Substitution of Moxifloxacin for Isoniazid during Intensive Phase Treatment of Pulmonary Tuberculosis

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***Rationale*: Moxifloxacin has potent activity against *Mycobacterium tuberculosis in vitro* and in a mouse model of antituberculosis (TB) chemotherapy, but data regarding its activity in humans are limited.**

***Objectives*: Our objective was to compare the antimicrobial activity and safety of moxifloxacin versus isoniazid during the first 8 weeks of combination therapy for pulmonary TB.**

***Methods*: Adults with sputum smear–positive pulmonary TB were randomly assigned to receive either moxifloxacin 400 mg plus isoniazid placebo, or isoniazid 300 mg plus moxifloxacin placebo, administered 5 days/week for 8 weeks, in addition to rifampin, pyrazinamide, and ethambutol. All doses were directly observed. Sputum was collected for culture every 2 weeks. The primary outcome was negative sputum culture at completion of 8 weeks of treatment.**

***Measurements and Main Results*: Of 433 participants enrolled, 328 were eligible for the primary efficacy analysis. Of these, 35 (11%) were HIV positive, 248 (76%) had cavitation on baseline chest radiograph, and 213 (65%) were enrolled at African sites. Negative cultures at Week 8 were observed in 90/164 (54.9%) participants in the isoniazid arm, and 99/164 (60.4%) in the moxifloxacin arm ($P = 0.37$). In multivariate analysis, cavitation and enrollment at an African site were associated with lower likelihood of Week-8 culture negativity. The proportion of participants who discontinued assigned treatment was 31/214 (14.5%) for the moxifloxacin group versus 22/205 (10.7%) for the isoniazid group (RR, 1.35; 95% CI, 0.81, 2.25).**

***Conclusions*: Substitution of moxifloxacin for isoniazid resulted in a small but statistically nonsignificant increase in Week-8 culture negativity.**

Clinical trial registered with www.clinicaltrials.gov (NCT00144417).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Moxifloxacin has potent activity against *Mycobacterium tuberculosis in vitro* and in a mouse model of combination antituberculosis chemotherapy.

What This Study Adds to the Field

This study demonstrates that, in patients with smear positive pulmonary tuberculosis, a regimen including moxifloxacin, rifampin and pyrazinamide given during the first 2 months of treatment was highly active, but not significantly more active than a regimen of isoniazid, rifampin, and pyrazinamide using a surrogate marker of Week-8 culture negativity.

Keywords: tuberculosis; antitubercular agents; mycobacterium infections

There is an urgent need for potent tuberculosis (TB) treatments that require fewer than 6 months duration for cure. Increasing rates of drug resistance further emphasize the need for new TB drugs.

Moxifloxacin has *in vitro* activity against *Mycobacterium tuberculosis* and in a murine model of combination TB chemotherapy. In the murine model, a regimen in which moxifloxacin was substituted for isoniazid and administered in combination with rifampin and pyrazinamide greatly reduced the time to lung sterilization and led to cure after only 4 months of treatment (1, 2). Moxifloxacin has a favorable pharmacokinetic profile (serum half-life of 10–12 h), few problematic drug–drug interactions, no need for dosage adjustment for renal and hepatic insufficiency, and a satisfactory safety profile in short-term use of up to 3 weeks for treatment of community-acquired pneumonia, sinusitis, and intra-abdominal and complicated skin and soft tissue infections (3–12).

The Tuberculosis Trials Consortium (TBTC) conducted a randomized, placebo-controlled, double-blind, phase 2 clinical trial to evaluate the antimicrobial activity and safety of moxifloxacin substituted for isoniazid during the first 2 months (intensive phase) of combination treatment for pulmonary TB. Sputum culture negativity at the completion of 8 weeks of treatment was used as a surrogate marker for treatment efficacy (13). Some of the results of this study have been previously reported in abstract form (14, 15).

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Preliminary results were presented at the 2007 Interscience Conference on Antimicrobial Agents and Chemotherapy and the 2007 meeting of the International Union Against Tuberculosis and Lung Disease. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

* A list of participating clinical sites can be found at the end of the article.

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METHODS

Study Setting, Population, and Design

Patients were enrolled in 26 TBTC sites, including 22 in North America and one each in Brazil, South Africa, Spain, and Uganda. A complete listing of eligibility criteria is in the online supplement. Briefly, adults with suspected pulmonary TB and acid-fast bacilli (AFB) in a sputum specimen were eligible. Exclusion criteria included receipt of greater than 7 days of antituberculosis treatment in the preceding 6 months or greater than 7 days of fluoroquinolone treatment in the preceding 3 months; pregnancy or breast-feeding; and initial sputum cultures that were negative for *M. tuberculosis* or grew a strain that was resistant to isoniazid, fluoroquinolones, rifampin, or pyrazinamide. All participants underwent HIV testing. The study was approved by the Centers for Disease Control and Prevention (CDC) and local institutional review boards. Participants gave informed consent.

Participants were randomly assigned to receive isoniazid (300 mg) plus moxifloxacin placebo, or moxifloxacin (400 mg) plus isoniazid placebo, once daily in addition to rifampin, pyrazinamide, ethambutol, and pyridoxine for the first 8 weeks of TB treatment. Randomization was stratified by the presence of cavitation on baseline chest radiograph and continent of enrollment (Africa or not Africa); randomization was not restricted within strata. Treatment was administered once daily for 5 days per week, and there was an option to administer treatment 7 days per week during the first 2 weeks. Dosages of isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine were in accordance with published guidelines (16). Completion of study treatment was defined as ingestion of 40 to 44 directly observed doses over 54 to 70 days. Moxifloxacin was donated by the Bayer Corporation through a partnership with the Global Alliance for TB Drug Development, and other study drugs were obtained from licensed suppliers in the United States or Europe. After completion of 8 weeks of treatment, participants completed TB treatment with a conventional continuation-phase regimen, typically isoniazid plus rifampin (16).

Information on symptoms, blood for serum aspartate aminotransferase (AST), bilirubin, creatinine, and complete blood count, and a sputum specimen were collected at baseline and at completion of Weeks 2, 4, 6, and 8 of treatment. Two sputum were collected at the completion of intensive-phase study treatment (Week 8). A participant was considered culture positive at Week 8 if either sputum sample was positive for *M. tuberculosis* when cultured on either solid or liquid medium. Sputa were also collected monthly during continuation-phase treatment unless two or more prior consecutive cultures were already negative. Cultures were performed at local laboratories, which were required to use both a solid and a liquid culture method for each specimen. Overall, 92% of liquid cultures were performed in a BACTEC MGIT 960 system (Becton, Dickinson and Co., Franklin Lakes, NJ) or a BACTEC 460TB system (Becton, Dickinson and Co.). Types of solid medium used by local laboratories included Lowenstein-Jensen, Middlebrook 7H10, and Middlebrook 7H11. *M. tuberculosis* isolates underwent confirmatory drug-susceptibility testing at CDC using the indirect agar proportion method for isoniazid, rifampin, ethambutol, and fluoroquinolones (ofloxacin and ciprofloxacin critical concentrations of 2 μg/ml) (17); MGIT 960 medium was used for pyrazinamide susceptibility testing.

Data Analysis

Sample size was calculated based on the assumption that substitution of moxifloxacin for isoniazid would increase the percentage of participants having negative cultures at the completion of 8 weeks of treatment by 13%—similar to the impact of adding pyrazinamide, a drug that allowed overall TB treatment shortening (13, 18–22). Assuming that 75% of isoniazid group participants would have negative cultures at 8 weeks for a two-sided test at the 0.05 level with 80% power, 154 subjects per arm were needed. This number was increased by 25% to compensate for participants whose baseline culture failed to grow *M. tuberculosis* or grew drug-resistant *M. tuberculosis* or who were lost to follow-up. The target was 205 participants per arm.

The primary efficacy outcome was the percentage of participants with negative cultures on both liquid and solid medium at the time of completion of intensive phase ("Week-8 culture negativity"). Time to stable culture conversion was a secondary endpoint and was defined as the number of days from study treatment initiation to the time of sputum collection yielding the first negative culture that was followed by at least one subsequent negative culture and no subsequent positive culture; data from sputa obtained during intensive and continuation phases were used for this analysis. The primary safety endpoint was permanent discontinuation of the assigned intensive-phase treatment.

Two efficacy analysis groups were prespecified. A modified intention-to-treat (MITT) group excluded participants whose enrollment specimen failed to grow *M. tuberculosis* or had proven resistance to isoniazid, rifampin, pyrazinamide, ciprofloxacin, or ofloxacin; and enrollees whose treatment was incorrectly allocated. A protocol-correct (PC) group excluded participants whose enrollment specimen failed to grow *M. tuberculosis* or was not proven susceptible to isoniazid, rifampin, pyrazinamide, ciprofloxacin, and ofloxacin; whose treatment was incorrectly allocated; who had contaminated Week-8 cultures; who died during intensive phase; who required more than 70 days to complete the study intensive-phase treatment; or who took nonstudy therapy for more than 14 days during the intensive phase. For safety analyses, all participants who received at least one dose of study treatment were included.

Data were analyzed using SAS (version 9.1.3; SAS Institute, Inc., Cary, NC) software package and the R environment (version 2.7.1; R Foundation for Statistical Computing, Vienna, Austria). For the primary efficacy analysis, the Pearson chi-square test and Wilson method for confidence intervals were used to compare proportions of participants having negative cultures. The McNemar test was used to compare proportions with cultures that were negative on different medium. Factors associated with Week-8 culture negativity were analyzed with logistic regression for the probability of Week-8 culture negativity. Spline methods were used to allow for flexible fitting of continuous variables; terms for treatment effect and the four allocation strata were retained in models without specific regard to statistical significance. The final multivariate model was obtained by iteratively including and excluding predictors based on apparent statistical significance, model stability, and scientific judgment. Time to stable conversion was analyzed with stratified Kaplan-Meier product-limit estimates; because of interval censoring these estimates were reviewed at intervals corresponding to protocol-specified sampling.

RESULTS

A total of 433 participants were enrolled from February 2006 to March 2007. As shown in Figure 1, 29 participants assigned to the isoniazid group and 23 participants assigned to the moxifloxacin group were omitted from the MITT analysis. An additional 21 participants assigned to the isoniazid group and 32 participants assigned to the moxifloxacin group were excluded from the PC analysis according to prespecified criteria.

Table 1 shows baseline characteristics for the 328 participants in the PC analysis group. More participants with cavitary disease were allocated to the isoniazid arm than to the moxifloxacin arm (80 vs. 71%), and the percentage of participants enrolled at African sites was lower in the isoniazid group than in the moxifloxacin group (61 vs. 69%). At the time of random treatment assignment, cavitation on chest radiograph was present in 77% (163/213) of individuals enrolled at African sites versus 74% (85/115) of individuals enrolled at non-African sites.

Efficacy

Results for the PC analysis group (328 participants) are presented in the text, and results for the MITT analysis group (381 participants) are in the online supplement; findings were similar for both groups. Results for the primary efficacy endpoint are shown in Table 2. Week-8 culture negativity was achieved for 54.9% (90/164) of PC participants treated with isoniazid versus 60.4% (99/164) of PC participants treated with moxifloxacin ($P = 0.37$).

We performed two *post hoc* analyses of the effect of treatment assignment on Week-8 culture negativity. First, we considered the results from African and non-African sites separately (Table 2).

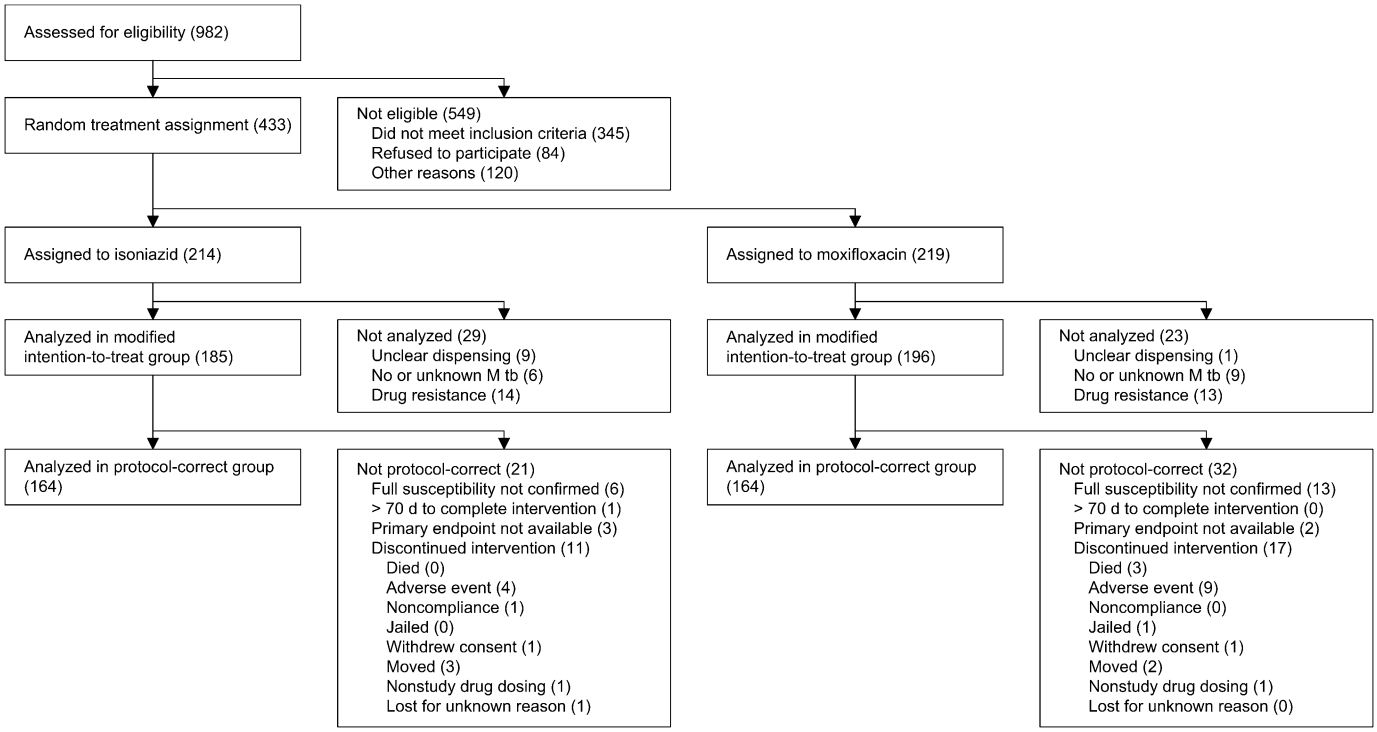

Figure 1. Enrollment and disposition of study participants.

There were no differences between treatment groups. However, with treatment groups combined, at African sites 48.4% (103/213) of participants were culture negative at Week 8, versus 74.8% (86/115) at non-African sites ($P < 0.01$). Among participants at African sites, 85% (180/213) took 44 doses of study treatment; at non-African sites 27% (31/115) took 44 doses. Second, we considered separately the Week-8 culture results using liquid medium and solid medium. Compared with the isoniazid arm, the moxifloxacin arm had a slightly higher percentage with negative Week-8 cultures with both liquid and solid medium, but neither difference was statistically significant. When treatment arms were combined, Week-8 culture negativity on liquid medium was 57.0% (187/328), versus 89.3% (293/328) on solid medium ($P < 0.01$). Larger differences in results by medium type were found in African sites than in non-African sites. In the isoniazid arm alone, for direct comparison with other studies, 41.0% (41/100) of Week-8 cultures in Africa were negative in liquid medium compared with 91.0% (91/100) ($P < 0.01$) on solid medium; outside Africa the results were 73.4% (47/64) versus 81.2% (52/64) ($P = 0.13$), respectively.

In univariate analysis, factors associated with not achieving Week-8 culture negativity ($P < 0.05$) were assignment strata of non-African cavitary, African noncavitary, and African cavitary; age; enrollment at an African site; history of smoking cigarettes; high bacillary load (defined as $\geq$1 AFB/field at $\times$1000) on baseline smear; and cavitation on baseline chest radiograph. Time to *M. tuberculosis* detection in liquid culture for the baseline culture was associated with achieving Week-8 culture negativity. Significant associations were not seen for treatment assignment or HIV infection (Table 3). In a multivariate logistic regression model, assignment stratum, high bacillary load on baseline smear, and age remained associated with not achieving Week-8 culture negativity (Table 4). Overall, the effect of treatment assignment was small and not significantly modified by other correlates of culture conversion.

A secondary endpoint was time to stable culture conversion. Differences were not significant between treatment groups overall ($P = 0.16$), or when solid ($P = 0.07$) and liquid ($P = 0.29$) cultures were considered separately (Figure 2) (Gehan-Wilcoxon test).

Safety

In the isoniazid arm, 10.7% (22/205) of participants discontinued the assigned treatment, versus 14.5% (31/214) in the moxifloxacin arm ($P = 0.25$) (Table 5). Proportions of participants with severe adverse events (SAEs) during intensive phase treatment were similar between arms (isoniazid 3.9% [8/205] vs. moxifloxacin 4.2% [9/214]; $P = 0.88$). Three SAEs attributed to study treatment during the first 2 months occurred among the moxifloxacin group and two in the isoniazid group (Table 5). Three participants, all in the moxifloxacin arm, died during intensive-phase TB treatment. Two of these died from advanced pulmonary TB judged not related to study drugs. The third participant, a 48-year-old African female, without known diabetes mellitus, developed diabetic ketoacidosis after 14 days of study treatment and died 5 days later in the hospital. The proximate cause of death as determined by site investigators was possible acute pulmonary embolus unrelated to study drugs; no autopsy was performed. Four deaths during continuation phase, all in the isoniazid arm, were judged unrelated to study drugs (two from complications of HIV infection, one from sequellae of severe pulmonary TB, and one from colon cancer). Other nonfatal SAEs occurring during intensive phase and judged unrelated to study treatment included complications associated with advanced TB, HIV-related complications, and incidental hospitalizations.

Nausea was more common among participants in the moxifloxacin arm than in the isoniazid arm (42 [19.6%] vs. 24 [11.7%], respectively; $P = 0.03$) (Table 5), although similar proportions in both groups reported vomiting. Gastrointestinal upset seldom necessitated discontinuation of assigned treatment. Proportions

TABLE 1. BASELINE CHARACTERISTICS OF PARTICIPANTS IN THE PROTOCOL-CORRECT EFFICACY ANALYSIS GROUP

Characteristic	Overall	Isoniazid	Moxifloxaxin
Total participants, n	328 (100)	164 (100)	164 (100)
African stratum, n (%)	213 (65)	100 (61)	113 (69)
Cavitary stratum*, n (%)	248 (76)	131 (80)	117 (71)
Non-African site, noncavitary, n (%)	30 (9)	14 (9)	16 (10)
Non-African site, cavitary, n (%)	85 (26)	50 (30)	35 (21)
African site, noncavitary, n (%)	50 (15)	19 (12)	31 (19)
African site, cavitary, n (%)	163 (50)	81 (49)	82 (50)
Age, years median (IQR)	30 (25, 38)	30 (25, 40)	31 (26, 37)
Female, n (%)	91 (28)	46 (28)	45 (27)
History of smoking cigarettes, n (%)	130 (40)	68 (41)	62 (38)
Region or country of enrollment, n (%)			
South Africa	31 (9)	17 (10)	14 (9)
Uganda	182 (55)	83 (51)	99 (60)
North America	84 (26)	46 (28)	38 (23)
Brazil	19 (6)	11 (7)	8 (5)
Spain	12 (4)	7 (4)	5 (3)
TB treatment before enrollment			
Any TB treatment within 14 days, n (%)	138 (42)	71 (43)	67 (41)
No. days of pre-study treatment, median (IQR)	4 (3, 6)	4 (3, 6)	4 (3, 6)
Clinical features at enrollment			
High bacillary load on smear†	221 (67)	112 (68)	109 (66)
No. days to detection in liquid system, median (IQR)	7 (5, 12)	7 (5, 11)	7 (5, 12)
Cavitation on chest radiograph‡, n (%)	244 (74)	126 (77)	118 (72)
Body mass index, kg/m^2, median (IQR)	19.6 (17.7, 21.8)	19.6 (18.0, 21.5)	19.8 (17.5, 22.0)
HIV-positive, n (%)	35 (11)	18 (11)	17 (10)
CD4 lymphocyte count, cells/μl, median (IQR) §	197 (112, 340)	130 (84, 282)	306 (187, 366)
White blood cell count ($\times 10^3$/mm^3), median (IQR)	8.4 (6.6, 10.4)	8.6 (6.7, 10.4)	8.0 (6.6, 10.5)
Hemoglobin, g/dL, median (IQR)	12.0 (10.5, 13.5)	11.8 (10.2, 13.5)	12.2 (10.8, 13.7)
AST > ULN, n (%)	53 (16)	26 (16)	27 (16)

Definition of abbreviations: AST = aspartate aminotransferase; IQR = interquartile range; ULN = upper limit of normal for the testing laboratory.

* Baseline cavitation for treatment arm allocation.

† Defined as one or greater acid fast bacilli/field at ×1000.

‡ Baseline cavitation as a clinical feature, after reassessment for some patients.

§ HIV-positive individuals.

of participants with hepatitis, defined as serum AST 3 times or greater than the upper limit of normal, were similar between treatment arms during intensive phase (isoniazid 3.4% [7/205] vs. moxifloxacin 3.3% [7/214]; $P = 0.93$). Frequencies of rash, visual changes, joint pain, and diarrhea were similar between arms. There were no reported cases of retinitis, optic neuritis, tendonopathy, or antibiotic-associated colitis. Changes in serum AST, bilirubin, creatinine, hemoglobin, hematocrit, platelet and white blood cell counts were not different between treatment arms.

DISCUSSION

Substitution of moxifloxacin for isoniazid during the intensive phase of TB treatment resulted in a small but statistically nonsignificant increase in the percentage of participants who were culture negative at Week 8. Moxifloxacin was well-tolerated by most recipients. Our results, based on the surrogate endpoint of Week-8 culture status, indicate that substitution of moxifloxacin for isoniazid during only the intensive phase is unlikely to allow marked shortening of overall treatment duration. However, moxifloxacin may be a suitable alternative to isoniazid during intensive phase in patients who are isoniazid intolerant or are infected with isoniazid-resistant *M. tuberculosis*.

Although our study is, to our knowledge, the first to examine the role of moxifloxacin when substituted for isoniazid, three other recent phase 2 studies have evaluated the activity and safety of moxifloxacin when substituted for ethambutol during intensive-phase treatment for smear-positive pulmonary TB. TBTC Study 27 was a multisite study in which participants were randomly assigned to receive either moxifloxacin or ethambutol in combination with isoniazid, rifampin, and pyrazinamide during intensive phase. In Study 27 there was no difference in the proportion of participants with negative cultures at the completion of 8 weeks of treatment, but participants receiving moxifloxacin more often had negative cultures at the completion of 4 weeks of treatment (23). Using nonlinear mixed effects

TABLE 2. PERCENTAGES OF PARTICIPANTS WITH NEGATIVE SPUTUM CULTURES AT COMPLETION OF WEEK 8, BY TREATMENT GROUP, FOR THE PROTOCOL CORRECT ANALYSIS GROUP

	Overall, n		Isoniazid, n		Moxifloxacin, n		Difference (95% CI)	*P* Value
Primary analysis	57.6	189/328	54.9	90/164	60.4	99/164	5.5 (−5.8, 16.8)	0.37
Post-hoc analyses								
African sites*	48.4	103/213	43.0	43/100	53.1	60/113	10.1 (−4.2, 24.4)	0.18
Non-African sites	74.8	86/115	73.4	47/64	76.5	39/51	3.0 (−14.6, 20.7)	0.88
Liquid medium†	57.0	187/328	53.7	88/164	60.4	99/164	6.7 (−4.6, 18.0)	0.26
Solid medium	89.3	292/328	87.2	143/164	91.5	150/164	4.3 (−3.0, 11.5)	0.28

* $P < 0.01$ for comparison of overall results for African sites versus non-African sites.

† $P < 0.01$ for comparison of overall results for liquid versus solid medium.

TABLE 3. FACTORS ASSOCIATED WITH NEGATIVE SPUTUM CULTURE AT COMPLETION OF 8 WK OF TREATMENT IN THE PROTOCOL CORRECT ANALYSIS GROUP

Characteristic	OR	95% CI	*P* Value
Design-based model			
Moxifloxacin vs. isoniazid	1.36	0.86, 2.17	0.19
Assignment stratum			
Non-African, noncavitary	1.0 (ref)		
Non-African, cavitary	0.12	0.03, 0.54	<0.01
African, noncavitary	0.07	0.02, 0.33	<0.01
African, cavitary	0.05	0.01, 0.22	<0.01
Adjusted for treatment assignment and 4 assignment strata			
Enrollment region			<0.01
North America	1.00 (ref)		
Brazil	0.60	0.20, 1.84	0.38
Spain	1.51	0.30, 7.57	0.62
South Africa	0.34	0.14, 0.80	0.01
Uganda	0.28	0.16, 0.51	<0.01
Age, years	0.97	0.95, 1.00	0.02
Female	1.56	0.92, 2.65	0.10
History of smoking cigarettes	0.53	0.31, 0.89	0.02
High bacillary load on baseline sputum smear*	0.41	0.24, 0.70	<0.01
Days to detection in liquid culture system†	1.04	1.01, 1.08	0.02
Cavitation on baseline chest x-ray	0.48	0.28, 0.83	<0.01
Body mass index (kg/m^2)	1.06	0.99, 1.14	0.11
HIV positive	1.32	0.62, 2.79	0.47
Any prestudy TB treatment	1.35	0.74, 2.47	0.33
Days of pre-study TB treatment, n	1.10	0.97, 1.24	0.15

Definition of abbreviations: CI = confidence interval; OR = odds ratio; ref = reference.

* Defined as one or greater acid fast bacilli/field at ×1000.

† For 322 participants with a baseline liquid culture positive for *M. tuberculosis*

modeling of serial sputum colony counts during the first 8 weeks of treatment, the Gatifloxacin for TB (OFLOTUB) study team showed that moxifloxacin, when substituted for ethambutol in the context of isoniazid, rifampin, and pyrazinamide, accelerated the killing of *M. tuberculosis* (24). In secondary analyses, moxifloxacin also accelerated culture conversion on solid medium, and the percentage of participants with negative sputum cultures on solid medium at Week 8 was higher in the moxifloxacin group than the ethambutol group (36/44 [82%] vs. 32/50 [64%]; $P = 0.058$) (24). Finally, in a single-site study in Brazil, substitution of moxifloxacin for ethambutol resulted in a 17% increase in the proportion of participants with negative culture results on Lowenstein-Jensen solid medium at Week 8 (59/74 [80%] vs. 45/72 [63%]; $P = 0.03$) (25).

TABLE 4. FINAL MULTIVARIATE LOGISTIC REGRESSION MODEL FOR SPUTUM CULTURE NEGATIVITY AT COMPLETION OF 8 WEEKS OF TREATMENT IN THE PROTOCOL CORRECT ANALYSIS GROUP

Characteristic	OR	95% CI	*P* Value
Moxifloxacin vs. Isoniazid	1.30	0.80, 2.12	0.29
Assignment stratum			
Non-African, noncavitary	1.00 (ref)		
Non-African, cavitary	0.11	0.02, 0.49	<0.01
African, noncavitary	0.06	0.01, 0.31	<0.01
African, cavitary	0.05	0.01, 0.21	<0.01
Age at enrollment (per year)	0.97	0.95, 1.00	0.03
High bacillary burden on baseline sputum smear*	0.45	0.26, 0.79	<0.01
Days to detection in liquid culture system for baseline sputum†	1.04	1.00, 1.07	0.03

See Table 3 for abbreviations.

* Defined as one or greater acid fast bacilli/field at ×1000.

† For 322 participants with a baseline liquid culture positive for *M. tuberculosis*

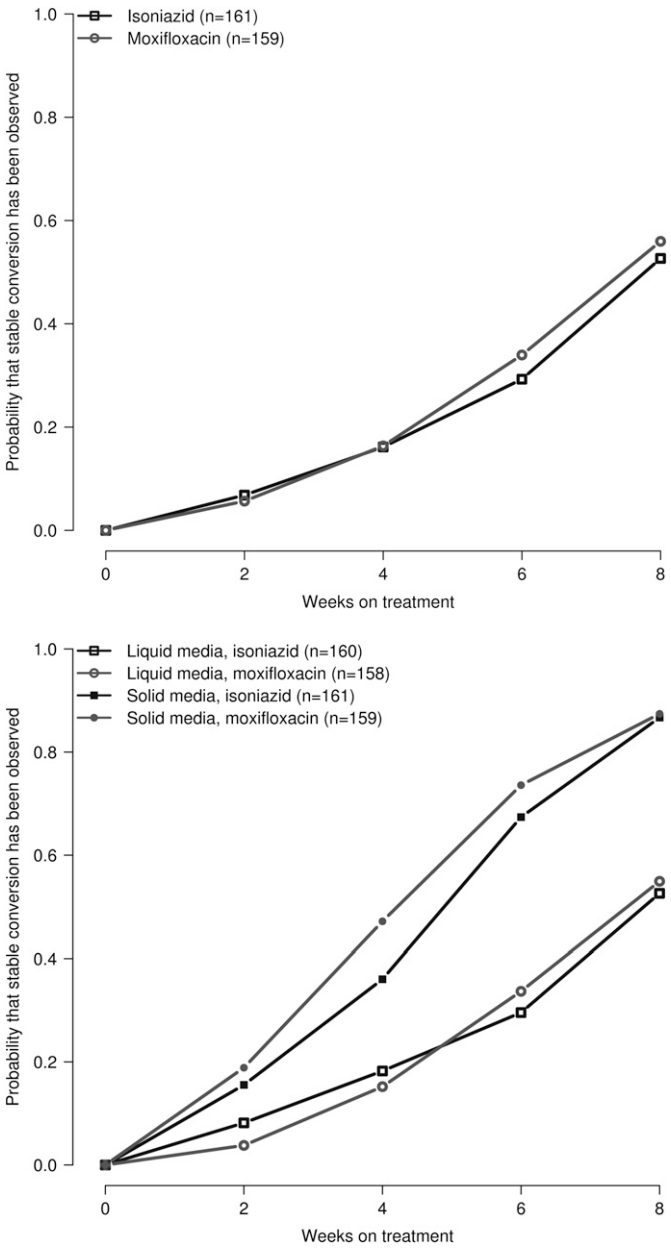

Figure 2. Time to stable sputum culture conversion for the protocol-correct analysis group, by treatment group, using (*1*) the combined result for both liquid and solid culture medium, and (*2*) separate results for liquid and solid culture medium.

In our study, Week-8 culture negativity was lower among participants at African compared with non-African sites. This was true even after adjustment for pulmonary cavitation and absence of TB treatment in the days before study enrollment. We do not believe that differences may be attributed to confounding of dose frequency with region because the proportion achieving negative culture was lower at African sites, where the total number of study treatment doses was higher on average. A lower rate of Week-8 culture negativity in African compared with non-African participants was also observed in TBTC Study 27 (23). Notably, for the control group in the current study, the percentage of Africa-enrolled participants with negative Week-8 cultures on liquid medium (41.0%), approximately 50% lower than that on solid medium, was generally similar to that described in another recent

TABLE 5. ADVERSE EVENTS REPORTED WITHIN 70 DAYS AFTER FIRST STUDY DRUG DOSE (UNLESS OTHERWISE SPECIFIED) IN PARTICIPANTS WHO RECEIVED AT LEAST ONE DOSE OF STUDY TREATMENT. HEPATITIS (AST ⩾3 TIMES ULN) AND SYMPTOMS REPORTED DURING STUDY PHASE FOLLOW-UP VISITS

Adverse Event or Symptom	Isoniazid n (%)	Moxifloxacin n (%)	Relative Risk (95% CI)	*P* Value*
n	205	214		
Study drugs permanently discontinued	22 (10.7)	31 (14.5)	1.35 (0.81, 2.25)	0.25
Any SAE	8 (3.9)	9 (4.2)	1.08 (0.42, 2.74)	0.88
SAE attributed to study treatment	2 (1.0)†	3 (1.4)‡	1.44 (0.24, 8.51)	1.00
Death during intensive phase treatment	0 (0)	3 (1.4)		0.25
Death anytime during TB treatment	4 (2.0)	3 (1.4)	0.72 (0.16, 3.17)	0.72
Grade 3 or greater toxicity	39 (19.0)	32 (15.0)	0.79 (0.51, 1.20)	0.27
Hepatitis (AST: 3 times ULN)	7 (3.4)	7 (3.3)	0.96 (0.34, 2.68)	0.93
Nausea	24 (11.7)	42 (19.6)	1.68 (1.05, 2.66)	0.03
Vomiting	20 (9.8)	22 (10.3)	1.05 (0.59, 1.87)	0.86
Diarrhea	12 (5.9)	17 (7.9)	1.36 (0.66, 2.77)	0.40
Rash	23 (11.2)	23 (10.8)	0.86 (0.53, 1.65)	0.88
Dizziness	19 (9.3)	30 (14.0)	1.51 (0.88, 2.60)	0.13
Joint pain or discomfort	61 (29.8)	68 (31.8)	1.07 (0.80, 1.42)	0.65

Definition of abbreviations: AST: aspartate aminotransferase; CI = confidence interval; SAE: serious adverse event; ULN = upper limit of normal for the testing laboratory.

* *P* values are not corrected for multiple comparisons.

† Isoniazid group SAEs: hyperuricemia, vasculitis.

‡ Moxifloxacin group SAEs: study drug overdose, diabetic ketoacidosis, hepatitis.

phase 2 moxifloxacin study performed in Africa (36%), which also found a higher culture conversion rate on solid medium (64%) (24). In our study, age, history of smoking, and high sputum bacillary load on baseline smear were negative predictors of Week-8 culture negativity; this is not surprising given that these factors have been identified in other studies as risk factors for TB relapse (26, 27).

With respect to safety, the percentage of participants with hepatotoxicity was similar in both treatment arms. The occurrence of diabetic ketoacidosis in a moxifloxacin recipient is notable. To our knowledge there are no published reports of clinically significant dysglycemias in TB patients treated with moxifloxacin. Pooled analyses from clinical trials and postmarketing studies have shown that moxifloxacin-related hypo- and hyperglycemic events are rare but do occur (10–12).

Our phase 2 study was limited in its focus on a surrogate marker, namely sputum culture negativity at completion of intensive-phase treatment, as the study endpoint rather than relapse after treatment completion. Two-month culture status on solid medium has been shown to be a good marker for the sterilizing activity of TB treatment regimens, but further work is needed to clarify the utility of liquid culture results as a surrogate marker for relapse (13). The large differences between findings on liquid and solid medium also require further evaluation, both for validation and for understanding their clinical significance. Sputum processing methods and the type of solid and liquid culture medium used varied across our study sites. However, a thorough review of laboratory methods, data quality, and randomization as implemented indicated that variation in culture methods did not materially affect the analysis of the primary endpoint. Our results are further bolstered by rigorous blinding of bacteriologic and safety assessments through use of placebos and a double-blind design, the administration of all doses of study treatment under supervision, and low loss to-follow-up.

The murine model of combination TB chemotherapy has reproducibly recapitulated human TB treatment with respect to duration of treatment required for cure (28, 29). The basis for the current study was evidence from the murine model that replacing isoniazid with moxifloxacin substantially increases the activity of the standard regimen of isoniazid, rifampin, and pyrazinamide (1, 2, 30, 31). How might the apparent discordance between murine results and results of this clinical study be explained? One possibility is that the activity of moxifloxacin was overestimated in the murine model. Moxifloxacin is cleared more rapidly by mice than humans, and to compensate for its rapid clearance, it is administered at 100 mg/kg in mice. At this dose the maximal serum concentration (C_{max}) is 14 μg/ml, or roughly 3 times the C_{max} of 4.3 μg/ml observed in humans (32, 33). However, the area under the curve $(AUC)_{0–24h}$ observed in the mouse at this dose (23.6 mg·h/L) is approximately half that observed in humans (45.5 mg·h/L). When moxifloxacin is administered in the mouse diet in a way that reproduces both the lower human C_{max} and the higher AUC, the activity of moxifloxacin increases, suggesting that AUC is a more important driver of its antituberculosis activity than C_{max} (32, 34). Thus, it seems unlikely that the activity of moxifloxacin itself is overestimated by use of the 100 mg/kg dose in the mouse. A second possibility is that isoniazid may antagonize the activity of rifampin and pyrazinamide in humans. In the murine model, removing isoniazid has a greater beneficial effect than adding the fluoroquinolone because isoniazid markedly antagonizes the activity of rifampin and pyrazinamide (1, 35–37). Like moxifloxacin, isoniazid is cleared more rapidly in mice, and a dose of 25 mg/kg is necessary to achieve a mean $AUC_{0–24h}$ of 27.6 mg·h/L, similar to that observed in humans (e.g., the mean value of 23.7 mg·h/L observed in slow acetylators after a 5 mg/kg dose) (38). The resultant C_{max} of 20.1 mg/L in the mouse is 4 to 5 times higher than that observed in humans. If the antagonism of isoniazid is related to the C_{max}, it could be overrepresented in mice. Such antagonism has not been observed *in vitro*, and whether it occurs in humans remains an open question (39). A pharmacokinetic interaction resulting in diminished pyrazinamide concentrations in mice treated with the combination of isoniazid, rifampin, and pyrazinamide cannot be formally discounted as another possible explanation for the greater potency of the combination of moxifloxacin, rifampin, and pyrazinamide over the combination of isoniazid, rifampin, and pyrazinamide in mice (1).

In conclusion, replacement of isoniazid with moxifloxacin during the first 2 months of pulmonary TB treatment resulted in a small but statistically nonsignificant increase in the percentage of participants with negative cultures at Week 8. Additional studies are ongoing to determine the optimal role of moxifloxacin in pulmonary TB treatment.

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