, given that invasive pulmonary aspergillosis (IPA) is the most common IFD in lung transplant recipients, it is important for these agents to reach an ideal intrapulmonary concentration. To the best of our knowledge, there are no studies comparing the intrapulmonary levels and prophylactic effectiveness between voriconazole and posaconazole in a homogenous group of lung transplant recipients.

The purpose of this retrospective study was to investigate the concentrations of voriconazole and posaconazole in bronchoalveolar lavage fluid (BALF) and plasma in lung transplant

Received: February 14, 2022. **Revised:** April 22, 2022. **Accepted:** August 25, 2022

recipients who were on the oral agents in a real-life setting. In addition, this study aimed to compare the prophylactic effectiveness and adverse events, rate of discontinuation, and survival rates between these two agents.

Methods

Study design and patients

This was a retrospective cohort study. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Patients who underwent lung transplantation or lung-heart transplantation at the First Affiliated Hospital of Guangzhou Medical University between 1 June 2017 and 30 December 2020 were screened. All organs were procured from organ procurement organizations and no organs were procured from prisoners. The inclusion criteria were as follows: (1) age $\geq$ 18 years; (2) had single-lung transplantation, double-lung transplantation, or combined heart-lung transplantation; (3) used posaconazole oral suspension or voriconazole oral tablets for universal antifungal prophylaxis. The exclusion criteria were as follows: (1) incomplete medical data; (2) missed the follow-up appointments; (3) became palliative during the antifungal prophylaxis courses.

The following data were collected for the donors and recipients: demographic data, CT scans on the donor lungs, indications for transplantation, operation-related data, treatment methods, and recipient chest/sinus CT scans performed prior to the transplantation, during prophylaxis, and within 7 days after drug discontinuation.

Antifungal prophylaxis

According to the antifungal prophylaxis protocol of our center, caspofungin was universally used for the first 7 days after transplantation, and either posaconazole oral suspension or voriconazole oral tablets were used thereafter, at the discretion of the physicians on a case-by-case basis. Voriconazole was routinely used at our center as it was covered by the national health insurance.

Posaconazole was selectively considered for patients who met any of the following criteria: (1) history of liver fibrosis, liver cirrhosis, or hepatitis; (2) elevated levels of liver enzymes or bilirubin; (3) history of drug-related hepatotoxicity. Before prescribing the azoles, the baseline liver function of the patient with liver cirrhosis was evaluated with the Child-Pugh scoring system (also known as the Child-Pugh-Turcotte score). The patients were categorized according to their liver function scores: Child-Pugh A, Child-Pugh B, and Child-Pugh C. Their original scoring system used five clinical and laboratory criteria to categorize patients: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status.[17]

Posaconazole (400 mg) was administered two times a day with meals. Voriconazole was administered with a loading dose of 6 mg/kg every 12 h on day 1, followed by 200 mg every 12 h on an empty stomach. Thereafter, the doses of voriconazole and posaconazole were adjusted every 2-3 days to reach the target plasma levels, which were defined according to the guidelines for therapeutic drug monitoring of antifungal agents by the British Society for Medical Mycology.[18] Because there is evidence that higher voriconazole plasma trough levels are associated with a higher incidence of adverse events, we adopted a target plasma trough level of 0.75–3 μg/ml for prophylaxis.[19] For posaconazole, the prophylactic threshold was set at 0.70–2.5 μg/ml.[20]

The plasma trough levels were monitored for each recipient once a week after the target level was reached and stayed in a steady state. The steady state of the plasma concentration was assumed being reached when the azoles had been taken for at least 10 continuous days since the first dose, which were two times of previously suggested.[18–20] The routine course was 3–4 months for antifungal prophylaxis at our center.

Blood collection

To measure the trough plasma levels of the azoles, 2 ml blood was drawn from each patient immediately before the administration of the medications and transferred into heparin lithium-containing tubes and placed on ice until centrifugation. The tubes were then spun at 1300 $\times$ g for 5 min in a Sigma 4K15 refrigerated centrifuge (4°C). The plasma was separated and frozen at least $-$ 20°C until it was assayed.

BALF collection

BALF was collected by bronchoscopy, which was one of the routine post-transplant care tests and performed with standardized protocol.[21,22] Written informed consent was obtained from each patient because of the invasiveness of bronchoscopy. BALF for the azoles assays was only collected after the plasma levels of the drugs had reach a steady sate for about 1 month, which was scheduled approximately 12 h after the last dose of the medication. BALF was collected concurrently with plasma samples in each patient.

Briefly, topical anesthesia with lidocaine was used for every patient. Low-dose systemic sedation was administered for part of the patients based on the individual condition. A fiberoptic bronchoscope (FB-18BS; Pentax, Montvale, NJ, USA) was inserted into the right lower lobe for right or double lung transplantation; otherwise, it was inserted into the left lower lobe. Four 50-ml aliquots of sterile 0.9% normal saline were infused, and each aliquot was immediately aspirated into a trap. The first aspirate was discarded. The aspirates from the second, third, and fourth instillations were pooled and iced. The recovery rate of the BALF was usually between 35–45%. A measured volume (30 ml) of the BALF was spun in a polypropylene tube at 400 $\times$ *g* for 5 min in a refrigerated (4°C) centrifuge (4K15; Sigma). The supernatant was separated frozen at $-$70°C until being assayed.

Posaconazole and voriconazole assay

The plasma and BALF concentrations of posaconazole and voriconazole were assayed by using liquid chromatography tandem triple quadrupole mass spectrometry at PPD, Inc. (Richmond, VA, USA). The drug concentrations in plasma and BALF were quantified against the human plasma and BALF calibration curves respectively. A 100-μl sample of plasma or BALF was transferred into a separate tube. To each aliquot, 900 μl acetonitrile containing posaconazole-d4 as the internal standard was added and vortexed, then centrifuged at 14 000 $\times$ g for 15 min at 4°C. The liquid layer of the sample was then transferred and analyzed using mass spectrometry (Agilent, USA). Separation was achieved by using an Agilent Poroshell 120 EC-C18 (3.0 $\times$ 50 mm, 2.7 μm) column. For high performance liquid chromatography, the mobile phase A contained 0.1% formic acid in acetonitrile (v/v), and the mobile phase B contained 0.1% formic acid in de-ionized water. A flow of 95% mobile phase B to 5% mobile phase B was used to separate the endogenous and exogenous compounds in both plasma and BALF with a column flow rate

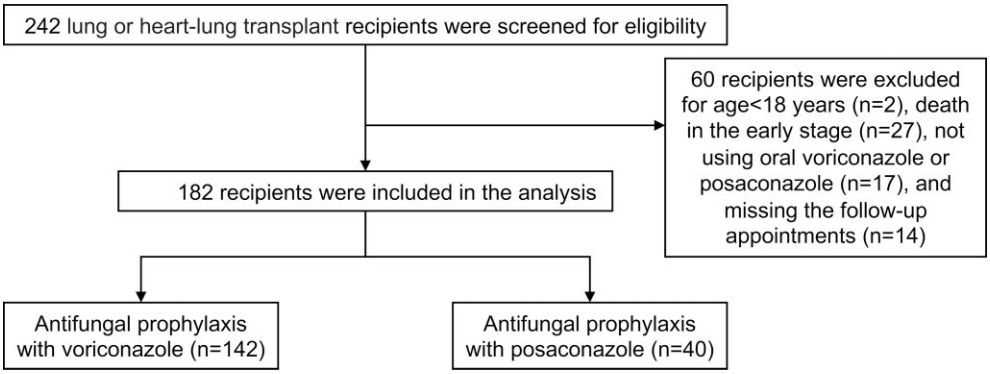

Figure 1. A flowchart of participant inclusion.

of 0.5 ml/min and a column temperature of 30°C. The electrospray ionization source was operated in the positive mode with a capillary voltage of 3000 V. All compounds were detected by multiple reaction monitoring with the ion transitions of m/z 701.3 to 683.3 (collision energy 35 eV) for posaconazole and 705.5 to 687.5 (collision energy 35 eV) for internal standard. The lower limit of quantification for the assay was 100 ng/ml for plasma and 0.50 ng/ml for BALF. The calibration range was 100 to 5000 ng/ml and 0.50 to 100 ng/ml for plasma and BALF, respectively.

Evaluation of prophylactic effectiveness and adverse events

IFDs classification adhered to the consensus criteria.[23,24] Proven cases were confirmed with fungal pathogen isolation. IFD onset was defined as the first day of suspicious CT abnormality or positive microbiology or pathological tests. Prophylactic effectiveness was evaluated with breakthrough IFDs, which were defined as IFDs occurred between 7 days after azole initiation and 7 days to drug discontinuation. The safety and tolerability of voriconazole and posaconazole were monitored by recording the adverse events that occurred throughout the prophylaxis.

Statistical analysis

The primary endpoint was the incidence of breakthrough IFD. The secondary endpoint was IFD-free survival. All eligible patients were included in the analysis of overall survival, and all patients who were given azoles were included in the safety assessment. Statistical analysis was performed by using SPSS 19.0 (IBM Corp., Armonk, NY, USA). Graphs were created with GRAPHPAD PRISM Version 5.04 for Windows. Normally distributed continuous data were expressed as means ± standard deviations and analyzed by using the independent samples *t*-test. Between group differences were analyzed by using the χ^2 test or the Fisher's exact test for categorical variables, and the Student's *t*-test for continuous variables. The level of statistical significance was set to $P < 0.05$.

Results

General characteristics of the recipients

A total of 182 recipients were included in this study, with 142 treated with voriconazole and 40 with posaconazole. The flowchart of patient inclusion and exclusion is shown in Figure 1. The baseline demographic and clinical characteristics of the recipients are summarized in Table 1. There was no significant difference in the proportion of the recipients who received immune induction therapy between voriconazole and posaconazole. All recipients received maintenance immunosuppressive therapy with standard triple therapy. Table 2 shows the indications for the use of posaconazole.

Plasma levels of the azoles

Plasma levels of voriconazole and posaconazole were assayed in all participants with 2303 and 145 samples, respectively. The plasma levels of azoles were assayed 1-3 times every month, resulting in 16.2 assays for voriconazole and 3.6 assays for posaconazole per capita.

Figure 2 shows the steady-state plasma trough levels of azoles and tacrolimus, a calcineurin inhibitor, which both reached the target levels. The plasma levels of voriconazole were comparable to those of posaconazole (1.65 ± 0.09 vs. 1.69 ± 0.03 μg/ml, $P = 0.55$; Figure 2A). Also, there were no significant difference in the trough levels of tacrolimus between patients with voriconazole and those with posaconazole (12.48 ± 0.31 vs. 13.56 ± 0.73 ng/ml, $P = 0.99$; Figure 2B).

BALF levels of the azoles

The BALF levels of voriconazole were assayed in 51 (35.9%) recipients with 86 samples and that of posaconazole were assayed in 19 (47.5%) recipients with 20 samples. The BALF levels of voriconazole were assayed only once in 36 (70.6%) recipients and 2∼4 times in 15 (29.4%) recipients when the drug concentration reached the steady state. The BALF levels of posaconazole were assayed only once in 18 recipients and twice in 1 recipient when the drug concentration reached the steady state. If measured twice, the mean value of the BALF drug concentrations was used.

The mean level of posaconazole in BALF was significantly higher than that of voriconazole (17.47 ± 11.51 vs. 0.56 ± 0.49 μg/ml, $P < 0.001$; Figure 3A). Also, the BALF/plasma posaconazole ratio was significantly higher than that of voriconazole (11.83 ± 9.05 vs. 0.42 ± 0.39, $P < 0.0001$; Figure 3B). In addition, the results showed that 12% of the recipients had a quick-metabolic genotype of *CYP2C19*.

Table 1. Demographic and clinical characteristics of the study participants.

	All (n = 182)	Voriconazole (n = 142)	Posaconazole (n = 40)	*P*-value
Age, year	55.4 ± 12.7	55.5 ± 12.7	54.8 ± 12.9	0.75
Male, n (%)	154 (84.6)	118 (83.1)	36 (90.0)	0.33
Body mass index, kg/m^2	20.2 ± 3.5	20.1 ± 3.4	20.7 ± 3.9	0.43
Hemoglobin, g/l	114.04 ± 14.2	114.4 ± 1.3	115.1 ± 1.2	0.34
Albumin, g/l	39.0 ± 3.7	39.0 ± 0.3	39.5 ± 0.6	0.25
Plasma creatinine, umol/l	92.7 ± 22.9	93.9 ± 24.2	88.9 ± 17.1	0.14
Indications for transplantation, n (%)				0.06
Bronchiectasis	12 (6.6)	7 (4.9)	5 (12.5)	
Chronic obstructive pulmonary disease	49 (26.9)	43 (30.3)	6 (15.0)	
Connective tissue disease	20 (11.0)	18 (12.7)	2 (5.0)	
Interstitial lung disease	66 (36.3)	51 (35.9)	15 (37.5)	
Pulmonary lymphangiomyomatosis	4 (2.2)	2 (1.4)	2 (5.0)	
Occupational lung disease	15(8.2)	11 (7.8)	4 (10.0)	
Pulmonary vascular disease	8 (4.4)	7 (4.9)	1 (2.5)	
Other	8 (4.4)	3 (2.1)	5 (12.5)	
Transplantation type, n (%)				0.42
Double lung transplantation	66 (36.3)	53 (37.3)	13 (32.5)	
Single lung transplantation	116 (63.7)	89 (62.7)	27 (67.5)	
Induction therapy, n (%)				0.97
Rabbit anti-thymocyte globulin	103 (56.6)	81 (57.0)	22 (55.0)	
Basiliximab	79 (43.4)	61 (43.0)	18 (45.0)	

Table 2. Indications for the use of posaconazole, n (%).

	Posaconazole (n = 40)
Liver cirrhosis	4 (10)
Child-Pugh A	2 (5)
Child-Pugh B	2 (5)
Child-Pugh C	0
Abnormal liver function	30 (75)
Abnormal bilirubin	24 (60)
Abnormal liver enzymes	30 (75)
Both	17 (42.5)
History of liver hepatitis	4 (10)
History of drug-related hepatotoxicity	2 (5)

Breakthrough IFDs

The incidence of breakthrough IFDs was comparable between the voriconazole group and the posaconazole group (10.6% vs. 7.5%, $P = 0.77$). The incidence of breakthrough aspergillosis also did not differ significantly between the voriconazole group and the posaconazole group (6.3% vs. 2.5%, $P = 0.35$). The specific pathogens of the IFDs are shown in Table 3.

Adverse events

There was no significant difference in the overall incidence of adverse events between the voriconazole group and the posaconazole group (13.4% vs. 12.5%, $P = 0.56$; Table 3). Gastrointestinal discomfort occurred in only one recipient receiving voriconazole (0.7%) but was significantly higher in the posaconazole group (12.5%). The

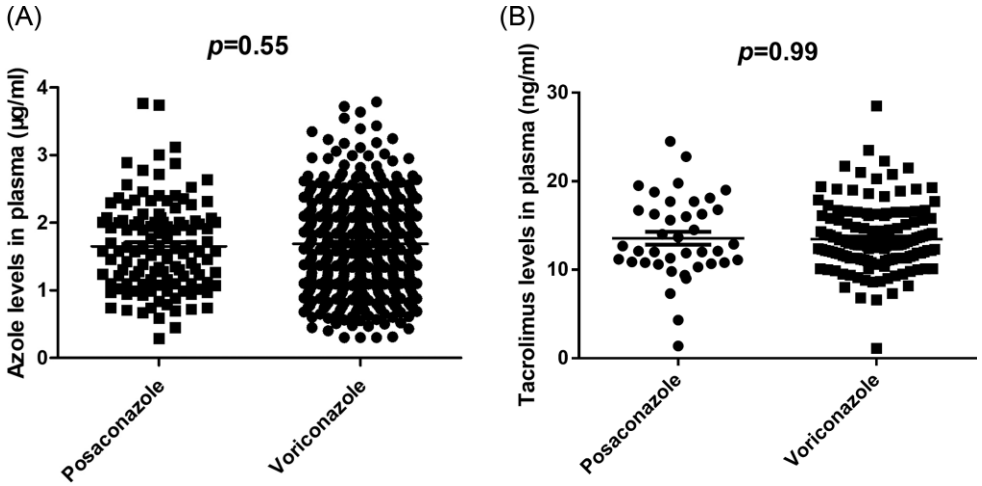

Figure 2. Plasma trough levels of azoles and tacrolimus. (A) There was no significant difference in the plasma levels between voriconazole and posaconazole. (B) There was no significant difference in the plasma levels of tacrolimus between patients with voriconazole and those with posaconazole. The upper and lower lines: interquartile range. The middle line: median.

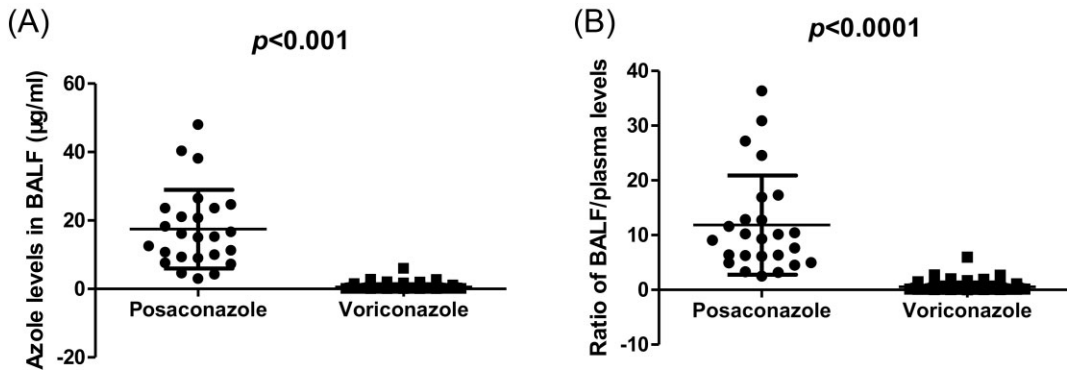

Figure 3. BALF levels of azoles. (A) The posaconazole levels in BALF was significantly higher than those of voriconazole. (B) The BALF/plasma posaconazole ratios were significantly higher than those of voriconazole. BALF, bronchoalveolar lavage fluid. The upper and lower lines: interquartile range. The middle line: median.

discontinuation rate also showed no significant difference between voriconazole and posaconazole group (12.7% vs. 15%, $P = 0.70$).

Survival and risk factors

The overall median follow-up was 19.7 months (range, 3.3–61.2 months). In the voriconazole group, 6 (40%) of the 15 patients with breakthrough IFD died, including 3 patients died of IFDs, 1 died of severe pulmonary infection other than IFDs, and 2 died of chronic lung allograft dysfunction. In the posaconazole group, 2 (66.7%) of the 3 patients with breakthrough IFDs died, with 1 patient died of IPA and the other died of chronic lung allograft dysfunction.

The survival probability of the posaconazole group was higher than that of the voriconazole group (87.4% vs. 75.8%; Figure 4). Liver dysfunction (odds ratio [OR]: 12.15; 95% confidence interval [CI]:1.03–142.8), elevated creatinine (OR: 1.02; 95% CI: 1.00–1.04), and a higher age (OR: 1.05; 95% CI:1.0–1.10) were identified as risk factors of survival (Table 4).

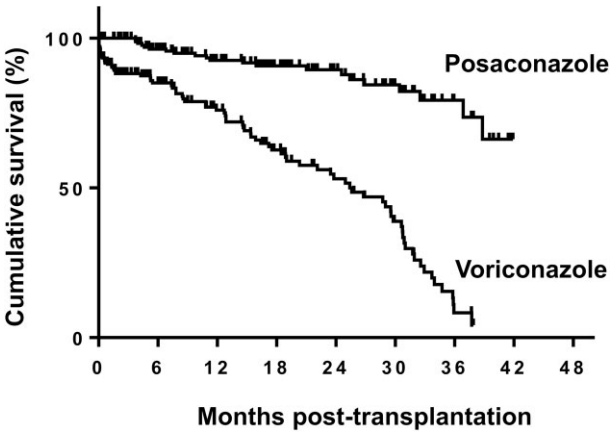

Figure 4. Cox regression analysis of overall survival between the posaconazole group and the voriconazole group.

Discussion

Posaconazole absorption is significantly influenced by food and gastrointestinal conditions, such as pH and motility.[25] As a result, it is difficult to achieve the ideal plasma levels of posaconazole. However, our study showed that oral intake of a normal or lower dose of posaconazole is sufficient to reach the therapeutic plasma levels of 0.75–2.5 μg/ml, which is above the MIC90 for *Aspergillus* spp.[26] Posaconazole was taken with high-fat foods according to the drug instructions

Table 3. Breakthrough IFDs and adverse events.

	Voriconazole (n = 142)	Posaconazole (n = 40)	*P*-value
Breakthrough IFDs, n (%)	15 (10.6)	3 (7.5)	0.77
Aspergillus	9 (6.3)	1 (2.5)	0.35
Candida albicans	1 (0.7)	1 (2.5)	0.34
Pneumocystis jiroveci	2 (1.4)	1 (2.5)	0.63
Mucorales	3 (2.1)	0	0.35
Adverse events, n (%)	19 (13.4)	5 (12.5)	0.56
Gastrointestinal discomfort	1 (0.7)	5 (12.5)	0.002
Elevated total bilirubin	7 (4.9)	0	0.15
Elevated liver enzymes	5 (3.5)	0	0.23
Visual dysfunction	3 (2.1)	0	0.35
Tacrolimus toxicity	2 (1.4)	0	0.45
Others	1 (0.7)	0	0.60
Discontinuation rate, n (%)	18 (12.7)	6 (15)	0.70
Adverse events	14 (9.9)	3 (7.5)	0.65
Financial reasons	4 (2.8)	3 (7.5)	0.17
Mortality among breakthrough IFDs	6 (40)*	2 (66.7)**	0.56

IFD, invasive fungal disease; *n = 15; **n = 3

Table 4. Risk factors of survival.

	B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Age	0.049	0.023	4.349	1	0.037	1.050	1.003	1.099
Liver dysfunction	2.497	1.257	3.943	1	0.047	12.145	1.033	142.803
Serum creatine level	0.023	0.010	5.642	1	0.018	1.024	1.004	1.043
Group	−1.037	1.234	0.706	1	0.401	0.355	0.032	3.979
Breakthrough IFD	0.577	0.634	0.829	1	0.363	1.781	0.514	6.175
Single or double LTx	0.097	0.600	0.026	1	0.871	1.102	0.340	3.574
Body mass index	0.014	0.073	0.039	1	0.844	1.015	0.879	1.171

CI, confidence interval; IFD, invasive fungal disease; LTx, lung transplantation

in our patients, which ensured or even improved the bioavailability of posaconazole and its plasma concentrations.

The plasma levels of voriconazole and posaconazole are subject to many influencing factors, among which the P450 genotypes (CYP2C19 and CYP3A4) are the most important.[27–29] In our study, 12% of the recipients had a quick-metabolic genotype of *CYP2C19*. This finding is consistent with the previous investigations in China,[30,31] as well as our clinical observation that a relatively higher dose of voriconazole was needed to reach the target plasma levels in a small portion of patients.

Despite the comparable plasma concentrations between posaconazole and voriconazole in our study, the BALF levels and the BALF/plasma ratios of posaconazole were significantly higher than those of voriconazole. Our findings were generally consistent with those of Jone E. et al.,[13] which showed the maximum concentrations of posaconazole in plasma, pulmonary epithelial lining fluid, and alveolar cells were 1.3 ± 0.4, 1.3 ± 1.7, and 55.4 ± 44.0 μg/ml in lung transplant recipients.[13] The BALF is a mixture of the alveolar cells and the pulmonary epithelial lining fluid, which explains the high BALF levels and the high BALF/plasma ratios of posaconazole in our study. All these findings suggest significantly higher intrapulmonary concentrations of posaconazole than in the plasma.

Higher BALF levels of posaconazole have clinical significance because its ability of inhibiting *Candida* spp. is concentration-dependent and greatly correlated with the ratio of the area under the concentration-time curve to the minimum inhibitory concentration.[32] These relationships may also be true for *Aspergillus* spp.[33] Thus, greater intrapulmonary drug concentrations are essential for preventing or treating IPA. However, we did not find significant differences in the incidence of breakthrough IFD or breakthrough aspergillosis between posaconazole and voriconazole. Considering that cirrhosis in patients on posaconazole is a risk factor for aspergillosis, this agent may provide better antifungal prophylaxis than voriconazole for patients with liver conditions. Both agents were recommended by the guidelines by the Infectious Diseases Society of America on prophylaxis against IPA in solid organ transplantation.[23] However, the antifungal prophylaxis strategies for lung transplant recipients still lack consensus and standard of care.[10]

In our study, there were three cases of breakthrough mucormycosis in the voriconazole group. One patient died and the other 2 patients were successfully treated with injection of polyene antifungal amphotericin B and oral posaconazole. Mucormycosis has a high mortality rate ranging from 40–70%, especially in immunosuppressed patients. It is seen as breakthrough infections when voriconazole is used for antifungal prophylaxis.[34] Amphotericin B has been approved for treating mucormycosis and posaconazole is usually used as a salvage treatment. Consistent with previous studies, our findings indicate that prophylactic posaconazole should be considered if *Mucor* spp. is targeted. In contrast, voriconazole shows no in vitro or in vivo activity against these fungi.[35,36]

No significant difference in the overall incidence of adverse events was noticed between the two azoles. Gastrointestinal discomfort was more common in the posaconazole group. Our results were consistent with Tang et al.[37] but not with Hachem et al.[15] who reported that symptomatic adverse events were more commonly associated with voriconazole, whereas hepatotoxicity was more commonly associated with posaconazole. The reason for the inconsistency might be the different study participants. Our study participants were lung transplant recipients and most of them had normal liver function at baseline. However, the study of Hachem et al.[15] included higher risk patients with hematological malignancies, thus graft versus host disease and the chemotherapeutic medications were more likely to cause hepatotoxicity.

Although our study is the first observational cohort study comparing the concentrations in both BALF and plasma, antifungal prophylactic effectiveness, and adverse effects of voriconazole with posaconazole in lung transplant recipients, it has some limitations. Firstly, the intrapulmonary levels of the azoles should be ideally assayed with BALF samples collected at multiple time points over a 24-hour period. However, BALF was collected only once for most of our participants and may not represent the true intrapulmonary levels of the azoles. Also, the intrapulmonary half-life of the drugs was not examined. Secondly, posaconazole was reserved for patients with impaired liver function, which is an inherent bias in patient selection of our study. Background diseases were largely different between the two groups; chronic obstructive pulmonary disease and connective tissue disease were obviously higher in the voriconazole group. Thirdly, our study was conducted at one center and may not have good representativeness. Lastly, this was a non-randomized study, and the prophylactic drugs were used at the discretion of the treating physician.

In conclusion, despite the significantly higher intrapulmonary concentrations of posaconazole compared to voriconazole, these two agents showed similar effectiveness and adverse events as prophylaxis against IFD among lung transplant recipients.

Availability of data and materials

The dataset supporting the conclusions of this article is available from the corresponding authors on reasonable request.

Ethical statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. All organs were procured from organ procurement organizations and no organs were procured from prisoners.

Funding

This work was supported by the State Key Laboratory of Respiratory Disease (grant number: SKLRD-QN-201 710), the Zhongnanshan Medical Foundation of Guangdong Province (grant number: ZNSA-2 020 013), and Guangzhou Institute of Respiratory Health (grant number: 2019GIRHZ04). The funders had no roles in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of interest

None.

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