ORIGINAL ARTICLE

A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis

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ABSTRACT

BACKGROUND

Talaromyces marneffei infection is a major cause of human immunodeficiency virus (HIV)–related death in South and Southeast Asia. Guidelines recommend initial treatment with amphotericin B deoxycholate, but this drug has substantial side effects, a high cost, and limited availability. Itraconazole is available in oral form, is associated with fewer unacceptable side effects than amphotericin, and is widely used in place of amphotericin; however, clinical trials comparing these two treatments are lacking.

METHODS

In this open-label, noninferiority trial, we randomly assigned 440 HIV-infected adults who had talaromycosis, confirmed by either microscopy or culture, to receive either intravenous amphotericin B deoxycholate (amphotericin) (219 patients), at a dose of 0.7 to 1.0 mg per kilogram of body weight per day, or itraconazole capsules (221 patients), at a dose of 600 mg per day for 3 days, followed by 400 mg per day, for 11 days; thereafter, all the patients received maintenance therapy with itraconazole. The primary outcome was all-cause mortality at week 2. Secondary outcomes included all-cause mortality at week 24, the time to clinical resolution of talaromycosis, early fungicidal activity, relapse of talaromycosis, development of the immune reconstitution inflammatory syndrome (IRIS), and the side-effect profile.

RESULTS

The risk of death at week 2 was 6.5% in the amphotericin group and 7.4% in the itraconazole group (absolute risk difference, 0.9 percentage points; 95% confidence interval [CI], −3.9 to 5.6; P<0.001 for noninferiority); however, the risk of death at week 24 was 11.3% in the amphotericin group and 21.0% in the itraconazole group (absolute risk difference, 9.7 percentage points; 95% CI, 2.8 to 16.6; P=0.006). Treatment with amphotericin was associated with significantly faster clinical resolution and fungal clearance and significantly lower rates of relapse and IRIS than itraconazole. The patients who received amphotericin had significantly higher rates of infusion-related reactions, renal failure, hypokalemia, hypomagnesemia, and anemia than patients in the itraconazole group.

CONCLUSIONS

Amphotericin was superior to itraconazole as initial treatment for talaromycosis with respect to 6-month mortality, clinical response, and fungicidal activity. (Funded by the Medical Research Council and others; IVAP Current Controlled Trials number, ISRCTN59144167.)

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The dimorphic fungus *Talaromyces* (previously *Penicillium*) *marneffei* causes a life-threatening mycosis in immunocompromised persons living in or traveling to Southeast Asia, China, and India.[1] Talaromycosis (previously penicilliosis) is a major cause of human immunodeficiency virus (HIV)–related death; its prevalence is surpassed only by the prevalence of tuberculosis and cryptococcosis,[2] and it leads to 4 to 15% of HIV-related hospital admissions in regions in which the disease is endemic.[3-7] Talaromycosis is increasingly diagnosed among patients who are not infected with HIV but who have other immunodeficiency conditions[8] and is reported to be the second most common cause of all bloodstream infections in southern Vietnam.[9] Despite a mortality rate of up to 30% among affected patients who receive antifungal therapy,[2,3,5,10,11] randomized trials evaluating treatment strategies are lacking. International guidelines recommend initial (induction) therapy with amphotericin B deoxycholate (amphotericin), at a dose of 0.7 to 1 mg per kilogram of body weight per day for 2 weeks, followed by itraconazole at a dose of 400 mg per day for 10 weeks,[12,13] on the basis of a noncomparative trial in Thailand that showed clinical resolution in 72 of 74 patients (97.3%) who received treatment according to this regimen.[14] Amphotericin has substantial renal, hematologic, and infusion-related toxic effects for which patients typically receive in-hospital care and close monitoring. In addition, access to amphotericin is hampered by cost and by inadequate supply chains in Asia. In Vietnam, a 2-week course of amphotericin costs approximately $350 (in U.S. dollars), excluding the costs of hospitalization and laboratory monitoring. In contrast, itraconazole is associated with fewer unacceptable side effects, is widely available, is available in oral form, and costs one seventh the price of amphotericin. According to large, retrospective case series from China, India, and Vietnam, itraconazole is the most commonly used treatment for talaromycosis and is similar to amphotericin with respect to clinical responses and mortality.[5-7,10,11,15]

We hypothesized that itraconazole would be noninferior to amphotericin as induction therapy for talaromycosis, with the advantages of fewer toxic effects, lower cost, availability as oral treatment that can be administered on an outpatient basis, and wider availability. To test this hypothesis, we conducted the Itraconazole versus Amphotericin B for Penicilliosis (IVAP) trial, a randomized, open-label, controlled trial that was powered to assess survival, in five trial centers in Vietnam.

Methods

Trial Design and Oversight

From October 2012 through December 2015, we enrolled patients at five referral hospitals located in the Vietnam provinces that have the highest prevalence of HIV.[16] Eligible patients were HIV-infected adults (≥18 years of age) who had talaromycosis that was confirmed by either microscopy or culture. Exclusion criteria were pregnancy, central nervous system involvement assessed either clinically or by analyses of cerebrospinal fluid, an allergy to either itraconazole or amphotericin, or the concomitant use of certain medications that interact with either itraconazole or amphotericin, an alanine aminotransferase or aspartate aminotransferase level of more than 400 U per liter, an absolute neutrophil count of less than 500 per cubic millimeter, a creatinine clearance of less than 30 ml per minute (calculated by the method of Cockcroft and Gault), a concurrent diagnosis of cryptococcal meningitis, concurrent treatment with rifampicin, or previous treatment for talaromycosis for more than 48 hours. Written informed consent was obtained from all the patients or their representatives. Details regarding the trial centers and recruitment procedures are provided in the trial protocol and in the Supplementary Appendix, both of which are available with the full text of this article at NEJM.org.

The protocol was approved by the independent ethics committee at each participating hospital, by the Vietnam Ministry of Health, and by the Oxford University Tropical Research Ethics Committee. The Vietnam Ministry of Health and an independent data monitoring and ethics committee oversaw the safety of the trial. The data monitoring and ethics committee performed a formal interim analysis after the enrollment of every 100 patients or after every 20 deaths. A trial steering committee supervised and monitored the progress of the trial. The investigators and associated research personnel collected and maintained the data. The trial statistician performed the final analysis. The trial was sponsored by the Medical Research Council, the Department for International Development, and the Wellcome

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Trust in the United Kingdom. The sponsors were not involved in the design or implementation of the protocol, the analysis of the data, or the preparation or review of the manuscript. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. Additional details about enrollment and monitoring of the trial can be found in Sections 3 and 4, respectively, in the Supplementary Appendix.

TREATMENT

In this open-label trial, patients were randomly assigned in a 1:1 ratio to receive treatment for 14 days with either intravenous amphotericin B deoxycholate (amphotericin) (purchased from Cipla, India) at a dose of 0.7 to 1.0 mg per kilogram per day or itraconazole capsules (purchased from Stada, Vietnam) at a dose of 300 mg twice daily for the first 3 days, followed by 200 mg twice daily for the remaining 11 days. Thereafter, all the patients received itraconazole at a dose of 200 mg twice daily for 10 weeks, followed by itraconazole at a dose of 100 mg twice daily until their CD4+ cell counts were higher than 100 cells per cubic millimeter for at least 6 months while they were receiving antiretroviral therapy (ART). Patients were instructed to take itraconazole immediately after a full meal or acidic beverage. All the patients received prophylactic treatment with trimethoprim–sulfamethoxazole for *Pneumocystis jiroveci* pneumonia. Patients who had not previously received ART were referred to HIV clinics for the initiation of first-line ART, which consisted of tenofovir, lamivudine, and efavirenz, administered according to the national guidelines. All the patients were hospitalized during the initial 2-week period of the trial, during which time administration of therapy was directly observed. Adherence to itraconazole was assessed during all the follow-up visits by means of patient-reported estimates of the number of missed doses during the preceding month.

RANDOMIZATION

Randomization was stratified according to trial center. A computer-generated randomization list with block sizes of 4 or 6 was prepared for each center by the trial pharmacist, who had no clinical involvement in the trial. The randomization lists, which were incorporated into a Web-based program that was accessible by authorized trial investigators, showed only the next assigned treatment. All the transactions on the Web server were logged, unchangeable, and auditable.

ASSESSMENTS

Patients were assessed daily during the first 2-week inpatient period and then monthly for 6 months in outpatient clinics. Side effects were monitored clinically and with the use of hematologic, chemical, and liver-enzyme testing performed at least twice weekly. All the patients were screened for tuberculosis by means of sputum microscopy. The number of fungal colony-forming units (CFUs) per milliliter of blood was measured on days 1 through 4 and every other day thereafter until the cultures became negative or until the patient was discharged from the hospital. The method for quantifying fungal CFUs was adapted from the method that has been used to quantify cryptococcal CFUs in cerebrospinal fluid[17] and is described in detail in Section 6 in the Supplementary Appendix.

OUTCOMES

The primary outcome measure was all-cause mortality, which was defined as the absolute risk of death from any cause during the first 2 weeks after randomization. The secondary outcome measures were mortality at week 24, the time to clinical resolution of talaromycosis, early fungicidal activity, relapse of talaromycosis, the development of the immune reconstitution inflammatory syndrome (IRIS), and the incidence of adverse events of grade 3 or higher. Clinical resolution of talaromycosis was defined as a temperature of less than 38°C (100°F) for 3 days, resolution of skin lesions, and sterile blood cultures. Early fungicidal activity was defined as the rate of decline in blood *T. marneffei* CFUs from serial blood cultures obtained during the first 2 weeks. Relapse of talaromycosis was defined as the recurrence of symptoms and a positive fungal culture from any sterile site that led to reinduction of therapy in patients who had achieved clinical resolution. IRIS was defined as unexpected worsening of symptoms associated with inflammation in patients who started ART and had increasing CD4+ cell counts. Adverse events were graded according to the 2009 National Institutes of Health Division of AIDS Grading of Adverse Events, version 1.0.[18] An independent expert review committee whose members were unaware of the treatment assignments

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adjudicated the IRIS and relapse events, assessed whether there was a causal relationship between serious adverse events and trial drugs, and assessed whether a patient's death was due to talaromycosis.

STATISTICAL ANALYSIS

Assuming a 15% risk of death during the first 2 weeks (on the basis of data from the Hospital for Tropical Disease in southern Vietnam between 2009 and 2011[5]), we calculated that a sample size of 440 patients would provide the trial with 80% power to show the noninferiority of itraconazole to amphotericin at a one-sided alpha level of 0.025 with the use of a noninferiority margin of 10 percentage points for the absolute risk difference (detailed justification is provided in Section 3.7.5 of the protocol). All the analyses were specified before the release of the randomization list, as detailed in the protocol and the statistical analysis plan. In brief, we estimated the risk of death at 2 weeks and at 24 weeks with the use of the Kaplan–Meier method. Confidence intervals and tests for the absolute risk difference were based on standard errors calculated with the use of Greenwood's formula. Cumulative mortality by week 24 was analyzed with the use of a Cox proportional-hazards model. The time to clinical resolution of talaromycosis and the time to relapse of talaromycosis and to the development of IRIS were analyzed with the use of competing-risks methods (cumulative incidence functions and Fine–Gray regression models) to account for the competing risk of death without a previous event. Cause-specific death was analyzed similarly. Declines in $\log_{10}$-transformed longitudinal measurements of fungal CFUs in blood were estimated for each patient with the use of a least-squares regression model. The comparison of declines in fungal CFUs between the two treatment groups was based on linear regression, with treatment as the main covariate and with adjustment for the baseline $\log_{10}$ fungal count. Statistical analyses were performed with the use of the R statistical package, version 3.3.1 (www.r-project.org/).[19]

RESULTS

TRIAL POPULATION

Of the 573 patients screened, 440 patients underwent randomization; 219 patients were assigned to the amphotericin group and 221 to the itraconazole group (Fig. 1). A total of 5 patients were excluded from the intention-to-treat analysis (as defined in the protocol) because the initial diagnosis of talaromycosis that was confirmed by microscopy was incorrect. An additional 8 patients were excluded from the modified intention-to-treat analysis because they did not receive the assigned intervention, and 8 other patients were excluded from the per-protocol analysis because of violations of the inclusion or exclusion criteria, withdrawal from the trial, or receipt of the trial drug for fewer than 7 days (Fig. 1). In 998 of 1067 outpatient visits (93.5%) in the amphotericin group and 984 of 1038 outpatient visits (94.8%) in the itraconazole group, the number of missed doses of itraconazole as maintenance therapy was recorded as zero.

PATIENT CHARACTERISTICS

Baseline characteristics were similar in the two treatment groups, with the exception of the duration of ART (which was approximately 1 month longer in the amphotericin group than in the itraconazole group) (Table 1, and Table S1 in the Supplementary Appendix). The median CD4+ cell count at enrollment was 10 cells per cubic millimeter. Skin lesions were present in 80.0% of the patients; the skin smear was positive for *T. marneffei* in 90.1% of the patients, and the skin culture was positive in 87.6% of the patients. The blood culture was positive for *T. marneffei* in 70.0% of the patients; the median number of fungal CFUs in blood was 2.35 $\log_{10}$ CFUs per milliliter.

PRIMARY OUTCOME

Key trial outcomes are summarized in Table 2. In the intention-to-treat analysis, 14 of 217 patients (6.5%) in the amphotericin group and 16 of 218 patients (7.4%) in the itraconazole group died by week 2 (absolute risk difference, 0.9 percentage points; 95% confidence interval [CI], −3.9 to 5.6; P<0.001 for noninferiority). The findings in the modified intention-to-treat and per-protocol populations were similar to those in the intention-to-treat population. No evidence of heterogeneity of effect was observed in the prespecified subgroups of the intention-to-treat population, which were defined according to baseline characteristics, including injection-

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drug use, ART status, CD4+ cell counts, fungemia, the number of fungal CFUs, dyspnea for which the patient received oxygen, and oropharyngeal ulcers (Fig. S1 in the Supplementary Appendix). A logistic-regression analysis (Table S2 in the Supplementary Appendix) identified a higher number of fungal CFUs at baseline as an independent predictor of death in the first 2 weeks (odds ratio per each additional 1 $\log_{10}$ CFU per milliliter, 2.18; 95% CI, 1.43 to 3.45; P<0.001).

SECONDARY OUTCOMES

Mortality by Week 24

By week 24, a total of 24 of the 217 patients (11.3%) in the amphotericin group and 45 of the 218 patients (21.0%) in the itraconazole group had died (absolute risk difference, 9.7 percentage points; 95% CI, 2.8 to 16.6; P=0.006). The results were consistent in the modified intention-to-treat and per-protocol populations (Table 2). The Kaplan–Meier curves showed a separation of the two treatment groups after 8 weeks, and the risk of death continued to increase in the itraconazole group until week 24 (Fig. 2A). No clear evidence of heterogeneity of effect was seen in the prespecified subgroups of the intention-to-treat population; however, there was evidence of a time-varying effect of the treatment assignment, whereby treatment with itraconazole increased the risk of death primarily during weeks 9 through 16 (hazard ratio, 11.20; 95% CI, 1.45 to 86.76; P=0.02) and during weeks 17 through 24 (hazard ratio, 8.55; 95% CI, 1.07 to 68.36; P=0.04) (Figs. S2 and S3 in the Supplementary Appendix). A multivariable Cox regression model identified treatment with itraconazole (hazard ratio, 1.86; 95% CI, 1.09 to 3.19; P=0.02) and the number of baseline fungal CFUs (hazard ratio, 1.45; 95% CI, 1.13 to 1.86; P=0.004) as independent predictors of death over the course of 24 weeks (Table S2 in the Supplementary Appendix). Among the patients in the trial who had not previously received ART, 101 of 124 patients (81.5%) in the amphotericin group and 96 of 123 patients (78.0%) in the itraconazole group initiated ART during the course of the trial after a median of 23 days (interquartile range, 16 to 36) in the amphotericin group and after a median of 22 days (interquartile range, 15 to 31) in the itraconazole group.

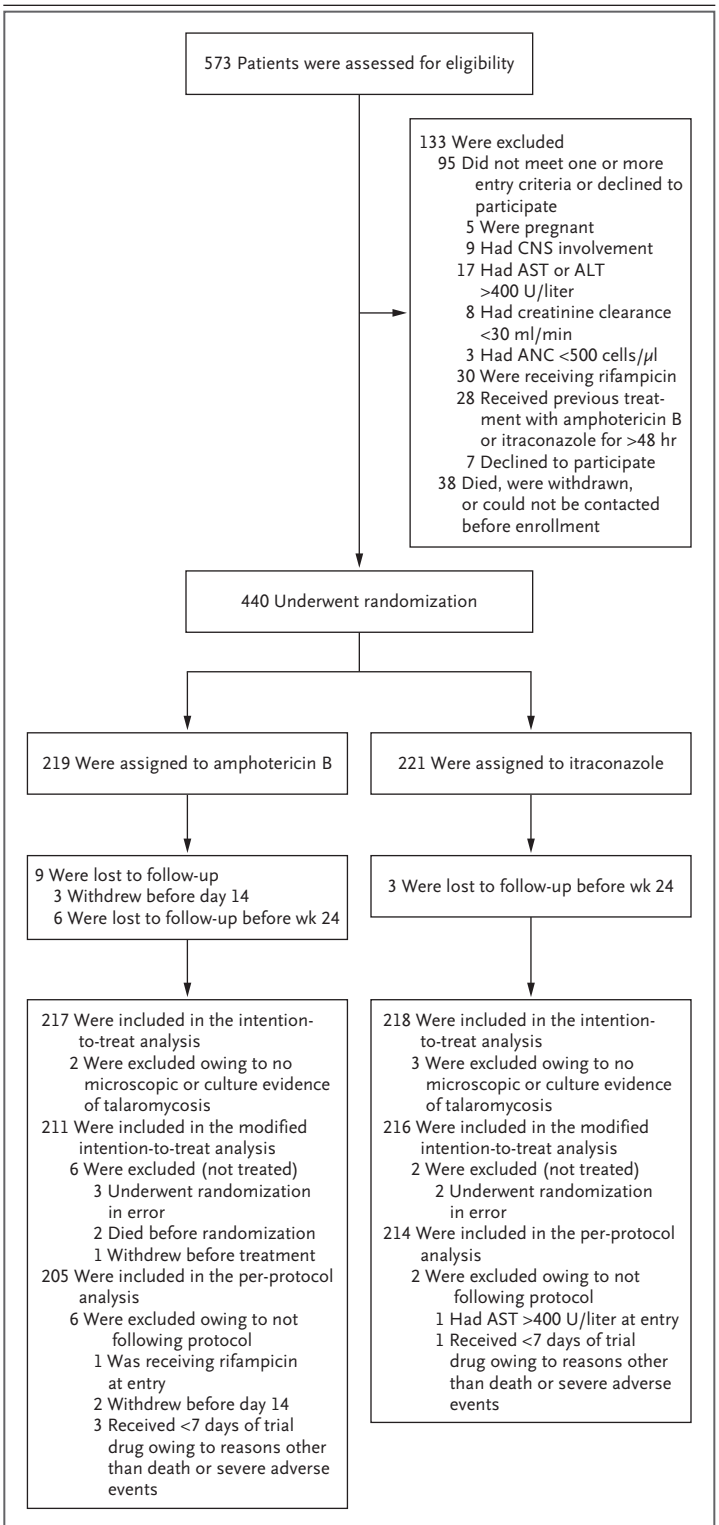

Figure 1. Enrollment, Randomization, and Follow-up.

ALT denotes alanine aminotransferase, ANC absolute neutrophil count, AST aspartate aminotransferase, and CNS central nervous system.

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Table 1. Clinical and Laboratory Characteristics of the Patients at Baseline.*

Characteristic	Amphotericin B (N=217)	Itraconazole (N=218)
Male sex — no./total no. (%)	152/215 (70.7)	144/217 (66.4)
Median age (IQR) — yr†	34 (30–38)	34 (29–38)
History of intravenous drug use — no./total no. (%)	70/215 (32.6)	66/217 (30.4)
Antiretroviral therapy		
Receiving therapy — no./total no. (%)	93/215 (43.3)	95/217 (43.8)
Median duration (IQR) — days‡	141 (60–1014)	106 (46–386)
Receiving therapy for >6 mo — no./total no. (%)	38/81 (46.9)	29/87 (33.3)
Laboratory data§		
Median white-cell count (IQR) — $\times 10^{-9}$ per liter	3.7 (2.3–5.3)	3.7 (2.4–5.9)
Median hemoglobin (IQR) — g/dl	8.9 (7.7–10.0)	8.8 (7.7–10.3)
Median platelet count (IQR) — $\times 10^{-9}$ per liter	121 (52–228)	118 (51–215)
Median CD4+ cell count (IQR) — cells per microliter	10 (6–19)	11 (6–27)
Median creatinine (IQR) — μmol per liter	67 (57–82)	69 (57–86)
Median aspartate aminotransferase (IQR) — U per liter	121 (72–208)	121 (68–193)
Median alanine aminotransferase (IQR) — U per liter	48 (31–82)	48 (30–73)
Median lactate dehydrogenase (IQR) — U per liter	411 (262–730)	483 (303–813)
Positive hepatitis B surface antigen — no./total no. (%)	38/194 (19.6)	40/195 (20.5)
Positive hepatitis C antibody — no./total no. (%)	78/195 (40.0)	62/194 (32.0)
Positive skin culture for *T. marneffei* — no./total no. (%)	117/135 (86.7)	131/148 (88.5)
Positive blood culture for *T. marneffei* — no./total no. (%)	156/214 (72.9)	145/216 (67.1)
Blood fungal count		
Patients with a detectable level — no./total no. (%)	143/201 (71.1)	148/200 (74.0)
Median count (IQR) — $\log_{10}$ CFU per milliliter¶	2.20 (1.54–3.13)	2.49 (1.54–3.17)

* There were no significant between-group differences in the characteristics evaluated at baseline, with the exception of the duration of antiretroviral therapy (P=0.047); the analyses were performed with the use of Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous data. Other clinical characteristics and radiographic findings are reported in Table S1 in the Supplementary Appendix. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. IQR denotes interquartile range, and CFU colony-forming unit.

† Data were missing for 2 patients in the amphotericin group and for 1 patient in the itraconazole group.

‡ Data were missing for 12 patients who received antiretroviral therapy in the amphotericin group and for 8 patients who received antiretroviral therapy in the itraconazole group.

§ For white-cell count, hemoglobin, platelet count, and creatinine, data were missing for 7 patients in the amphotericin group and for 5 patients in the itraconazole group. For CD4+ cell count, data were missing for 12 patients in the amphotericin group and for 6 patients in the itraconazole group. For aspartate aminotransferase and alanine aminotransferase, data were missing for 7 patients in the amphotericin group and for 4 patients in the itraconazole group. For lactate dehydrogenase, data were missing for 76 patients in the amphotericin group and for 82 patients in the itraconazole group.

¶ This analysis included data from the 143 patients in the amphotericin group and the 148 patients in the itraconazole group who had a detectable level.

Time to Clinical Resolution

The time to clinical resolution of talaromycosis was 8 days (interquartile range, 6 to 11) in the amphotericin group, as compared with 9 days (interquartile range, 6 to 12) in the itraconazole group (P=0.049). Poor response to treatment, which was defined as persistent or worsening symptoms and a positive culture after day 7, was observed in 1 patient who was receiving amphotericin and in 13 patients who were receiving itraconazole; 9 of these 13 patients were switched to amphotericin by the treating clinician.

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Table 2. Overview of Primary and Secondary Outcomes.*

Outcome	Amphotericin B (N=217)	Itraconazole (N=218)	Estimate (95% CI)	P Value
Primary outcome: death at 2 weeks — no./total no. (%)†			**Absolute risk difference**	
Intention-to-treat population	14/217 (6.5)	16/218 (7.4)	0.9 (–3.9 to 5.6)‡	0.73
Modified intention-to-treat population	11/211 (5.2)	16/216 (7.4)	2.2 (–2.4 to 6.8)‡	0.35
Per-protocol population	11/205 (5.4)	15/214 (7.0)	1.6 (–3.0 to 6.2)‡	0.48
Death at 24 weeks — no./total no. (%)†			**Absolute risk difference**	
Intention-to-treat population	24/217 (11.3)	45/218 (21.0)	9.7 (2.8 to 16.6)	0.006§
Modified intention-to-treat population	21/211 (10.0)	45/216 (21.0)	11.0 (4.2 to 17.8)	0.002
Per-protocol population	21/205 (10.3)	43/214 (20.3)	10.0 (3.2 to 16.8)	0.004
Time to clinical resolution¶‖			**Subdistribution hazard ratio**	
Patients who had clinical resolution — no. (%)	199 (93.4)	196 (90.7)	0.83 (0.69 to 1.00)	0.049
Median time to clinical resolution (IQR) — days	8 (6 to 11)	9 (6 to 12)		
Relapse of talaromycosis, development of IRIS, or death by week 24 — no. (%)¶**			**Absolute risk difference**	
Relapse	3 (1.5)	15 (7.0)	5.4 (1.6 to 9.3)	0.005
IRIS	0	14 (6.6)	6.6 (3.2 to 9.9)	<0.001
Death without previous relapse or IRIS	24 (11.3)	40 (18.6)	7.3 (0.6 to 14.0)	0.03
Death by week 24 according to cause — no. (%)¶			**Subdistribution hazard ratio**	
Death related to talaromycosis	15 (7.0)	25 (11.6)	1.66 (0.87 to 3.14)	0.12
Death related to other causes	7 (3.3)	14 (6.6)	1.97 (0.80 to 4.89)	0.14
Death with insufficient information to assess cause	2 (0.9)	6 (2.8)	2.95 (0.60 to 14.63)	0.18
Median decrease in blood fungal count during first 14 days of treatment (IQR) — $\log_{10}$ CFU/ml/day††	–0.95 (–1.29 to –0.53)	–0.36 (–0.70 to –0.19)	**Mean difference in estimated change** 0.52 (0.41 to 0.63)	<0.001

* IRIS denotes immune reconstitution inflammatory syndrome.

† Absolute risk differences, which are expressed in percentage points, were estimated with the use of the Kaplan–Meier method, so percentage points may not calculate mathematically.

‡ P<0.001 for noninferiority. The tests for noninferiority were one-sided tests of the null hypothesis that the absolute risk difference between the two treatment groups would be 10% or more in favor of amphotericin.

§ The prespecified analysis (Cox regression of the time to death by week 24) resulted in a hazard ratio of 1.88, with a 95% CI of 1.15 to 3.09 (P=0.01). However, a test for proportional hazards that was calculated on the basis of weighted Schoenfeld residuals provided evidence for nonproportionality (P=0.005), which complicated the interpretation of the hazard ratio. Hence, the prespecified alternative analysis of the absolute mortality risks at 24 weeks is reported in the table instead.

¶ This analysis was based on the intention-to-treat population. Absolute risks (expressed as percentage points) were estimated with the cumulative incidence function accounting for competing events (death without a previous treatment response, in the case of the time to treatment response). The comparisons of cumulative incidence functions of the time to clinical resolution and cause-specific deaths between treatment groups were calculated with the use of Fine–Gray regression models, with treatment as the only covariate, which resulted in a subdistribution hazard ratio as a measure of the effect size. Subdistribution hazard ratios of greater than 1 indicate a larger cumulative incidence of the event in the itraconazole group than in the amphotericin group.

‖ Clinical resolution of talaromycosis was defined as a temperature of less than 38°C (100°F) for 3 days, resolution of skin lesions, and sterile blood cultures.

** A relapse was defined as the recurrence of symptoms and a positive fungal culture from any sterile site for which reinduction therapy was administered in patients who had achieved clinical resolution. IRIS was defined as unexpected worsening of symptoms associated with inflammation in patients who started antiretroviral therapy and had increasing CD4+ cell counts.

†† This analysis was evaluated in patients who had a detectable blood fungal count at enrollment and had at least one follow-up blood fungal count (139 patients in the amphotericin group and 147 patients in the itraconazole group). The median number of blood fungal count measurements in this population was 6 (interquartile range, 5 to 7). The calculation of the mean difference in decline between the two treatment groups was based on linear regression, with treatment as the main covariate and with adjustment for the baseline $\log_{10}$ blood fungal count.

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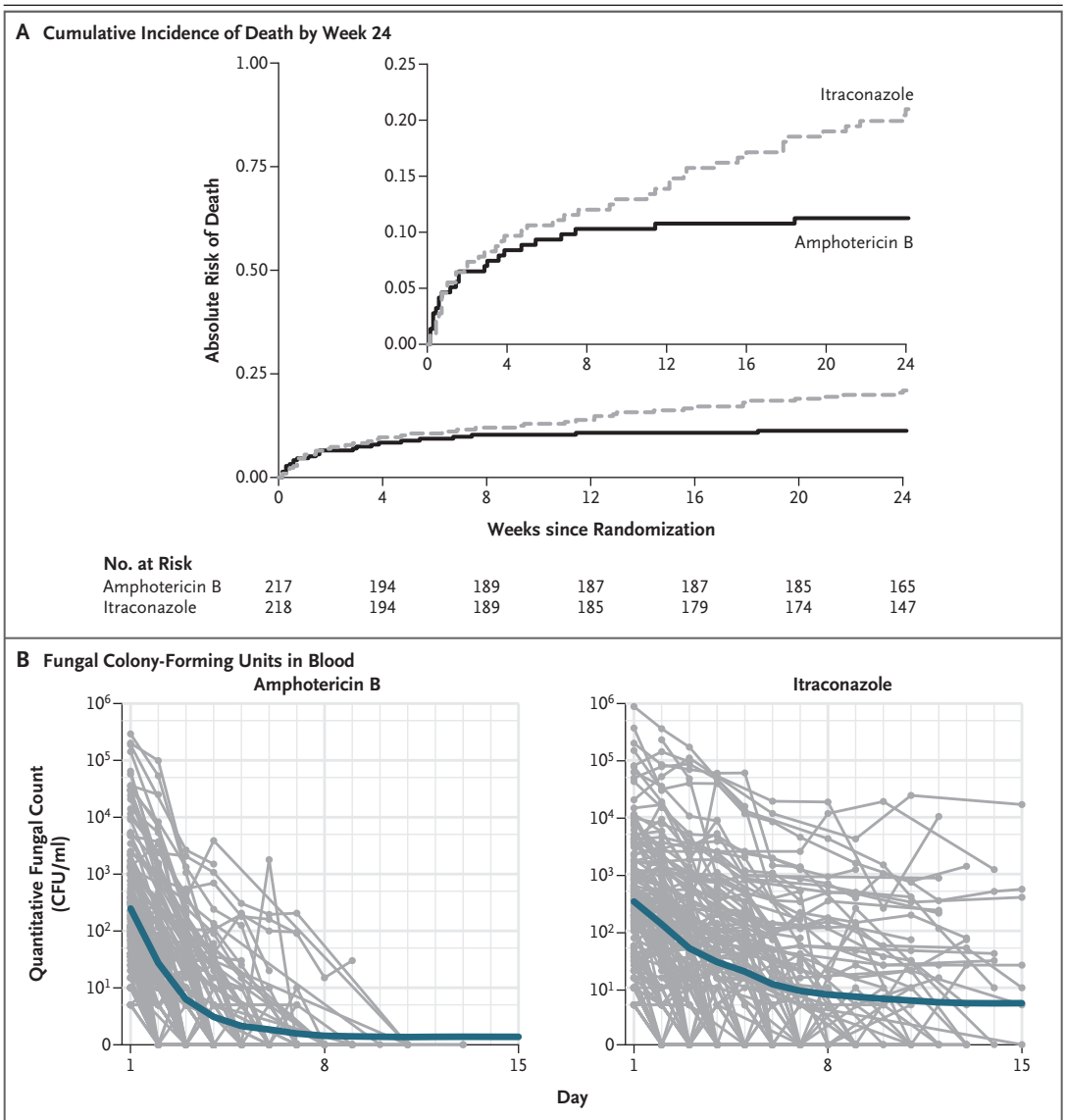

Figure 2. Cumulative Incidence of Death by Week 24 and Fungal Colony-Forming Units in Blood.

Panel A shows the cumulative incidence of death over the course of 24 weeks in the two groups, estimated with the use of the Kaplan–Meier method. The estimated risks of death at week 2 (the primary outcome) were 6.5% in the amphotericin group and 7.4% in the itraconazole group. At week 24, the estimated risks of death were 11.3% in the amphotericin group and 21.0% in the itraconazole group. The inset shows the same data on an expanded y axis. Panel B shows all recorded quantitative fungal colony-forming units (CFUs) in blood among patients who had detectable fungal CFUs at enrollment (143 patients in the amphotericin group and 148 patients in the itraconazole group) from the day of randomization (day 1) until day 15. The gray lines indicate data for individual patients. The blue lines represent a linear interpolation of observed mean $\log_{10}$ CFUs for each day after linear extrapolation of fungal CFU measurements for each patient through day 15 (to avoid overrepresentation of patients who did not yet have sterile cultures at late time points). The decrease in blood fungal CFUs during the first 14 days was significantly slower among patients in the itraconazole group than among patients in the amphotericin group: –0.95 $\log_{10}$ CFUs per milliliter per day in the amphotericin group versus –0.36 $\log_{10}$ CFUs per milliliter per day in the itraconazole group (estimated difference, 0.52; 95% CI, 0.41 to 0.63; P<0.001).

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Early Fungicidal Activity

Figure 2B shows the results of a longitudinal assessment of fungal CFUs in patients with fungemia (143 patients in the amphotericin group and 148 patients in the itraconazole group). Early fungicidal activity up to day 14 was significantly greater in the amphotericin group than in the itraconazole group: a decrease of 0.95 $\log_{10}$ CFUs per milliliter per day versus a decrease of 0.36 $\log_{10}$ CFUs per milliliter per day (estimated difference, 0.52; 95% CI, 0.41 to 0.63; P<0.001). A post hoc analysis also showed that more patients in the amphotericin group than in the itraconazole group had sterile cultures by day 8 (118 of 119 patients [99.2%] vs. 78 of 115 patients [67.8%], P<0.001). Further exploratory joint modeling of longitudinal fungal CFUs and cumulative mortality showed that the number of fungal CFUs at baseline (hazard ratio per each additional 1.0 $\log_{10}$ CFUs per milliliter, 1.49; 95% CI, 1.09 to 2.00) and early fungicidal activity (hazard ratio per 0.1 $\log_{10}$ less decrease in CFUs per milliliter, 1.20; 95% CI, 1.07 to 1.36) were associated with mortality up to 24 weeks, independent of treatment assignment.

Relapse of Talaromycosis and Development of IRIS

A relapse of talaromycosis and the development of IRIS were more common in the itraconazole group than in the amphotericin group. Talaromycosis relapse occurred in 15 of 218 patients (7.0%) in the itraconazole group as compared with 3 of 217 patients (1.5%) in the amphotericin group (absolute risk difference, 5.4 percentage points; 95% CI, 1.6 to 9.3; P=0.005). IRIS developed in 14 of 218 patients (6.6%) in the itraconazole group versus 0 of 217 patients in the amphotericin group (absolute risk difference, 6.6 percentage points; 95% CI, 3.2 to 9.9; P<0.001).

Adverse Events

Clinical adverse events of grade 3 or higher (i.e., adverse events that were considered to be severe or life-threatening or that resulted in death) were reported in 229 patients (52.6%); the incidence was similar in the two groups (Table 3). However, a higher number of patients in the itraconazole group than in the amphotericin group had complications from talaromycosis, including relapse (15 patients vs. 3 patients, P=0.006), poor response to treatment (13 patients vs. 1 patient, P=0.002), and IRIS (14 patients vs. no patients, P<0.001). In contrast, a higher number of patients in the amphotericin group than in the itraconazole group had infusion-related reactions (49 patients vs. 1 patient, P<0.001), blood and lymphatic disorders (16 patients vs. 3 patients, P=0.002), and renal failure (10 patients vs. 1 patient, P=0.006) (Table S3 in the Supplementary Appendix). New acquired immunodeficiency syndrome (AIDS)–associated stage III or IV diseases were reported in 80 patients (18.4%), and the incidence was similar in the two groups, with tuberculosis being the most common of these events (67.5% of patients). Adverse events that led to a change in the patient's randomized treatment were reported in 10 patients (4.6%) in the amphotericin group and in 9 patients (4.1%) in the itraconazole group (P=0.82). New abnormalities in laboratory variables were termed laboratory adverse events and were defined as any worsening of a laboratory value to grade 3 or 4 (including changes from grade 3 to grade 4) as compared with the patient's previous laboratory value. Laboratory adverse events were significantly more common among patients who received amphotericin than among patients who received itraconazole, including anemia (hemoglobin level of <7.4 g per deciliter) (89 patients vs. 64 patients, P=0.01), hypokalemia (potassium level of <2.4 mmol per liter) (25 patients vs. 7 patients, P<0.001), and hypomagnesemia (magnesium level of <0.44 mmol per liter) (10 patients vs. 2 patients, P=0.02) (Table 3).

Serious adverse events were reported in 158 patients (36.3%) and were more common among patients who received itraconazole than among those who received amphotericin: 100 of 218 patients (45.9%) versus 58 of 217 patients (26.7%) (P<0.001) (Table S4 in the Supplementary Appendix). A total of 32 of the 218 patients (14.7%) in the itraconazole group and 14 of the 217 patients (6.5%) in the amphotericin group were judged by the expert review committee to have serious adverse events that were possibly, probably, or definitely related to the trial drugs (P=0.007).

DISCUSSION

In this randomized, controlled trial of treatment for talaromycosis, we found that itraconazole induction therapy was noninferior to amphotericin

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Table 3. Overview of Clinical and Laboratory Adverse Events (Grade 3 or Higher) by Week 24.*

Event	Amphotericin B (N=217)	Itraconazole (N=218)	P Value
Clinical adverse events — total no. of events	180	160	0.27
Patients with at least one event — no. (%)	119 (54.8)	110 (50.5)	0.39
Complication of talaromycosis	19 (8.8)	57 (26.1)	<0.001
Respiratory failure	10 (4.6)	12 (5.5)	0.83
Wasting syndrome owing to talaromycosis	5 (2.3)	6 (2.8)	1.00
Poor response to treatment for talaromycosis†	1 (0.5)	13 (6.0)	0.002
Relapse of talaromycosis	3 (1.4)	15 (6.9)	0.006
IRIS	0	14 (6.4)	<0.001
Allergic and immune disorder	52 (24.0)	3 (1.4)	<0.001
AIDS-associated stage III or IV disease	37 (17.1)	43 (19.7)	0.54
Other infection	12 (5.5)	19 (8.7)	0.26
Nutritional or metabolic disorder	9 (4.1)	3 (1.4)	0.09
Blood and lymphatic disorder	16 (7.4)	3 (1.4)	0.002
Central nervous system disorder	1 (0.5)	3 (1.4)	0.62
Cardiovascular disorder	2 (0.9)	0	0.25
Respiratory disorder	2 (0.9)	1 (0.5)	0.62
Gastrointestinal disorder	8 (3.7)	10 (4.6)	0.81
Renal disorder	10 (4.6)	1 (0.5)	0.006
Laboratory adverse events — total no. of events	346	235	<0.001
Patients with at least one laboratory adverse event — no. (%)‡	148 (68.2)	117 (53.7)	0.002
White-cell count $<1.49 \times 10^9$ per liter	31 (14.3)	21 (9.6)	0.14
Hemoglobin <7.4 g/dl	89 (41.0)	64 (29.4)	0.01
Platelet count $<49 \times 10^9$ per liter	43 (19.8)	36 (16.5)	0.39
Potassium <2.4 mmol/liter	25 (11.5)	7 (3.2)	<0.001
Magnesium <0.44 mmol/liter	10 (4.6)	2 (0.9)	0.02
Creatinine >3.5 times ULN	6 (2.8)	2 (0.9)	0.18
Total bilirubin >5 times ULN	11 (5.1)	12 (5.5)	1.00
Aspartate aminotransferase >10 times ULN	28 (12.9)	34 (15.6)	0.49
Alanine aminotransferase >10 times ULN	23 (10.6)	13 (6.0)	0.08

* Listed are the numbers of patients who had at least one clinical adverse event or laboratory adverse event of the respective type. The P values for all comparisons were calculated with the use of Fisher's exact test, with the exception of the comparisons of the total number of clinical adverse events or laboratory adverse events, for which the P values were calculated with the use of modified Poisson regression models with a quasi-likelihood adjustment for overdispersion, with treatment as the only covariate. ULN denotes upper limit of the normal range.

† A poor response to treatment was defined as persistent or worsening fever or skin lesions and persistent positive results of cultures that led to prolonged hospitalization, hospital readmission, or a change of antifungal therapy.

‡ A laboratory adverse event was defined as any worsening of a laboratory value to grade 3 or 4 (including changes from grade 3 to grade 4) as compared with the patient's previous laboratory value. In addition, we used a conservative approach with regard to missing baseline values; if a patient's baseline laboratory value was missing, the first post-baseline laboratory value was also considered to be a new laboratory adverse event if the event was assessed as grade 3 or 4.

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with respect to the primary outcome of death at week 2; however, this effect was soon lost, and by week 24, the risk of death in the itraconazole group was almost twice that in the amphotericin group (21.0% vs. 11.3%). Consistent with this higher risk of death, the time to clinical resolution of talaromycosis was longer and more cases of relapse and IRIS were reported among patients who received itraconazole than among patients who received amphotericin. The differences in the risk of death were not evident during the first 8 weeks of follow-up but became evident during weeks 9 to 24. This finding suggests that the between-group difference in early fungicidal activity had an ongoing effect on disease progression and that a substantial portion of the deaths were directly due to talaromycosis. Concomitant opportunistic infections, such as tuberculosis, occurred with similar frequency in the two treatment groups and are unlikely to explain the differences between the two groups in risk of death and in complications of talaromycosis. The previous case series did not show a difference in outcomes between patients receiving amphotericin and those receiving itraconazole[5-7,10,11]; these results may in part be a reflection of insufficient durations of follow-up. Our trial emphasizes the importance of prolonged follow-up in trials of antifungal treatment.

We assessed quantitative fungal cultures and rates of decline of fungal CFUs in blood, which showed that treatment with amphotericin was associated with early fungicidal activity that was almost four times as fast as that with itraconazole, with 99.2% fungemia clearance by day 8 in the amphotericin group as compared with 67.8% in the itraconazole group. The greater early fungicidal activity observed with amphotericin treatment provides a biologically plausible explanation for the mortality benefit of amphotericin. Similar relationships between cerebrospinal fluid fungal clearance and clinical outcomes have been observed among patients with HIV-associated cryptococcal meningitis.[20-22] Furthermore, we found baseline fungal CFUs in blood to be an independent predictor of mortality at weeks 2 and 24, and early fungicidal activity to be associated with mortality at 24 weeks, independent of the antifungal treatment regimen. These data suggest that early fungicidal activity may be an appropriate biomarker to screen antifungal activity of new treatment regimens for talaromycosis.

Unsurprisingly, infusion-related reactions, elevated creatinine levels, electrolyte disturbance, and anemia were more common in the amphotericin group than in the itraconazole group; however, few of these events were classified as serious adverse events, and the number of patients in the amphotericin group who had a change in therapy was similar to that in the itraconazole group. All the patients in our trial received prehydration and preemptive electrolyte supplementation in accordance with World Health Organization guidelines for amphotericin administration,[23] which may explain the small number of serious toxic effects associated with amphotericin. Shorter courses of 5 to 7 days of amphotericin have been shown to substantially reduce its toxic effects,[24] and data from studies in animals and in humans have shown that fungicidal responses with 3-to-5-day courses of amphotericin are similar to those with 14-day courses for the treatment of cryptococcal meningitis.[25,26] Our data also suggest that 8 days of amphotericin treatment resulted in sterile cultures in almost all the patients; thus, there is scope to shorten the duration of amphotericin treatment for talaromycosis. A shorter course of treatment, which would further reduce the number of toxic effects, the duration of hospitalization, and costs, warrants further studies.

A limitation of our trial was its open-label design, which may have introduced bias in the assessment of adverse events and clinical resolution. However, we reduced this risk by using the objective outcomes of mortality and fungal clearance. The assessments of relapse of talaromycosis, the development of IRIS, the relationship between serious adverse events and trial drugs, and the causes of death were reviewed by members of an independent expert committee whose members were unaware of the treatment assignments. This trial was pragmatic, in that the formulations of the treatments assessed were affordable and the trial had few exclusion criteria; these factors may help to enhance the potential generalizability of the trial across Asia.

In conclusion, this trial showed that the antifungal drug amphotericin B was superior to itraconazole as induction therapy for HIV-associated talaromycosis.

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