Moxifloxacin versus Ethambutol in the First 2 Months of Treatment for Pulmonary Tuberculosis

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Rationale: **Moxifloxacin has promising preclinical activity against *Mycobacterium tuberculosis*, but has not been evaluated in multidrug treatment of tuberculosis in humans.**

Objective: **To compare the impact of moxifloxacin versus ethambutol, both in combination with isoniazid, rifampin, and pyrazinamide, on sputum culture conversion at 2 mo as a measure of the potential sterilizing activity of alternate induction regimens.**

Methods: **Adults with smear-positive pulmonary tuberculosis were randomized in a factorial design to receive moxifloxacin (400 mg) versus ethambutol given 5 d/wk versus 3 d/wk (after 2 wk of daily therapy). All doses were directly observed.**

Measurements: **The primary endpoint was sputum culture status at 2 mo of treatment.**

Results: **Of 336 patients enrolled, 277 (82%) were eligible for the efficacy analysis, 186 (67%) were male, 175 (63%) were enrolled at African sites, 206 (74%) had cavitation on chest radiograph, and 60 (22%) had HIV infection. Two-month cultures were negative in 71% of patients (99 of 139) treated with moxifloxacin versus 71% (98 of 138) treated with ethambutol ($p = 0.97$). Patients receiving moxifloxacin, however, more often had negative cultures after 4 wk of treatment. Patients treated with moxifloxacin more often reported nausea (22 vs. 9%, $p = 0.002$), but similar proportions completed study treatment (88 vs. 89%). Dosing frequency had little effect on 2-mo culture status or tolerability of therapy.**

Conclusions: **The addition of moxifloxacin to isoniazid, rifampin, and pyrazinamide did not affect 2-mo sputum culture status but did show increased activity at earlier time points.**

Keywords: efficacy; moxifloxacin; randomized trial; toxicity; tuberculosis

New agents are needed for the treatment of drug-susceptible and drug-resistant tuberculosis. Treatment of drug-susceptible tuberculosis is very effective, but the need for 6 mo of therapy poses challenges to patients and tuberculosis control programs. A major goal of tuberculosis research is to identify shorter treatment regimens. The newer fluoroquinolone antibiotics, moxifloxacin and gatifloxacin, have potent activity *in vitro* and in animal models of tuberculosis treatment (1–3). In a murine model of tuberculosis treatment, moxifloxacin adds to the sterilizing activity of multidrug therapy with isoniazid, rifampin, and pyrazinamide (4). In addition, moxifloxacin has been shown to have potent activity in the first few days of tuberculosis treatment (early bactericidal activity) as monotherapy (5–7) or with isoniazid (8). The activity and tolerability, however, of moxifloxacin in multidrug treatment of human tuberculosis have not been evaluated previously.

The definitive measure of the sterilizing activity of a multidrug tuberculosis treatment regimen is its ability to prevent treatment failure and relapse. Trials using treatment failure plus relapse as endpoints, however, require large sample sizes ($> 1{,}000$ patients) and follow-up for 1 to 2 yr after completion of therapy. Previous trials have shown a strong correlation between the rate of relapse and the ability of a regimen to convert sputum cultures to negative after 2 mo of therapy (9–11). Two-month sputum culture conversion is an appropriate surrogate marker for the initial evaluation of a new drug regimen for tuberculosis treatment.

Intermittent dosing fosters the use of directly observed therapy. An important part of the assessment of a new drug for tuberculosis is an evaluation of its suitability for intermittent dosing. In a factorial design, the Tuberculosis Trials Consortium evaluated the activity and tolerability of moxifloxacin substituted for ethambutol and the effect of 5 d/wk versus 3 d/wk dosing during the first 8 wk of tuberculosis therapy. We reasoned that if moxifloxacin significantly improved 2-mo sputum culture conversion rates, a larger phase 3 trial of moxifloxacin to shorten therapy would be justified. Preliminary results of this study were reported in a presentation at the 2005 Interscience Conference on Antimicrobial Agents and Chemotherapy (12).

METHODS

Patients 18 yr or older with suspected pulmonary tuberculosis and acid-fast bacilli in an expectorated sputum sample were eligible for enrollment. Patients were excluded if they had received more than 7 d of a fluoroquinolone antibiotic or tuberculosis treatment within the previous 6 mo; were pregnant or breast-feeding; or if the initial sputum cultures were negative for *Mycobacterium tuberculosis* or grew a strain resistant to rifampin, fluoroquinolones, or pyrazinamide (patients whose isolates were resistant to isoniazid were included) (13). All patients underwent HIV testing. A complete listing of inclusion and exclusion criteria is available in the online supplement. The study was approved by the Centers for Disease Control and Prevention (CDC) and local institutional review boards, and patients gave informed consent.

Patients were randomized in a factorial design to two interventions: moxifloxacin (400 mg) versus ethambutol, and treatment 5 d/wk versus thrice weekly, following an initial 2 wk of daily therapy. Randomization was stratified by continent of enrollment and presence of pulmonary cavitation. Patients received moxifloxacin or matching placebo and ethambutol or matching placebo. Isoniazid, rifampin, and pyrazinamide were obtained from licensed suppliers in the United States or Europe (*see* Table 1 for doses). All doses were supervised. Completion of study therapy was defined as ingestion of 40 doses (5 d/wk treatment) or

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TABLE 1. DOSES OF STUDY MEDICATIONS DURING THE INTENSIVE PHASE

Drug	Dose for Daily Therapy	Dose for Thrice-Weekly Therapy
Moxifloxacin	400 mg	400 mg
Rifampin		
⩽ 45 kg	450 mg	450 mg
> 45 kg	600 mg	600 mg
Isoniazid	300 mg	15 mg/kg, max. dose 900 mg
Pyrazinamide		
40–55 kg	1,000 mg	1,500 mg
56–75 kg	1,500 mg	2,500 mg
76–90 kg	2,000 mg	3,000 mg*
Ethambutol		
40–55 kg	800 mg	1,200 mg
56–75 kg	1,200 mg	2,000 mg
76–90 kg	1,600 mg	2,400 mg*

* Maximum dose, regardless of weight.

28 doses (thrice-weekly therapy). After completion of the first 2 mo of treatment, patients completed tuberculosis treatment with a recommended regimen (14).

Sputum cultures were performed at local laboratories that were required to use both broth and solid culture media. *M. tuberculosis* isolates underwent confirmatory drug-susceptibility testing at the CDC using the proportion method (15). Fluoroquinolone resistance was defined as growth in the presence of 2 μg/ml of ciprofloxacin (16).

Data Analysis

The study was designed to detect a difference in sputum culture conversion that has been associated with the ability to shorten treatment. The addition of pyrazinamide, an intervention that allowed treatment to be shortened by 3 mo, increased 2-mo culture conversion rates by an average of 13% (17–20). To detect this difference using a one-sided test at the 0.05 level and 80% power requires 125 patients per group for the two primary comparisons (e.g., moxifloxacin vs. ethambutol). We increased this by 30% to compensate for patient drop-out, and missing or overgrown cultures.

The primary efficacy endpoint was the proportion of patients with negative cultures after 2 mo of treatment. Following the practice of the British Medical Research Council, we excluded (*1*) patients who took nonstudy therapy or required more than 70 d to complete the intensive phase, (*2*) patients who died during the intensive phase of therapy, and (*3*) patients whose sputum cultures were overgrown with bacteria or yeast. Patients who received at least one dose of study drug were included in the safety analysis.

We analyzed data using SAS (version 8.2; SAS Institute, Inc., Cary, NC) and EpiInfo (version 6.04: CDC, Atlanta, GA) software packages.

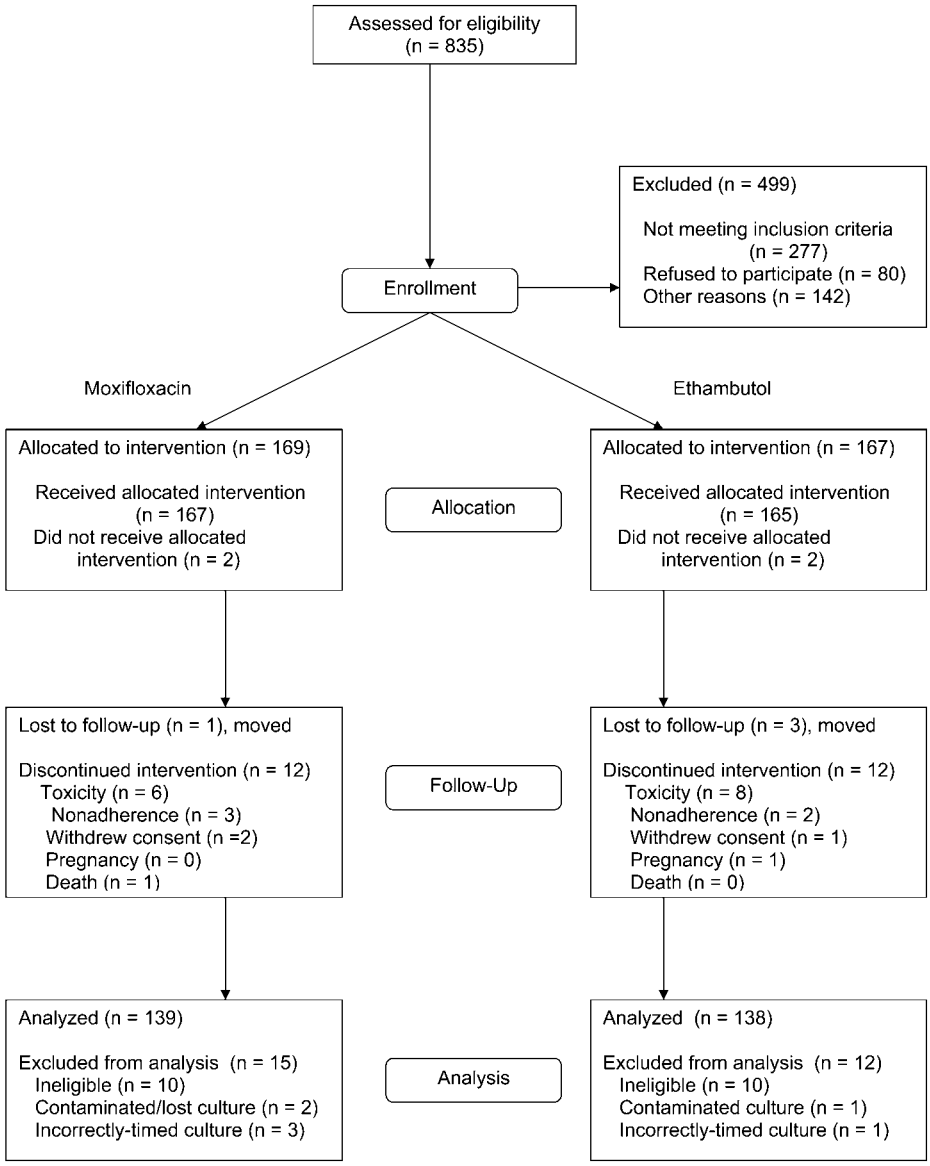

Figure 1. Enrollment and disposition of patients.

TABLE 2. CHARACTERISTICS OF PATIENTS INCLUDED IN THE EFFICACY ANALYSIS (n = 277)

	Moxifloxacin		Ethambutol	
Characteristic	5 d/wk (*n = 68*)	3 d/wk (*n = 71*)	5 d/wk (*n = 68*)	3 d/wk (*n = 70*)
Median age, yr (IQR)	30 (23–40)	32 (27–44)	30 (23–39)	32 (25–42)
Male, n (%)	43 (63)	55 (78)	41 (60)	47 (67)
Continent of enrollment, n (%)				
Africa	43 (63)	44 (62)	42 (62)	46 (66)
North America	25 (37)	27 (38)	26 (38)	24 (34)
Race or ethnicity, n (%)				
Non-Hispanic black	55 (81)	50 (70)	52 (77)	47 (67)
Non-Hispanic white	4 (6)	3 (4)	1 (2)	3 (4)
Hispanic	4 (6)	12 (17)	8 (12)	15 (22)
Asian and Pacific Islander	4 (6)	5 (7)	6 (9)	4 (6)
Other	1 (1)	1 (1)	1 (2)	1 (1)
Sociologic features (within the past year), n (%)				
Less than high school education	46 (68)	45 (63)	48 (71)	54 (77)
Homeless	4 (6)	2 (3)	4 (6)	1 (1)
Injection drug use	2 (3)	0 (0)	1 (2)	0 (0)
Excess alcohol use	7 (10)	9 (13)	3 (4)	5 (7)
Clinical features				
Median body weight, kg (IQR)	56 (50–62)	56 (51–62)	54 (48–61)	53 (48–61)
Median body mass index (IQR)	20 (18–22)	20 (19–22)	20 (18–22)	19 (18–22)
Cavitation on chest radiograph, n (%)	50 (74)	52 (73)	51 (75)	53 (76)
Bilateral disease on chest radiograph, n (%)	38 (57)	47 (66)	41 (60)	43 (62)
Laboratory features				
Isoniazid-resistant isolate, n (%)	10 (15)	5 (7)	5 (7)	5 (7)
Median hemoglobin, g/dl (IQR)	11.6 (10.4–13.2)	11.8 (10.5–13.3)	11.5 (10.1–13.1)	11.6 (9.4–13.1)
HIV infection, n (%)	15 (22)	15 (21)	16 (24)	14 (20)
Median CD4 lymphocyte count, cells/mm^3 (IQR)	136 (85–279)	234 (106–446)	254 (151–357)	176 (108–314)
Median plasma HIV RNA level, $\log_{10}$ copies/ml (IQR)	4.9 (4.7–5.1)	5 (4.8–5.9)	5 (4.1–5.4)	5 (4.8–5.2)
Tuberculosis treatment before enrollment				
Any treatment within 7 d, n (%)	29 (43)	25 (35)	30 (44)	28 (40)
Median number of days of treatment (IQR)*	5 (3–6)	4 (3–5)	5 (3–6)	5 (3–6)

Definition of abbreviation: IQR = interquartile range.
* Among patients with any treatment before enrollment.

We evaluated factors associated with a negative 2-mo culture using the χ^2 test. Multivariate logistic regression was performed, using backward elimination, considering the same factors. Treatment regimen and all variables with multivariate $p < 0.05$ are shown in a final model.

More details on methods can be found in the online supplement.

RESULTS

A total of 336 patients with suspected smear-positive pulmonary tuberculosis were enrolled from July 2003 through March 2005. Four patients did not receive study drug, so 332 patients are included in the safety analysis (Figure 1). Twenty patients were found to be ineligible after enrollment (negative culture, 5; growth of a nontuberculous mycobacterium, 4; resistance to rifampin, fluoroquinolones, or pyrazinamide, 11). An additional 35 patients could not be assessed for 2-mo culture status (stopped assigned therapy because of toxicity, 14; nonadherence, 5; contaminated or lost cultures, 3; inappropriately timed cultures, 4; withdrew consent, 3; pregnancy, 1; death, 1; moved, 4). A total of 277 patients (82% of those enrolled) were included in the efficacy analysis, with similar proportions from each of the four study arms being included in the efficacy analysis.

Table 2 shows demographic and clinical characteristics of the 277 patients included in the efficacy analysis. The median age was 31 yr (interquartile range, 24–40 yr); 186 (67%) were male; 175 (63%) were enrolled at African sites; 206 (74%) had cavitation on chest radiograph; and 60 (22%) had HIV infection. Patients with HIV infection had a median CD4 lymphocyte count of 196 cells/mm^3 (interquartile range, 112–319) and median plasma HIV RNA level of 5 (4.5–5.3) $\log_{10}$ copies/ml. A higher proportion of those receiving thrice-weekly moxifloxacin were male; otherwise, the study arms were well balanced for baseline characteristics. Of the 277 patients in the efficacy analysis, 274 (99%) had sputum specimens obtained at the 2-mo time point.

There was no significant interaction between the two interventions evaluated (moxifloxacin vs. ethambutol, treatment 5 d/wk vs. 3 d/wk, $p = 0.27$), so the analysis proceeded using the factorial design. Two-month cultures were negative in 99 (71%) of 139 patients treated with moxifloxacin versus 98 (71%) of 138 patients treated with ethambutol ($p = 0.97$; Table 3). Two-month culture status was also similar among patients who received therapy 5 d/wk versus 3 d/wk (100 [74%] of 136 vs. 97 [69%] of 141 patients, $p = 0.39$). We performed two *post hoc* analyses of the effect of treatment assignment (*see* online supplement for additional

TABLE 3. TWO-MONTH SPUTUM CULTURE CONVERSION, BY STUDY ARM AND THE FACTORIAL DESIGN

	Treatment Frequency		
Treatment	5 d/wk	3 d/wk	Combined‡
Moxifloxacin	48/68 (71%)†	51/71 (72%)†	99/139 (71%)
Ethambutol	52/68 (76%)†	46/70 (66%)†	98/138 (71%)
Combined*	100/136 (74%)	97/141 (69%)	

† Overall, $p = 0.52$.
‡ Comparing drug treatment arms, $p = 0.97$.
* Comparing treatment frequency arms, $p = 0.39$.

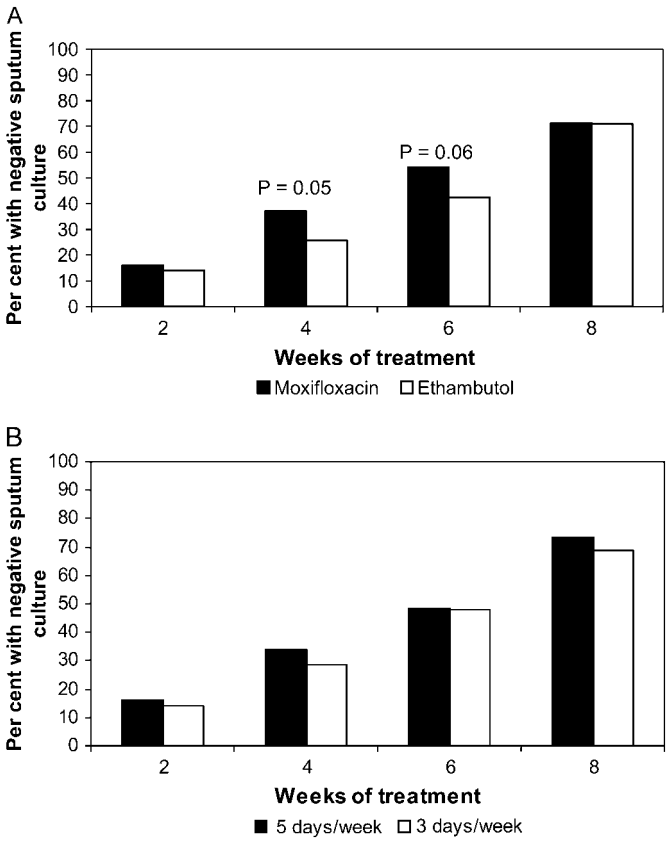

Figure 2. Proportion of sputum cultures negative at Weeks 2, 4, 6, and 8 of treatment by study drug (*A*) and dosing frequency (*B*).

details). First, in an analysis of all patients with a 2-mo culture result (whether or not they remained on or completed their assigned regimen), there was no difference between moxifloxacin and ethambutol (cultures were negative in 113 [72%] of 156 and 109 [71%] of 153 patients, respectively). Second, 2-mo culture status was not affected by treatment assignment among the 252 patients having isoniazid-susceptible isolates (cultures were negative in 88 [71%] of 124 and 91 [71%] of 128 patients receiving moxifloxacin and ethambutol, respectively).

A secondary endpoint of the trial was sputum culture status at time points earlier in therapy. Sputum cultures were more likely to be negative among patients who received moxifloxacin both at Week 4 (37% [62 of 167] vs. 26% [43 of 165], $p = 0.05$) and at Week 6 (54% [90 of 167] vs. 42% [69 of 165], $p = 0.06$; Figure 2). Dosing frequency did not have a significant effect on sputum culture results at any of the time points assessed.

Pulmonary cavitation was associated with markedly lower 2-mo culture conversion (66% [137 of 206] vs. 84% [60 of 71] among those without cavitation, $p < 0.005$; Table 4). As anticipated in designing enrollment stratification by both region and cavitation, more African patients had baseline pulmonary cavitation (142 [81%] of 175) than did non-African patients (64 [63%] of 102, $p = 0.0007$). Enrollment at an African site was also associated with markedly lower culture conversion (63% [110 of 175] vs. 85% [87 of 102] of patients enrolled at North American sites, $p = 0.0001$). Notably, among evaluable patients at the two African sites in our study, 2-mo culture status was somewhat lower in patients enrolled in Kampala (61% [90 of 147]) compared with patients enrolled in Durban (71% [20 of 28], $p = 0.31$). Because randomization was stratified both by cavitation and continent of enrollment, adjustment for these factors did not affect the analyses of moxifloxacin versus ethambutol and dosing frequency. HIV serostatus was not associated with culture conversion at 2 mo (43 [72%] of 60 HIV-positive patients converted cultures vs. 153 [71%] of 216 HIV-negative patients). In multivariate analysis, pulmonary cavitation, enrollment at an African site, and age greater than 31 yr (the median value) were significantly associated with lower 2-mo sputum culture conversion (Table 4).

Tolerability and Safety

Similar proportions of patients randomized to moxifloxacin and ethambutol completed the assigned regimen (88% [145 of 165] and 89% [148 of 167], respectively; $p = 0.83$). Rates of serious adverse events also were similar, and most serious adverse events were hospitalizations thought to be unrelated to the study treatment (Table 5). The one death during the first 2 mo of treatment was thought to be caused by pulmonary embolism, unrelated to tuberculosis therapy. Patients who received moxifloxacin more often reported nausea (21.6 vs. 9.1%, $p = 0.002$), but this symptom seldom necessitated temporary or permanent discontinuation of study therapy (Table 5). Joint pain was somewhat more frequently reported by patients on moxifloxacin (34% [57 of 167] vs. 27% [44 of 165], $p = 0.15$), but no cases of tendonopathy or arthritis were recognized. Although visual changes were reported in all study groups, no cases of retinitis or optic neuritis were diagnosed.

There was no evidence of differential laboratory toxicity by study arm. Maximum values for hepatic and renal function tests and minimum values for hematology tests through the first month after the last study dose were similar between study arms, both by study drug and by treatment schedule (*see* the online supplement). Furthermore, no differences in adverse event rates or in symptoms were found between study arms during the first month after the last study dose (*see* the online supplement).

DISCUSSION

Substitution of moxifloxacin for ethambutol did not have an effect on 2-mo sputum culture status but did result in a higher frequency of negative cultures at earlier time points among patients with smear-positive pulmonary tuberculosis. These results suggest that moxifloxacin has sterilizing activity, but insufficient activity when used in the manner evaluated in this trial (i.e., added to isoniazid, rifampin, and pyrazinamide) to support treatment shortening based on the surrogate marker of 2-mo culture conversion. Although associated with more nausea, moxifloxacin was generally well tolerated. Compared with ethambutol as a fourth drug, similar proportions of patients completed their assigned study therapy. The second part of the factorial design evaluated a modest difference in dosing frequency, 5 d/wk compared with 3 d/wk (after 2 wk of daily therapy). As in previous studies of dosing frequency, this difference (40 vs. 28 doses) had little effect on activity and tolerability.

Investigators in Chennai sparked interest in the possible use of fluoroquinolones to shorten the treatment of drug-susceptible tuberculosis. Despite the lack of an appropriate control group, they reported very high 2-mo culture conversion rates (> 90% for all arms of the study) when ofloxacin was added to regimens including isoniazid, rifampin, and pyrazinamide (21). Our results are similar to those of a previous trial evaluating the addition of levofloxacin to standard four-drug therapy for HIV-related tuberculosis. Levofloxacin did not increase 2-mo culture conversion but was associated with a somewhat higher prevalence of negative cultures at earlier time points (22). The results of this and previous controlled trials (22, 23) are consistent in showing that the addition of a fluoroquinolone to current standard therapy

TABLE 4. FACTORS ASSOCIATED WITH 2-mo SPUTUM CULTURE STATUS (n = 277)

Factor	2-mo Culture Status, Number with Negative Cultures/Total (%)	Unadjusted OR (*95% CI*)	p Value	Adjusted OR (*95% CI*)†	p Value
Age, yr					
> 31 (median)	89/134 (66)	0.6 (0.4–1.1)	0.10	0.4 (0.2–0.8)	0.003
⩽ 31	108/143 (76)				
Sex					
Female	63/91 (69)	0.9 (0.5–1.5)	0.63		
Male	134/186 (72)				
Continent of enrollment					
Africa	110/175 (63)	0.3 (0.2–0.6)	0.0001	0.3 (0.1–0.5)	< 0.0001
North America	87/102 (85)				
Race or ethnicity					
Black, non-Hispanic	134/204 (66)	0.3 (0.2–0.6)	0.001		
Other	63/73 (86)				
Body mass index					
> 19.74 (median)	101/138 (73)	1.2 (0.7–2.1)	0.45		
⩽ 19.74	96/139 (69)				
Hemoglobin					
> 11.6 g/dl (median)	104/137 (76)	1.6 (0.9–2.7)	0.08		
⩽ 11.6 g/dl	93/140 (66)				
HIV status					
HIV-infected	43/60 (72)	1 (0.6–2)	0.90		
HIV-uninfected	153/216 (71)				
Pulmonary cavitation					
Present	137/206 (66)	0.4 (0.2–0.7)	0.005	0.4 (0.2–0.9)	0.03
Absent	60/71 (84)				
Extent of chest radiographic abnormalities					
Bilateral	110/169 (65)	0.5 (0.3–0.8)	0.008		
Unilateral	85/106 (80)				
Pre-enrollment tuberculosis treatment*					
Any	89/112 (79)	2 (1.2–3.6)	0.01		
None	108/165 (65)				
Isoniazid-resistant isolate at baseline					
Present	18/25 (72)	1 (0.4–2.6)	0.92		
Absent	179/252 (71)				
Rifampin dose, mg/kg					
> 11.00 mg/kg (median)	92/136 (68)	0.7 (0.4–1.2)	0.21		
⩽ 11.00 mg/kg	105/141 (74)				
Study drug					
Moxifloxacin	99/139 (71)	1 (0.6–1.7)	0.97	1 (0.6–1.7)	0.87
Ethambutol	98/138 (71)				
Dosing frequency					
5 d/wk	100/136 (74)	1.26 (0.75–2.12)	0.39		
3 d/wk	97/141 (69)				

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

* Tuberculosis treatment during the 7 d before enrollment.

† Multivariate logistic regression was performed, using backward elimination, considering all the factors in the table. Treatment regimen and all variables with multivariate $p < 0.05$ are shown in the adjusted model.

has some sterilizing activity (negative cultures at earlier time points), but does not have a significant effect on the 2-mo sputum culture. Earlier differences in sputum conversion might be important for treatment shortening, but data in support of this are currently lacking.

Recent studies suggest that the activity of moxifloxacin may be dependent on the drugs with which it is used. In a murine model of tuberculosis treatment, the replacement of isoniazid by moxifloxacin was much more potent than the addition of moxifloxacin to isoniazid, rifampin, and pyrazinamide (2.5 $\log_{10}$ greater killing at the 2-mo time point) (4). Furthermore, when moxifloxacin was used in place of isoniazid, all animals were culture negative by 3 mo of treatment, and treatment could be shortened to 4 mo (24). Despite the failure of our study to show enhanced 2-mo culture conversion, fluoroquinolone antibiotics may still allow significant shortening of the treatment of drug-susceptible tuberculosis.

Sputum culture conversion was substantially lower among patients enrolled in the two African sites than among patients enrolled at North American sites. In addition, the 2-mo culture conversion rates at African sites in our study were lower than those in previous studies in east Africa (17–19), perhaps in part because of the higher sensitivity of using both broth and solid culture media in the present study (whereas earlier studies used solid media alone). Patients enrolled at African sites more often had pulmonary cavitation and less often had received any tuberculosis treatment before study enrollment, both of which were associated with lower sputum culture conversion. Enrollment at an African site, however, retained an association with 2-mo culture status after adjustment for these two factors. It is possible that some of the difference between African and North American patients was caused by a greater overall severity of illness that was not reflected in the relatively crude measure of the presence or absence of pulmonary cavitation. Other possible

TABLE 5. ADVERSE EVENTS AND REPORTED SYMPTOMS DURING THE FIRST 2 mo OF TREATMENT, BY TREATMENT ARM

Adverse Event	Moxifloxacin (*n = 167*)	Ethambutol (*n = 165*)	p Value	Relative Risk (*95% CI*)
Death	1 (0.6)	0 (0)	1.0	3 (0.1–72.2)
Hospitalization	8 (5)	6 (4)	1.0	0.9 (0.4–2.3)
Any serious adverse event*	10 (6)	8 (5)	0.81	1.2 (0.5–3.1)
Serious adverse event attributed to study therapy†	0 (0)	1 (0.6)	0.50	0.3 (0.01–8)
Study drug temporarily or permanently discontinued	17 (10)	18 (10)	0.86	0.9 (0.5–1.8)
Any grade 3 or 4 toxicity	31 (19)	19 (12)	0.091	1.6 (0.95–2.7)
Hepatotoxicity	6 (4)	7 (4)	0.79	0.9 (0.3–2.5)
Nausea or vomiting	4 (2)	0 (0)	0.12	8.9 (0.5–164)
Vision change	10 (6)	9 (6)	1.00	1.1 (0.5–2.6)
Diarrhea	3 (2)	0 (0)	0.25	6.9 (0.4–133)
Selected symptoms (any grade)				
Nausea	36 (22)	15 (9)	0.002	2.4 (1.4–4.2)
Vomiting	20 (12)	15 (9)	0.48	1.3 (0.7–2.5)
Diarrhea	12 (7)	6 (4)	0.23	2 (0.8–5.1)
Fevers	29 (17)	20 (12)	0.22	1.4 (0.9–2.4)
Dizziness	24 (14)	15 (9)	0.17	1.6 (0.9–2.9)
Joint pain	57 (34)	44 (27)	0.15	1.3 (0.9–1.8)

Definition of abbreviation: CI = confidence interval.

* Death, hospitalization, disabling event, grade 4 adverse event.

† Definite, probable, or possible relationship to study drug, per local investigator.

explanations (drug malabsorption, inadequate drug formulation) are being investigated, although all patients were treated with drugs approved by national regulatory agencies in the United States or Europe. Although not fully explained at this time, the difference between bacteriologic response rates of African and North American patients in our trial clearly demonstrates the need to evaluate new treatments for tuberculosis in a diverse patient population.

In this and previous studies, fluoroquinolone antibiotics were well tolerated when given for 2 mo or longer. Our trial design compared moxifloxacin with ethambutol, the best tolerated of the first-line antituberculosis drugs. Nausea, a side effect previously associated with the fluoroquinolones, was more common among patients treated with moxifloxacin, but seldom resulted in drug discontinuation. Similar to the previous trial of the addition of levofloxacin (22), there was no association between moxifloxacin and more serious side effects. These data add to the growing and favorable experience with prolonged use of fluoroquinolones in the treatment of multidrug resistant tuberculosis (25, 26) and *Chlamydia pneumoniae* (27). All of these studies suggest that moxifloxacin has an acceptable safety profile that allows it to be used in studies of treatment of drug-susceptible tuberculosis (28, 29). The recent report of the association between dysglycemia and the use of gatifloxacin is a reminder of the eventual need for larger phase 3 studies to evaluate more fully the safety of fluoroquinolones in tuberculosis treatment (30).

Intermittent dosing fosters directly observed therapy by decreasing the number of encounters necessary to ensure treatment compliance. Intermittent dosing during the intensive phase of therapy using current standard therapy may increase the risk of relapse, however, among patients with cavitary pulmonary tuberculosis (31). Several lines of evidence suggest that moxifloxacin may be effective when dosed intermittently. The serum half-life of moxifloxacin is approximately 12 h (32), substantially longer than that of isoniazid, rifampin, and streptomycin, all of which have good activity when dosed intermittently (33). Furthermore, once-weekly moxifloxacin had favorable activity in the continuation phase of treatment in a murine model (34). Our results are similar to those of previous randomized trials of daily versus thrice-weekly therapy during the intensive phase: slightly lower rates of sputum culture conversion with intermittent therapy (not statistically significant in any previous trial) and similar tolerability (17–20). The lack of a significant difference in 2-mo culture status in our study may also be caused by the modest difference in dosing frequency evaluated; "daily therapy" was defined as dosing 5 d/wk. The role of intermittent therapy during the intensive phase requires additional research.

Our study has several limitations. We used 2-mo culture status as a surrogate marker for sterilizing activity and did not monitor patients for relapse, the definitive marker of sterilizing activity. Studies powered to compare relapse require large sample sizes, however, and it is very difficult to evaluate all new drugs, doses, and drug combinations using studies comparing relapse rates. There are uncertainties about the use of 2-mo culture status as a surrogate marker and a need for further research on surrogate markers of drug activity in tuberculosis treatment. Two-month culture status does correlate with sterilizing potential, however, and its use as a primary end point allows comparisons of regimens using sample sizes that are feasible for early drug development efforts. We evaluated only one dosage of one of the potent fluoroquinolone antibiotics. In a study of early bactericidal activity, moxifloxacin, gatifloxacin, and high-dose levofloxacin had comparable early bactericidal activity (7). Similarly, we only evaluated one way of using moxifloxacin (substitution for ethambutol), and the decreased activity of regimens including both moxifloxacin and isoniazid in a murine model of rifamycin-containing tuberculosis treatment (4, 35) suggest that we may not have used moxifloxacin in an optimal regimen in our trial. This trial was powered to detect a relatively large effect of the addition of moxifloxacin (an increase of 13% in culture negativity at 2 mo) because our interest is in identifying more potent induction phase regimens that would allow treatment shortening. Moxifloxacin may have a smaller effect on 2-mo culture status that was not detected in this study. Finally, we did not use a standard method for mycobacterial culture at all sites, but because randomization was stratified by continent of enrollment, this should not have confounded the comparison of moxifloxacin versus ethambutol.

CONCLUSIONS

We have shown that the addition of moxifloxacin to isoniazid, rifampin, and pyrazinamide has sterilizing activity, but is unlikely to allow for significant shortening of tuberculosis treatment. The activity and tolerability of moxifloxacin in this study support additional evaluation of moxifloxacin in the treatment of drug-susceptible tuberculosis.

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