Efficacy and Safety of Voriconazole Versus Amphotericin B Deoxycholate Induction Treatment for HIV-Associated Talaromycosis: A Prospective Multicenter Cohort Study in China

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ABSTRACT

Introduction: Current guidelines recommend amphotericin B as the preferred drug for induction therapy; however, amphotericin B is not available in certain settings. Induction therapy with amphotericin B deoxycholate or voriconazole has been shown to be an effective treatment for talaromycosis. However, prospective clinical trials comparing these two antifungal drugs are absent from the literature. *Methods*: In this open-labeled, multicenter, prospective controlled trial, we enrolled patients at 15 hospitals in China from 2019 to 2020. Participants received induction treatment with either amphotericin B deoxycholate intravenously at a dose of 0.5 to 0.7 mg per kilogram per day or voriconazole at a dose of 6 mg/kg

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intravenously twice daily for the first day, followed by 4 mg/kg intravenously twice daily for 3 days, and then voriconazole was given either intravenously (4 mg/kg intravenously twice daily) or orally (200 mg twice daily) for the remaining 10 days. The primary outcome was all-cause mortality during 48 weeks after baseline. Secondary outcomes were mortality at week 2 or week 24, clinical resolution of talaromycosis, and fungal clearance at week 2. A propensity score (PS) matching analysis was performed to control confounding factors.

Results: We observed no difference in the risk of death at week 2, at week 24, or at week 48 in either the unmatched cohort or the matched cohort. Both in the unmatched and the matched cohorts, logistic regression analysis revealed a significantly lower odds ratio of clinical resolution (OR 0.450, 95% CI 0.291–0.696, $p < 0.001$; OR 0.443, 95% CI 0.261–0.752, $p = 0.003$) and fungal clearance (OR 0.514, 95% CI 0.333–0.793, $p = 0.003$; OR 0.542, 95% CI 0.318–0.923, $p = 0.024$) in voriconazole users compared to amphotericin B deoxycholate users over the course of 2 weeks. In the induction therapy without ART subgroup patients in the amphotericin B deoxycholate group showed a significantly higher rate of clinical resolution and fungal clearance than those in the voriconazole group (56.1% vs. 30.4%, 95% CI 13.4–36.5, $p = 0.000$; 63.8% vs. 40.4%, 95% CI 11.1–34.7, $p = 0.000$), whereas there was no significant difference in clinical resolution and fungal clearance in the induction therapy combined with ART subgroup.

Conclusions: Induction therapy using voriconazole had a similar efficacy, in terms of all-cause mortality rate, to induction therapy using amphotericin B deoxycholate in HIV-infected patients with talaromycosis over a 48-week observation period. Amphotericin B deoxycholate contributed to earlier fungal clearance and earlier clinical resolution of symptoms in the induction therapy without ART subgroup, whereas amphotericin B deoxycholate use did not contribute to a significant difference in clinical resolution and fungal clearance in the induction therapy combination with ART subgroup.

Key Summary Points

Why carry out this study?

Even in the present era of widespread antiretroviral therapy (ART) availability and use, HIV-associated talaromycosis remains common in endemic areas globally. Current guidelines recommend amphotericin B as the preferred drug for induction therapy; however, amphotericin B is not available in certain settings.

Induction therapy with amphotericin B deoxycholate or voriconazole has been shown to be an effective treatment for talaromycosis. However, evidence from prospective clinical trials for the optimal antifungal regimen to use in HIV-infected patients with talaromycosis is not currently available in the literature.

What was learned from the study?

Induction therapy using voriconazole had a similar efficacy, in terms of all-cause mortality rate, to induction therapy using amphotericin B deoxycholate in HIV-infected patients with talaromycosis over a 48-week observation period. Amphotericin B deoxycholate contributed to earlier fungal clearance and earlier clinical resolution of symptoms.

Amphotericin B deoxycholate contributed to earlier fungal clearance and earlier clinical resolution of symptoms in the induction therapy without ART subgroup, whereas there was no significant difference between amphotericin B deoxycholate and voriconazole in the time to clinical resolution in the induction therapy combined with ART subgroup.

INTRODUCTION

Talaromycosis (formerly penicilliosis) is an invasive fungal disease caused by *Talaromyces marneffei*, and is more likely to occur in patients infected with HIV or in those using immunosuppressive agents. The prognosis of people living with HIV has been enhanced to a great extent as overall access to antiretroviral therapy (ART) has improved. However, HIV-associated talaromycosis is far from rare in endemic areas, even in the present era of widespread ART [1]. Talaromycosis is also increasingly diagnosed in people living outside of endemic regions [2, 3]. Current guidelines recommend liposomal amphotericin B or amphotericin B deoxycholate as the preferred induction therapy for HIV-infected patients with talaromycosis [4]. In addition, itraconazole is no longer considered to be an appropriate choice for talaromycosis induction therapy according to results from the Itraconazole versus Amphotericin B for Penicilliosis (IVAP) trial [5]. In settings where liposomal amphotericin B is not available, induction therapy with amphotericin B deoxycholate or voriconazole has been shown to be effective [6–8].

In a recent retrospective study, Huang et al. compared amphotericin B deoxycholate and voriconazole for the management of talaromycosis, and they observed that patients in the voriconazole group had a shorter duration of induction and hospital stay than patients in the amphotericin B deoxycholate group, which indicates that voriconazole is potentially a more appropriate induction choice for the treatment of talaromycosis [9]. However, the safety and efficacy of voriconazole in HIV-infected patients with talaromycosis has not been empirically compared with that of amphotericin B deoxycholate in prospective studies. We therefore conducted a prospective cohort study to compare voriconazole and amphotericin B deoxycholate as induction agents for the treatment of talaromycosis.

METHODS

Study Design and Setting

In this multicenter prospective cohort study, we enrolled patients at 15 hospitals located in 12 cities in China from February 19, 2019 through November 30, 2020. These hospitals included Chongqing Public Health Medical Center, Beijing Youan Hospital of Capital Medical University, Harbin Medical University, the First Hospital of Changsha, Guangzhou Eighth People's Hospital, Liuzhou General Hospital, the Third People's Hospital of Guilin, the Third People's Hospital of Shenzhen, Guiyang Public Health Clinical Center, Kunming Third People's Hospital, Yunnan Provincial Infectious Disease Hospital, the Fourth People's Hospital of Nanning, Guangxi Longtan Hospital, the First Affiliated Hospital of Zhejiang University, and Xixi Hospital of Hangzhou. The trial was funded by the National Science and Technology Major Project of China during the 13th Five-year plan period (2018ZX10302104). The independent ethics committee of each participating hospital approved the trial protocol (Approval No. 2019-003-02-KY). The overall progress of the trial was monitored by the trial steering committee. Data were collected and maintained by the investigators and associated research personnel, and the final statistical analysis was performed by the trial statistician. All trial support activities, including project coordination, medical review, data management, site monitoring, and statistical oversight and analyses, were performed at Chongqing Public Health Medical Center.

Study Participants

Eligible patients were HIV-infected adults of 18 years of age or older, who had talaromycosis confirmed by either microscopy or culture. Exclusion criteria included pregnancy, allergy to itraconazole, voriconazole, or amphotericin B, previous treatment for talaromycosis for more than 48 h, systemic antifungal therapy within the first month of enrollment, a hemoglobin level of less than 60 g/L, a white blood

cell count of less than 1.0×10^9/L, a neutrophil count of less than 0.5×10^9/L, a platelet count of less than 30×10^9/L, a blood amylase level of more than two times the reference level upper limit, a serum creatinine level of more than 1.5 times the reference level upper limit, an aspartate aminotransferase level, alanine aminotransferase level, or alkaline phosphatase level of more than five times the reference level upper limit, a total bilirubin level of more than two times the reference level upper limit, and a serum creatine phosphokinase (CK) level of more than two times the reference level upper limit. Written informed consent was obtained from all patients or their representatives.

Study Interventions

In this multicenter prospective cohort study, patients received induction treatment for 14 days with either amphotericin B deoxycholate at a dose of 0.5–0.7 mg per kilogram per day or intravenous voriconazole at a dose of 6 mg/kg twice daily for the first day, followed by 4 mg/kg intravenously twice daily for 3 days, and then voriconazole was given either intravenously (4 mg/kg twice daily) or orally (200 mg twice daily) for the remaining 10 days. Induction treatment regimens were chosen by the attending physician according to current clinical guidelines. Thereafter, all the patients in both groups received itraconazole at a dose of 200 mg twice daily for 10 weeks as consolidation therapy, followed by itraconazole at a dose of 100 mg twice daily as maintenance therapy, until their CD4$^+$ T cell counts were higher than 100 cells/mm^3 for at least 6 months while receiving ART. If patients received induction therapy together with ART, attending physicians appropriately adjusted drug dosages to avoid drug–drug interactions, as per current prescribing guidelines [10]. Each individual was invited to participate in 48 weeks of follow-up. Study visits were scheduled at weeks 1, 2, 4, 8, 12, 24, 36, and 48.

Assessments

At the follow-up visits at week 1, 2, 4, 8, 12, 24, 36, and 48, outcomes and adverse events of patients were evaluated, and we periodically evaluated vital signs, clinical symptoms, hematological indices, biochemical and liver enzyme tests, and blood cultures.

Outcomes and Definitions

The primary outcome was all-cause mortality during the 48 weeks after baseline. Secondary outcomes were mortality at week 2 and at week 24, clinical resolution of talaromycosis, fungal clearance at week 2, and occurrence of adverse events. HIV-associated talaromycosis was defined as occurring in HIV-infected adults who also had a concomitant diagnosis of talaromycosis confirmed by either microscopy or culture [5]. Fungal clearance was defined as blood cultures testing negative after antifungal treatment. Adverse events were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [11]. Respiratory failure and heart failure were defined as the major potential adverse events (grade 3–4) occurring in the respiratory and cardiovascular systems, respectively, as described in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [11]. Clinical resolution of talaromycosis was defined as a body temperature of less than 37.3 °C for three consecutive days, resolution of skin lesions, and fungal clearance. An independent expert panel that was unaware of therapeutic drug assignments to participants arbitrated with regards to the putative causal relationships between serious adverse events and administration of specific trial drugs.

Statistical Analysis

The underlying study assumption was a reduction of the primary event rate from 21.0% to 10.0% [5], with at least 80% power and an overall two-sided alpha level of 0.05. The test statistic used was the two-sided Z test, with

pooled variance. A sample size of 131 patients was calculated to be required in the voriconazole group and 262 patients in the amphotericin B deoxycholate group.

To improve comparability between groups, cases of the voriconazole and the amphotericin B deoxycholate groups were matched on the estimated propensity scores of each group via a 1:1 optimal pair matching process before comparisons were made. We estimated the propensity scores using a multivariable logistic model based on the following key a priori selected variables measured at diagnosis: sex (male vs. female), age (continuous), drinker (yes vs. no), smoker (yes vs. no), antiretroviral therapy (yes vs. no), tuberculosis (yes vs. no), fever (yes vs. no), cough (yes vs. no), sputum (yes vs. no), hemoptysis (yes vs. no), dyspnea (yes vs. no), abdominal pain (yes vs. no), diarrhea (yes vs. no), headache (yes vs. no), skin lesions (yes vs. no), white blood cell count (continuous), hemoglobin (continuous), platelets (continuous), $CD4^+$ T cell counts (continuous), creatinine (continuous), total bilirubin (continuous), aspartate aminotransferase (continuous), alanine aminotransferase (continuous), sodium (continuous), and potassium (continuous). The pre-matching group consisted of 269 patients in the amphotericin B deoxycholate group and 141 participants in the voriconazole group. Subsequently, we obtained 122 matched case–control pairs after performing an optimal nearest-neighbor matching process.

At the time of admission, the demographic, clinical, and laboratory variables of patients were analyzed by standard descriptive statistics. Continuous variables were described as median with interquartile ranges (IQR). Categorical variables were expressed as frequency rates and percentages. We compared continuous variables using the t test or the Mann–Whitney U test, and compared categorical variables using Fisher's exact test or the chi-squared (χ^2) test, as appropriate. Primary and secondary outcomes were compared between the two trial groups using a Cox proportional hazards model and via logistic regression. We used the variance inflation factor (VIF) to quantify the severity of multicollinearity. If the VIF was higher than 5,

then multicollinearity was present. All study data were analyzed using Statistical Package for the Social Sciences software, Version 25.0 (IBM-SPSS Statistics, Armonk, New York, USA).

RESULTS

Patient Characteristics

A total of 489 hospitalized HIV-infected patients diagnosed with talaromycosis were screened. Forty-nine patients were excluded as they did not have their diagnosis of talaromycosis confirmed by either microscopy or culture, and 30 patients were excluded after withdrawal of consent. Thus, in the present study, 410 patients were included. Among them, 269 patients were assigned to the amphotericin B deoxycholate group, and 141 patients to the voriconazole group, as shown in Fig. 1.

Table 1 shows the baseline characteristics of study participants, stratified by induction antifungal regimen. Propensity score matching of the 25 variables matched 122 of the 269 patients who used amphotericin B as induction antifungal therapy to 122 of the 141 patients who used voriconazole as induction antifungal therapy.

Primary and Secondary Outcomes

Figure 2 illustrates the 48-week cumulative proportion of survival in patients with talaromycosis who received amphotericin B induction treatment compared with those who received voriconazole induction treatment. No significant difference in survival proportion between the amphotericin B group and the voriconazole group was observed, whether in the unadjusted cohorts or the propensity-matched cohorts. In the unmatched cohort, 26 (6.3%) patients succumbed during a median follow-up of 29 (IQR 13.115) days. The median time of death in patients treated with amphotericin B deoxycholate and in patients treated with voriconazole was 26 (IQR 11.75) days and 14 (IQR 12.185) days, respectively. Crude 48-week mortality in patients treated with
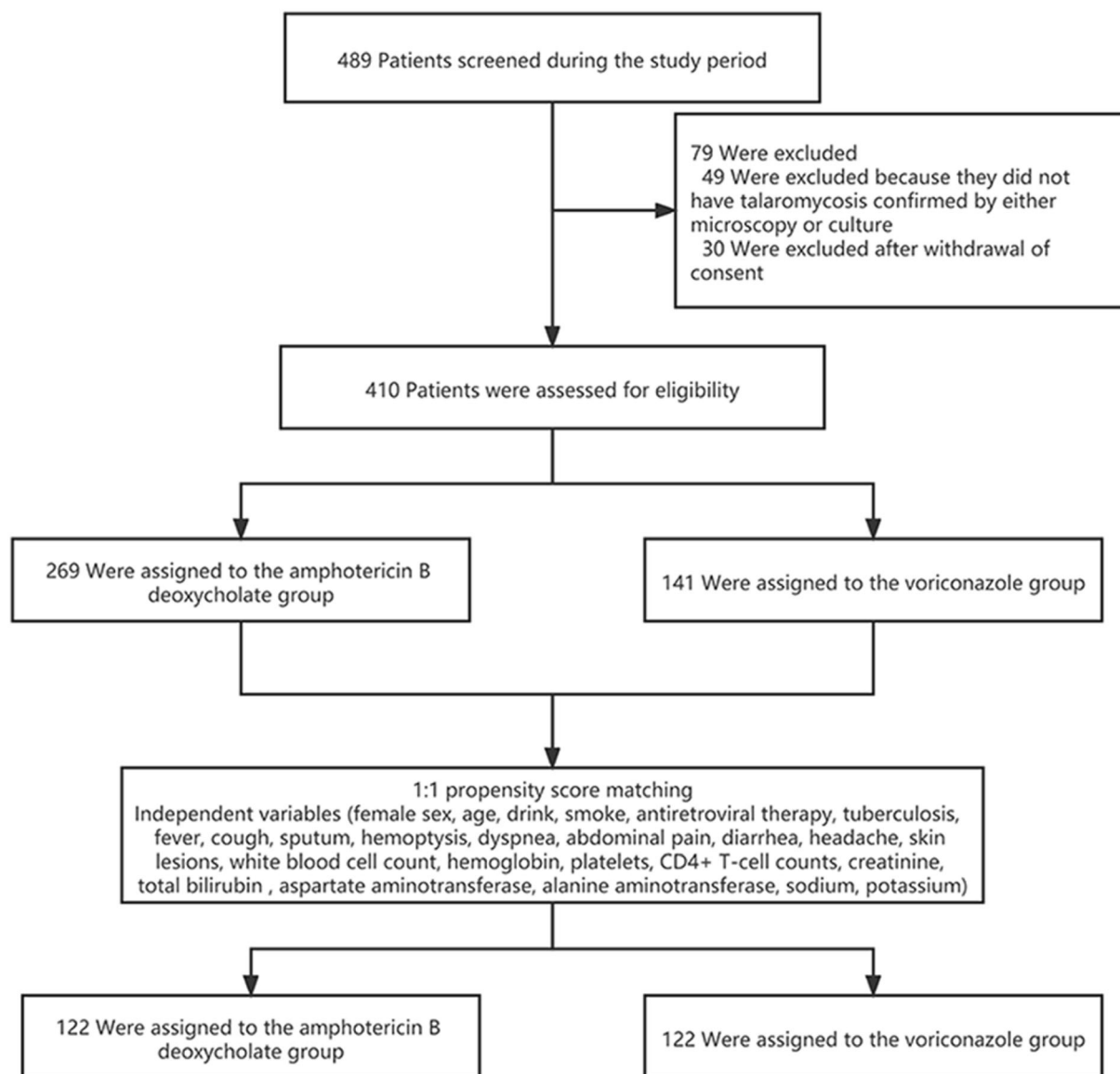
Fig. 1 Study flowchart

amphotericin B deoxycholate vs. voriconazole was 7.1% (95% CI 4.6–10.8%) vs. 5.0% (95% CI 4.4–11.0%), respectively. The corresponding unadjusted hazard ratio (HR) for voriconazole use was 0.794 (95% CI 0.334–1.890, $p = 0.602$). In the matched cohort, 26 (6.3%) patients succumbed during a median follow-up of 29 (IQR 13.115) days. In the amphotericin B deoxycholate group and voriconazole group, the median time of death was 26 (IQR 11.75) and 14 (IQR 12.185) days, respectively, and crude 48-week mortality was 7.1% (95% CI 4.6–10.8%) vs. 5.0% (95% CI 4.4–11.0%). The corresponding unadjusted HR for voriconazole use was 0.794 (95% CI 0.334–1.890, $p = 0.602$), as shown in Fig. 2 and Table 2.

At week 2, in both the unmatched and the matched cohorts, the clinical resolution rate and the fungal clearance rate in the amphotericin B deoxycholate group were both higher than that in the voriconazole group. Corresponding unadjusted odds ratios (OR) of clinical resolution for voriconazole use was 0.450 (95% CI 0.291–0.696, $p < 0.001$) and 0.443

Table 1 Clinical and laboratory characteristics of patients at baseline, before and after matching

Characteristic	Before matching			After matching		
	Amphotericin B (N = 269)	Voriconazole (N = 141)	p	Amphotericin B (N = 122)	Voriconazole (N = 122)	p
Sociodemographic						
Female sex, no. (%)	56 (20.8)	32 (22.7)	0.660	24 (19.7)	28 (23.0)	0.532
Age, median (IQR), years	41 (33–51)	39 (30–48)	0.045	38 (31–48)	39 (32–48)	0.649
Drinker, no. (%)	41 (15.2)	12 (8.5)	0.054	16 (13.1)	12 (9.8)	0.422
Smoker, no. (%)	73 (27.1)	29 (20.6)	0.144	21 (17.2)	28 (23.0)	0.263
Tuberculosis, no. (%)	25 (9.3)	13 (9.2)	0.980	8 (6.6)	12 (9.8)	0.351
Symptoms and signs						
Fever, no. (%)	221 (82.2)	99 (30.9)	0.006	94 (77.0)	91 (74.6)	0.654
Cough, no. (%)	150 (55.8)	90 (63.8)	0.115	74 (60.7)	75 (61.5)	0.896
Sputum, no. (%)	118 (43.9)	67 (47.5)	0.480	54 (44.3)	57 (46.7)	0.700
Hemoptysis, no. (%)	2 (0.7)	0	0.548	0	0	–
Dyspnea, no. (%)	1 (0.4)	2 (1.4)	0.273	1 (0.8)	1 (0.8)	1.000
Abdominal pain, no. (%)	42 (15.6)	18 (12.8)	0.438	17 (13.9)	16 (13.1)	0.852
Diarrhea, no. (%)	18 (6.7)	9 (6.4)	0.905	6 (4.9)	9 (7.4)	0.424
Headache, no. (%)	12 (4.5)	4 (2.8)	0.420	6 (4.9)	4 (3.3)	0.518
Skin lesions, no. (%)	78 (29.0)	44 (31.2)	0.642	39 (32.0)	36 (29.5)	0.677
Laboratory results						
White blood cell count, median (IQR), $\times 10^9$/L	3.7 (2.52–5.25)	3.69 (2.73–5.86)	0.356	3.91 (2.70–5.69)	3.64 (2.70–5.24)	0.376
Hemoglobin, median (IQR), g/L	91 (79–107)	91 (79–109)	0.990	94 (79–108)	91 (80–109)	0.875
Platelets, median (IQR), $\times 10^9$/L	129 (63–199)	125 (63–203)	0.957	129 (61–187)	125 (64–205)	0.680
CD4$^+$ T cell counts, median (IQR), cells/μL	13 (7–31)	11 (6–22)	0.015	12 (7–25)	11 (5–23)	0.313
Creatinine, median (IQR), μmol/L	63 (51.2–77.3)	65.5 (53–77.15)	0.497	66.35 (49.75–81.25)	64.5 (51.83–76.83)	0.651
Creatinine clearance, median (IQR), mL/min/1.73 m^2	99 (75–127)	100 (79–122)	0.978	102 (74–127)	102 (79–122)	0.850
Total bilirubin, median (IQR), mg/dL	9.3 (6.84–14.3)	8.6 (6.20–13.37)	0.234	9.33 (7.18–14.30)	8.62 (6.20–14.00)	0.308

Table 1 continued

Characteristic	Before matching			After matching		
	Amphotericin B (N = 269)	Voriconazole (N = 141)	p	Amphotericin B (N = 122)	Voriconazole (N = 122)	p
Aspartate aminotransferase, median (IQR), U/L	82 (43.5–137.9)	69 (38.2–126.35)	0.091	70 (45–132)	71.50 (38.93–136.00)	0.788
Alanine aminotransferase, median (IQR), U/L	39 (22–64)	36 (21–60)	0.376	40 (23–63)	36 (20–61)	0.473
Sodium, median (IQR), mmol/L	133 (130–137)	133 (130–137)	0.996	133 (130–135)	134 (131–137)	0.253
Potassium, median (IQR), mmol/L	3.63 (3.29–4.00)	3.67 (3.44–4.00)	0.194	3.7 (3.3–4.07)	3.69 (3.44–4.09)	0.650
Antiretroviral therapy before antifungal therapy						
Receiving therapy, no. (%)	34 (12.6)	16 (11.3)	0.704	12 (9.8)	15 (12.3)	0.540
Median duration (IQR), days	29 (10–754)	14 (9–297)	0.399	25 (6–781)	14 (9–297)	0.642
Containing integrase inhibitors, no. (%)	3 (1.1)	3 (2.1)	0.418	2 (1.6)	3 (2.5)	1.000
Containing protease inhibitors, no. (%)	5 (1.9)	1 (0.7)	0.669	2 (1.6)	1 (0.8)	1.000
Containing NNRTIs, no. (%)	26 (9.7)	12 (8.5)	0.702	8 (6.6)	12 (9.8)	0.351

*IQR* interquartile range, *NNRTIs* non-nucleoside reverse transcriptase inhibitors

(95% CI 0.261–0.752, $p = 0.003$) in the unmatched and the matched cohorts, respectively. Corresponding unadjusted odds ratios (OR) of fungal clearance for voriconazole use were 0.514 (95% CI 0.333–0.793, $p = 0.003$) and 0.542 (95% CI 0.318–0.923, $p = 0.024$) in the unmatched and the matched cohorts, respectively, as shown in Table 2.

In the Cox proportional hazards model, there was no difference in mortality risk at week 2 or at week 24 between the amphotericin B deoxycholate group and the voriconazole group in both the unmatched or the matched cohorts, as shown in Table 2.

Adverse Events

A higher number of patients in the amphotericin B deoxycholate group than in the voriconazole group had a hemoglobin level below 74 g/L (122 of 269 patients vs. 45 of 141 patients, respectively, $p = 0.009$), a creatinine clearance level below 30 mL/min (17 of 269 patients vs. 1 of 141 patients, respectively, $p = 0.008$), and a potassium level below 2.4 mmol/L (22 of 255 patients vs. 2 of 141 patients, respectively, $p = 0.006$). The incidence of clinical adverse events (respiratory failure, heart failure, drug eruptions, and altered mental status) and laboratory adverse events (white cell
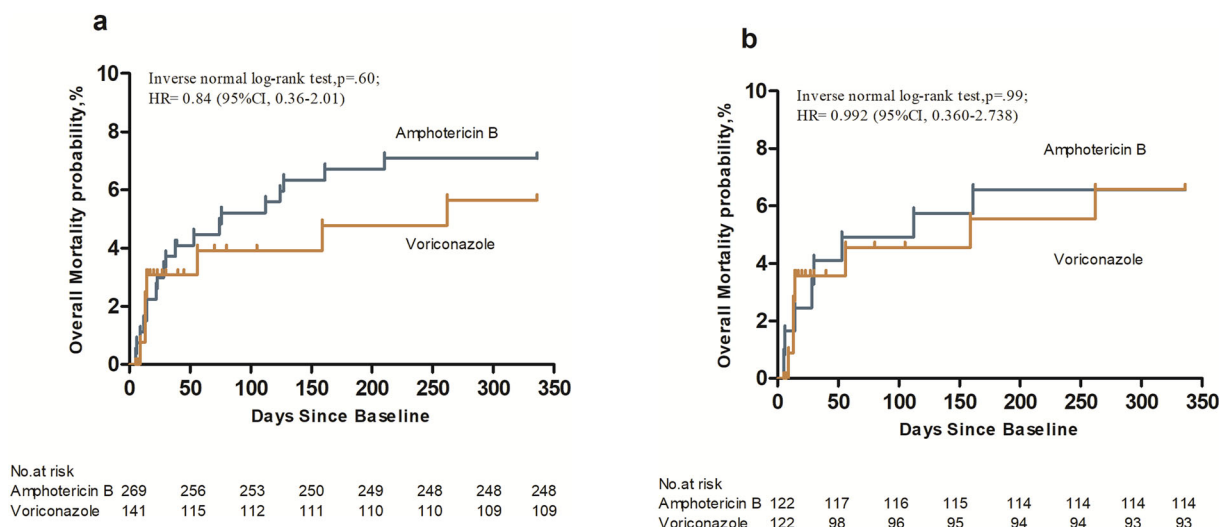
Fig. 2 One-year cumulative event rates of all-cause mortality among patients in two treatment groups in the unadjusted and propensity-matched cohorts. Kaplan–Meier curve of the **a** unmatched study cohort and **b** matched study cohort

count below 1.49×10^9 /L, platelet count below 49×10^9/L, creatinine more than 3.5 times the upper limit of normal (ULN), total bilirubin more than five times ULN, aspartate aminotransferase more than 10 times ULN, and alanine aminotransferase more than 10 times ULN) were similar in the two groups (Table 3). After propensity matching, a higher number of patients in the amphotericin B deoxycholate group than in the voriconazole group had a creatinine clearance level below 30 mL/min (7 of 122 patients vs. 0 of 122 patients, respectively, $p = 0.021$); however, no significant statistical differences were observed between the two groups in the incidence of other clinical and laboratory adverse events (Table 3).

Outcomes in the Subgroups

There was no significant difference in mortality between the two therapeutic groups in the induction therapy without ART subgroup, the induction therapy with ART subgroup, the induction therapy with integrase inhibitors subgroup, the induction therapy with protease inhibitors subgroup, and in the induction therapy with non-nucleoside reverse transcriptase inhibitors subgroup (Table 4).

In the induction therapy without ART subgroup, patients in the amphotericin B deoxycholate group showed significantly higher rates of clinical resolution and fungal clearance at 2 weeks than those in the voriconazole group (56.1% vs. 30.4%, 95% CI 13.4–36.5, $p = 0.000$; 63.8% vs. 40.4%, 95% CI 11.1–34.7, $p = 0.000$). There was no significant difference in the rates of clinical resolution and fungal clearance at 2 weeks between the two therapeutic groups in the induction therapy with ART subgroup, the induction therapy with integrase inhibitors subgroup, the induction therapy with protease inhibitors subgroup, and in the induction therapy with non-nucleoside reverse transcriptase inhibitors subgroup.

DISCUSSION

The present multicenter prospective cohort trial involved participants from hospitals in 12 cities in China, and included hospitals in endemic and non-endemic areas for talaromycosis. Our results are thus likely to be generally applicable to all of China. In this study, the overall 48-week mortality rate for HIV-infected patients with talaromycosis was 6.3%, and is similar to that of patients receiving amphotericin B deoxycholate induction treatment, and also

Table 2 Outcomes before and after matching, over 48 weeks

	Events		Effect size (95% CI)[a]	p
	Amphotericin B (N = 269)	Voriconazole (N = 141)		
Before matching	N = 269	N = 141		
Death at 2 weeks[b]	6 (2.2%)	4 (2.8%)	1.357 (0.383, 4.808)	0.637
Death at 24 weeks[b]	18 (6.7%)	6 (4.3%)	0.716 (0.284, 1.804)	0.478
Death at 48 weeks[b]	19 (7.1%)	7 (5.0%)	0.794 (0.334, 1.890)	0.602
Clinical resolution at 2 weeks[c]	147 (56.1%)	46 (36.5%)	0.450 (0.291, 0.696)	0.000
Fungal clearance at 2 weeks[c]	166 (63.8%)	59 (47.6%)	0.514 (0.333, 0.793)	0.003
After matching	N = 122	N = 122		
Death at 2 weeks[b]	3 (2.5%)	4 (3.3%)	1.415 (0.317, 6.326)	0.649
Death at 24 weeks[b]	8 (6.6%)	6 (4.9%)	0.846 (0.293, 2.440)	0.757
Death at 48 weeks[b]	8 (6.6%)	7 (5.7%)	0.992 (0.360, 2.738)	0.988
Clinical resolution at 2 weeks[c]	72 (59.5%)	43 (39.4%)	0.443 (0.261, 0.752)	0.003
Fungal clearance at 2 weeks[c]	79 (65.3%)	54 (50.5%)	0.542 (0.318, 0.923)	0.024

[a]All HR or OR estimates are vs. amphotericin B
[b]Calculated using a Cox proportional hazards method
[c]Calculated using a logistic regression model

concurs with figures reported in other studies [5, 12, 13]. In addition, we observed that the use of voriconazole resulted in no differences in mortality compared with that using amphotericin B deoxycholate at 2 weeks, at 24 weeks, or at 48 weeks. However, at 2 weeks, voriconazole had a less robust effect on pathogen elimination and clinical resolution than amphotericin B deoxycholate.

Previous studies have indicated that voriconazole does have a favorable effect against *T. marneffei*. In in vitro studies, voriconazole shows good activity against the 57 known strains of *T. marneffei* [14]. The minimal inhibitory concentrations (MIC) of voriconazole and amphotericin B are both low (≤ 0.008 to $0.06 \, \mu g/mL$ and $\leq 0.12–1 \, \mu g/mL$, respectively) in the yeast phase [15]. Moreover, an earlier clinical study observed that eight of nine patients with talaromycosis who received voriconazole therapy achieved favorable outcomes, based on clinical and mycological

responses [8]. In the investigation by Ouyang et al. [7], only one of 14 patients with talaromycosis was determined to have failed to respond to voriconazole, which again demonstrates the efficacy of voriconazole in patients with talaromycosis. The findings of other recent studies have further suggested that voriconazole is noninferior to amphotericin B deoxycholate as induction therapy for talaromycosis [9]. This conclusion is also supported by the results of our prospective study. Conversely, Ying et al. observed that induction therapy with azoles (voriconazole or itraconazole) correlates with a higher mortality rate than that of amphotericin B [16].

Early ART initiation should be actively considered for HIV-infected patients with talaromycosis [17]. When HIV-infected patients receive induction therapy together with ART, potential drug interactions are more likely to occur, especially with voriconazole (one of the triazole fungicidal agents) use, which has

Table 3 Adverse events before and after matching, over 48 weeks

	Before matching			After matching		
	Amphotericin B (N = 269)	Voriconazole (N = 141)	p	Amphotericin B (N = 122)	Voriconazole (N = 122)	p
Clinical adverse events						
Respiratory failure, no. (%)	3 (1.1)	2 (1.4)	1.000	1 (0.8)	2 (1.6)	1.000
Heart failure, no. (%)	3 (1.1)	1 (0.7)	1.000	2 (1.6)	1 (0.8)	1.000
Drug eruptions, no. (%)	1 (0.4)	2 (1.4)	0.568	0	2 (1.6)	0.478
Altered mental status, no. (%)	0	1 (0.7)	0.344	0	1 (0.8)	1.000
Laboratory adverse events						
White cell count $< 1.49 \times 10^9$ /L, no. (%)	32 (11.9)	10 (7.1)	0.128	14 (11.5)	10 (8.2)	0.390
Hemoglobin < 74 g/L, no. (%)	122 (45.4)	45 (31.9)	0.009	50 (41.0)	38 (31.1)	0.110
Platelet count $< 49 \times 10^9$ /L, no. (%)	44 (16.4)	21 (14.9)	0.700	18 (14.8)	18 (14.8)	1.000
Potassium < 2.4 mmol/L, no. (%)	22 (8.2)	2 (1.4)	0.006	7 (5.7)	1 (0.8)	0.072
Creatinine > 3.5 times ULN, no. (%)	1 (0.4)	1 (0.7)	1.000	1 (0.9)	0	1.000
Creatinine clearance < 30 mL/min	17 (6.3)	1 (0.7)	0.008	7 (5.7)	0	0.021
Total bilirubin > 5 times ULN, no. (%)	6 (2.2)	4 (2.8)	0.967	2 (1.7)	4 (3.3)	0.679
Aspartate aminotransferase > 10 times ULN, no. (%)	4 (1.5)	2 (1.4)	1.000	1 (0.8)	2 (1.6)	1.000
Alanine aminotransferase > 10 times ULN, no. (%)	1 (0.4)	0	1.000	1 (0.8)	0	1.000

ULN upper limit of the normal range

potent activity against a broad spectrum of fungi. Clearance of voriconazole occurs through the liver via N-oxidation by the hepatic cytochrome P450 (CYP) isoenzymes CYP2C19, CYP2C9, and CYP3A4, which implies that potential drug interactions are much more likely to occur, especially in HIV-infected patients with talaromycosis requiring induction therapy while concomitantly taking ART. It is unfortunate that blood drug concentrations of voriconazole were not determined in our study. However, our subgroup analysis observed that voriconazole had a less robust effect on pathogen elimination and clinical resolution than amphotericin B deoxycholate in the induction therapy without ART subgroup, whereas there

Table 4 Outcomes in the subgroups over 48 weeks

	Events		95% CI for difference in proportions	P value
	Amphotericin B (*N* = 269)	Voriconazole (*N* = 141)		
Induction therapy without ART subgroup, no. (%)	197	97		
Death at 2 weeks	5 (2.5)	4 (4.1)	− 2.5 to 7.8	0.702
Death at 24 weeks	16 (8.1)	6 (6.2)	− 5.4 to 7.7	0.553
Death at 48 weeks	17 (8.6)	7 (7.2)	− 6.2 to 7.4	0.677
Clinical resolution at 2 weeks	110 (56.1)	28 (30.4)	13.4 to 36.5	0.000
Fungal clearance at 2 weeks	125 (63.8)	38 (40.4)	11.1 to 34.7	0.000
Induction therapy combined with ART subgroup, no. (%)	72	44		
Death at 2 weeks	1 (1.4)	0 (0)	− 6.7 to 7.5	1.000
Death at 24 weeks	2 (2.8)	0 (0)	− 5.5 to 9.6	0.525
Death at 48 weeks	2 (2.8)	0 (0)	− 5.5 to 9.6	0.525
Clinical resolution at 2 weeks	37 (53.6)	18 (42.9)	− 8.2 to 28.5	0.271
Fungal clearance at 2 weeks	41 (60.3)	21 (51.2)	− 9.7 to 27.3	0.354
Induction therapy combined with integrase inhibitors subgroup, no. (%)	20	22		
Death at 2 weeks	0	0	–	–
Death at 24 weeks	0	0	–	–
Death at 48 weeks	0	0	–	–
Clinical resolution at 2 weeks	9 (47.4)	9 (40.9)	− 22.1 to 40.9	0.678
Fungal clearance at 2 weeks	11 (57.9)	9 (42.9)	− 14.8 to 41.5	0.342
Induction therapy combined with protease inhibitors subgroup, no. (%)	11	4		
Death at 2 weeks	1 (8.3)	0	− 41.1 to 35.4	1.000
Death at 24 weeks	1 (8.3)	0	− 41.1 to 35.4	1.000
Death at 48 weeks	1 (8.3)	0	− 41.1 to 35.4	1.000
Clinical resolution at 2 weeks	7 (63.6)	2 (50.0)	− 31.3 to 54.6	1.000
Fungal clearance at 2 weeks	7 (63.6)	3 (75.0)	− 31.3 to 54.6	1.000
Induction therapy combined with NNRTIs subgroup, no. (%)	38	17		
Death at 2 weeks	0	0	–	–
Death at 24 weeks	1 (2.5)	0	− 16.9 to 12.9	1.000

Table 4 continued

	Events		95% CI for difference in proportions	P value
	Amphotericin B (N = 269)	Voriconazole (N = 141)		
Death at 48 weeks	1 (2.5)	0	− 16.9 to 12.9	1.000
Clinical resolution at 2 weeks	21 (53.8)	6 (42.9)	− 17.9 to 37.0	0.480
Fungal clearance at 2 weeks	23 (60.5)	7 (50.0)	− 17.6 to 37.6	0.496

ART antiretroviral therapy, *NNRTIs* non-nucleoside reverse transcriptase inhibitors

was no significant difference in the rate of clinical resolution and fungal clearance at 2 weeks between the two groups in the induction therapy combined with ART subgroup. This implies that patients receive equal benefit when using either voriconazole or amphotericin B deoxycholate for induction therapy when treatment occurs together with ART. At the same time, when HIV-infected patients receive induction therapy without ART, induction therapy using amphotericin B deoxycholate contributes to earlier fungal clearance and earlier clinical resolution of symptoms when compared to when voriconazole is used without ART.

Anemia occurs commonly in HIV-infected patients with talaromycosis before receiving amphotericin B, with a prevalence of around 80–95.6% [16, 18]. Up to 40% of HIV-infected patients with talaromycosis with or without anemia at baseline go on to develop severe anemia when they receive amphotericin B deoxycholate [5]. Hypokalemia and nephrotoxicity are also common in patients using amphotericin B deoxycholate [5, 19]. In our study, and before propensity matching, more patients in the amphotericin B deoxycholate group than in the voriconazole group had a hemoglobin level of less than 74 g/L, a creatinine clearance level below 30 mL/min, and a potassium level of less than 2.4 mmol/L, without observable differences in hemoglobin, creatinine clearance, and potassium levels at baseline. However, after propensity matching, there was no significant difference in the incidence of clinical and laboratory adverse events between the two therapeutic groups. This

implies that cases of hemoglobin levels of less than 74 g/L or potassium levels of less than 2.4 mmol/L may well be related to other factors, such as age, presence of fever, and $CD4^+$ T cell counts, which were calculated to be statistically significantly different at baseline.

One limitation of our study is its non-randomized design, which may have introduced a degree of bias from potential differences in baseline characteristics and physician selection strategies. We have endeavored to reduce this risk via statistical methods. In addition, in our study, we only analyzed all-cause mortality, and acknowledge that some instances of mortality may have likely been attributable to causes other than talaromycosis. Also, our study population included only Chinese subjects, which limits the overall generalizability of our findings.

CONCLUSIONS

Induction therapy using voriconazole had a similar efficacy in terms of all-cause mortality rate to induction therapy using amphotericin B deoxycholate in HIV-infected patients with talaromycosis over a 48-week observation period. Amphotericin B deoxycholate contributed to earlier fungal clearance and earlier clinical resolution of symptoms.

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Author Contributions. YC, YZ and YQ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YC, YZ, YQ, YL, JY, JN and Min Liu contributed to conceptualization. YC, YZ, and YQ contributed to project administration, supervision, and formal analysis. QT, KL, GZ, YQ, KH, JY, ZJ, JL, and SL conducted investigation, data curation, and resources. YC contributed to funding acquisition. YC, YZ, YQ, and VH contributed to drafting of the manuscript and writing, revision, copy-editing, and proofreading. All authors contributed to critical revision of the manuscript for important intellectual content.

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Compliance with Ethics Guidelines. The independent ethics committee of each participating hospital approved the trial protocol (Chongqing Public Health Medical Center, Beijing Youan Hospital of Capital Medical University, Harbin Medical University, the First Hospital of Changsha, Guangzhou Eighth People's Hospital, Liuzhou General Hospital, the Third People's Hospital of Guilin, the Third People's Hospital of Shenzhen, Guiyang Public Health Clinical Center, Kunming Third People's Hospital, Yunnan Provincial Infectious Disease Hospital, the Fourth People's Hospital of Nanning, Guangxi Longtan Hospital, the First Affiliated Hospital of Zhejiang University, and Xixi Hospital of Hangzhou). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. The trial was registered at Chinese Clinical Trial Registry (Chictr.org.cn, ChiCTR1900021195).

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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