

Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial

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Summary

Background New treatments are needed to shorten the time required to cure tuberculosis and to treat drug-resistant strains. The fluoroquinolone moxifloxacin is a promising new agent that might have additive activity to existing antituberculosis agents. We assessed the activity and safety of moxifloxacin in the initial stage of tuberculosis treatment.

Methods We undertook a phase II, double-blind, randomised controlled trial of a regimen that included moxifloxacin in adults with sputum smear-positive tuberculosis at one hospital in Rio de Janeiro, Brazil. 170 participants received isoniazid, rifampicin, and pyrazinamide at standard doses and were assigned by permuted block randomisation to receive either moxifloxacin (400 mg) with an ethambutol placebo (n=85) or ethambutol (15–20 mg/kg) plus moxifloxacin placebo (n=85) 5 days per week for 8 weeks. The primary endpoint was the proportion of patients whose sputum culture had converted to negative by week 8. Analysis was by modified intention to treat (ITT); patients whose baseline cultures were negative, contaminated, or contained drug-resistant *Mycobacterium tuberculosis* were excluded from the analysis. Additionally, all missing 8-week results were deemed treatment failures. This study is registered with ClinicalTrials.gov, number NCT00082173.

Findings 74 patients assigned to the moxifloxacin group and 72 in the ethambutol group were included in the modified ITT population. 125 patients had 8-week data (moxifloxacin n=64, ethambutol n=61); the main reason for absence of data was culture contamination. At 8 weeks, culture conversion to negative had occurred in 59 (80%) of 74 patients in the moxifloxacin group compared with 45 (63%) of 72 in the ethambutol group (difference 17.2%, 95% CI 2.8–31.7; p=0.03). There were 16 adverse events (eight in each group) in 12 patients. Only one event was judged related to study drug (grade 3 cutaneous reaction in the ethambutol group).

Interpretation Moxifloxacin improved culture conversion in the initial phase of tuberculosis treatment. Trials to assess whether moxifloxacin can be used to shorten the duration of tuberculosis treatment are justified.

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Introduction

The development of new drug regimens for tuberculosis is an urgent global health priority.¹ Although so-called short-course treatment can effectively cure drug-susceptible tuberculosis in 6 months, a large proportion of patients in whom tuberculosis is diagnosed do not complete a course of treatment.² New drugs that shorten the duration of tuberculosis treatment would substantially reduce the likelihood of disease recurrence and death caused by inadequate therapy. Additionally, since every year there are 500 000 reported cases of tuberculosis caused by strains of *Mycobacterium tuberculosis* that are resistant to the key first-line drugs isoniazid and rifampicin, agents that are active in multidrug-resistant tuberculosis are also needed.³

Moxifloxacin is a fluoroquinolone that has potent in-vitro activity against *M tuberculosis*.^{4,5} Early studies of moxifloxacin in murine models of tuberculosis showed that the drug had good bactericidal activity that was

additive to isoniazid.^{6,7} On the basis of these studies, we designed a phase II clinical trial to test the hypothesis that the substitution of ethambutol, an agent used primarily to prevent the emergence of drug resistance, with moxifloxacin would significantly increase the proportion of patients with negative sputum cultures after 8 weeks of treatment. 8-week sputum conversion has proved a useful surrogate marker of the sterilising activity of tuberculosis regimens,⁸ and a substantial improvement in this endpoint after moxifloxacin treatment would support progression to a phase III trial to assess whether a regimen including this drug could shorten the duration of tuberculosis treatment.

Methods

Patients

We undertook a single-centre, randomised, double-blind, double-dummy trial of moxifloxacin versus ethambutol in patients with sputum smear-positive tuberculosis

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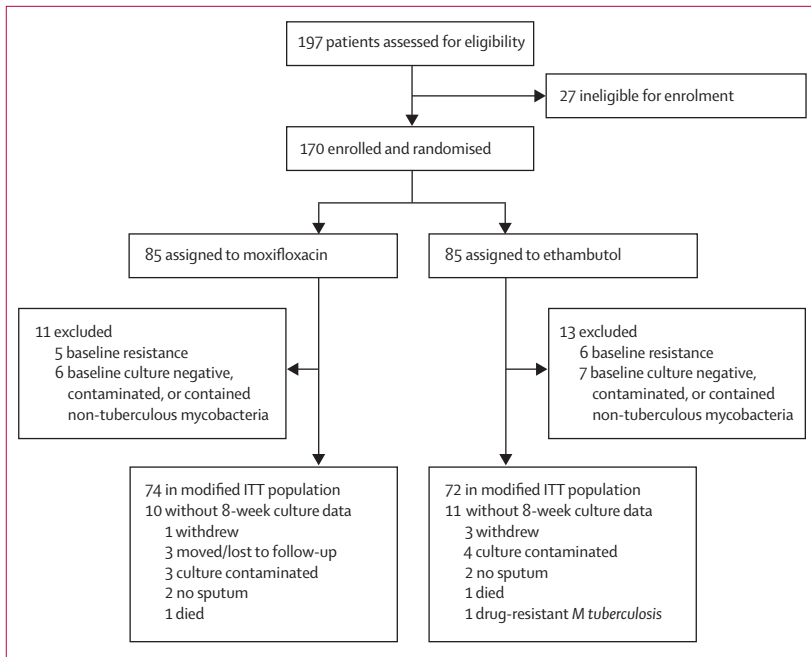


Figure 1: Trial profile
ITT=intention-to-treat.

with no previous history of treatment in Hospital Clementino Fraga Filho, Rio de Janeiro, Brazil. Patients aged 18 years or older were eligible for enrolment if they had clinical signs and symptoms of pulmonary tuberculosis, including an abnormal chest radiograph and at least one sputum smear with acid-fast bacilli visible by Ziehl-Neelsen staining. Potential participants underwent baseline screening that included blood cell counts, liver-function testing, kidney-function testing, HIV serology, chest radiography, and culture and drug susceptibility testing for mycobacteria. Exclusion criteria were: haemoglobin concentration less than 70 g/L; aspartate aminotransferase or alanine aminotransferase concentration more than three times the upper limit of normal; serum creatinine concentration more than twice the upper limit of normal; an electrocardiogram with a QTc interval more than 450 ms; pregnancy or breastfeeding; silicotuberculosis; a history of severe adverse reactions to fluoroquinolone drugs or any other study agent; and seropositivity for HIV with a CD4-cell count less than 200 cells per μL , since this finding would be an indication for antiretroviral therapy, which could be affected by interactions with antituberculosis drugs. Randomised patients were excluded if their baseline culture did not grow *M tuberculosis* or grew a strain of *M tuberculosis* that was resistant to isoniazid, rifampicin, or ethambutol.

Written informed consent was obtained from study participants before enrolment. Ethical review of the protocol was obtained from the Johns Hopkins Medicine Institutional Review Board and the Ethics Committee of the Federal University of Rio de Janeiro, the National

Ethics Committee of the Ministry of Health (CONEP), Brasilia, and the Agencia Nacional de Vigilância Sanitária (ANVISA), Brazil.

Procedures

Patients were stratified by HIV serostatus and assigned by permuted block randomisation with blocks of four to receive treatment with either moxifloxacin 400 mg with an ethambutol placebo or ethambutol 15–20 mg/kg plus moxifloxacin placebo (control). Treatment allocation was concealed and allocation slips sealed in opaque envelopes that were opened after enrolment. The study statistician, who generated the randomisation sequence, had no involvement in the conduct of the study. The study was designed to ensure that all patients received an effective regimen for tuberculosis irrespective of the contribution of the two experimental agents; therefore, all patients received isoniazid 300 mg, rifampicin 450 mg (weight <50 kg) or 600 mg (weight >50 kg), and pyrazinamide 20–25 mg/kg by directly observed treatment. Patients, study clinicians, and study staff were unaware of the treatment allocation, with the exception of the pharmacist who dispensed medication packets. All treatment was given by direct supervision either in the hospital clinic or in the community by study personnel, 5 days per week. At the end of 8 weeks, all patients were placed on open-label treatment with isoniazid and rifampicin two times per week to complete another 4 months of treatment. Moxifloxacin and matching placebo were provided by Bayer Healthcare (West Haven, CT, USA) and ethambutol, ethambutol placebo, isoniazid, rifampicin, and pyrazinamide were provided by Farmanguinhos (Rio de Janeiro, Brazil). All study agents were produced under good manufacturing processes.

Patients visited the clinic once a week to assess clinical status and to monitor for adverse reactions. Aminotransferase concentration, serum creatinine concentration, and complete blood counts were measured every month, and an electrocardiogram was obtained at weeks 2, 4, 6, and 8. A sputum specimen (spontaneous or induced) was obtained every week for smear and culture. Sputum specimens were digested and decontaminated by the N-acetyl-L-cysteine-sodium hydroxide method.^{9,10} Pellets were resuspended in a final volume of 2 mL and used immediately for inoculation of Löwenstein-Jensen culture medium. Löwenstein-Jensen slants were prepared from a commercial powder medium base (BD, Sparks, MD, USA), according to the manufacturer's instructions. 200 μL of each decontaminated respiratory specimen was inoculated onto each of two slants. Slants were incubated at 37°C in ambient carbon dioxide and examined visually for growth twice a week for 8 weeks by laboratory personnel who were not involved in the study and blinded to treatment status. Growth on slants was quantified by number of visible colonies, and then examined by acid-fast staining to confirm the presence of mycobacteria; isolates were

speciated by use of standard biochemical tests.¹⁰ Drug susceptibility testing of all baseline cultures growing *M tuberculosis* was done by the proportions method.¹⁰

The primary endpoint of the study was the proportion of patients with negative sputum cultures after 8 weeks of treatment. Patients were followed up for at least 12 months after completion of their 6-month course of treatment.

Statistical analysis

We assumed that the conversion rate in the control group (ethambutol) would be 65%,⁸ and that moxifloxacin would lead to an increase of 20% to a rate of 85%. To achieve a power of 0·8 with an alpha of 0·05, we needed 70 patients with 8-week data in each group of the trial. We aimed to enrol 85 patients per group to allow for exclusions based on negative initial culture, growth of non-tuberculous mycobacteria, or baseline drug resistance. The primary endpoint of the trial, culture conversion, was assessed by modified intention-to-treat (ITT) analysis; patients whose baseline cultures were negative, contaminated, or contained drug-resistant *M tuberculosis* were excluded and all missing 8-week results were deemed treatment failures. We also analysed all patients with available 8-week cultures. *p* values were calculated by χ^2 test. Multivariate logistic regression was done with treatment allocation and selected baseline characteristics as covariates and culture conversion as the dependent variable. Time to conversion of sputum cultures to negative was estimated by the Kaplan-Meier method and the difference in median times compared by the log-rank test. All analyses were done with SAS version 9. This study is registered with ClinicalTrials.gov, number NCT00082173.

Role of the funding source

The funding agencies were not involved in the design, conduct, or analysis of the study. The Investigational New Drug Office of the US FDA reviewed the protocol and made suggestions about the study design before initiation of the trial, but this was unrelated to any funding decisions. The decision to publish was made solely by the authors and the funding agencies did not review or approve the manuscript. Bayer Healthcare donated moxifloxacin and matching placebo for the trial, but had no input into the study design, execution, or analysis. The corresponding author had full access to all data in the study.

Results

From October, 2004, up to March, 2007, 197 patients were screened for participation in the trial. Figure 1 shows the trial profile. 74 patients assigned to the moxifloxacin group and 72 assigned to the ethambutol group were assessed for the primary outcome. In the modified ITT analysis, all missing data were deemed treatment failures.

	Moxifloxacin (n=74)	Ethambutol (n=72)
Age (years)	32·5 (11·7)	35·7 (12·0)
Female	34 (46%)	22 (31%)
White	30 (41%)	32 (44%)
HIV seropositive	3 (4%)	2 (3%)
Current or past smoker	29 (39%)	37 (51%)
Duration of treatment before enrolment (days)	6·4 (3·2)	5·6 (2·5)
Socioeconomic status		
Income (R\$ per month)	636 (550)	847 (724)
Formal employment	35 (47%)	41 (57%)
Weight (kg)	54·3 (9·6)	58·2 (9·9)
Baseline sputum acid-fast bacilli smear		
<1 per high-power field	42 (57%)	33 (46%)
1–10 per high-power field	10 (14%)	17 (24%)
>10 per high-power field	22 (30%)	22 (31%)
Baseline radiograph		
Infiltrate	74 (100%)	72 (100%)
Bilateral disease	34 (46%)	31 (43%)
Cavitation	59 (80%)	41 (57%)
Adenopathy	8 (11%)	11 (15%)
Pleural effusion	4 (5%)	7 (10%)
Baseline symptoms		
Productive cough	59 (80%)	57 (79%)
Haemoptysis	25 (34%)	20 (28%)
Fever	59 (80%)	58 (81%)
Night sweats	61 (82%)	57 (79%)
Weight loss	66 (89%)	70 (97%)
Baseline blood results		
White blood cells (per mL)	9324 (2961)	9728 (3921)
Packed-cell volume (%)	36·4 (5·7)	36·9 (5·1)
Haemoglobin (g/L)	123 (18)	123 (18)
Neutrophils (per mL)	6784 (2530)	7072 (3398)
Alkaline phosphatase (IU/L)	116·4 (62·3)	121·2 (49·2)
Alanine aminotransferase (IU/L)	35·8 (22·3)	35·6 (18·9)
Aspartate aminotransferase (IU/L)	27·8 (16·3)	26·8 (14·4)
Total bilirubin (μ mol/L)	9·4 (6·0)	8·4 (4·4)
Gamma-glutamyl transpeptidase (IU/L)	72·6 (50·5)	96·1 (89·3)
Creatinine (μ mol/L)	70·7 (17·7)	70·7 (8·8)

Data are n (%) or mean (SD).

Table 1: Baseline characteristics of study participants

Baseline characteristics of the patients are shown in table 1. A higher proportion of patients assigned to moxifloxacin had cavitation on chest radiograph than those assigned to ethambutol. The mean baseline weight was about 4 kg lower in the moxifloxacin group than in the ethambutol group.

59 (80%) of 74 patients in the moxifloxacin group and 45 (63%) of 72 in the ethambutol group had negative sputum cultures at week 8 (difference 17·2%, 95% CI 2·8–31·7; *p*=0·03). Of patients with sputum culture data available at week 8, 59 (92%) of 64 had negative cultures in the moxifloxacin group compared with 45 (74%) of 61 controls (difference 18·4%, 5·6–31·3; *p*=0·006).

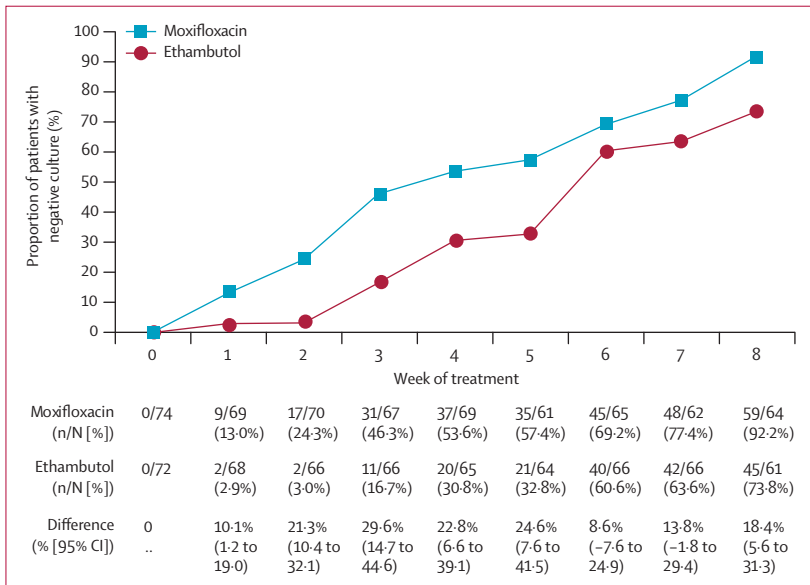


Figure 2: Proportion of patients with negative sputum cultures during 8 weeks of treatment
Data are for patients with 8-week culture data available at each timepoint.

Patients assigned to moxifloxacin became culture negative more rapidly than those assigned to ethambutol. After only 1 week, nine (13%) of 69 patients in the moxifloxacin group had negative sputum cultures compared with two (3%) of 68 in the ethambutol group ($p=0.03$). At every week after enrolment, patients assigned to moxifloxacin had a higher rate of culture conversion than those assigned to ethambutol, and this difference was significant at all timepoints apart from weeks 6 and 7 (figure 2). The median time to consistently negative cultures was 35.0 days (IQR 22.0–55.0) for patients in the experimental group compared with 48.5 days (41.0–56.0) for controls (log rank $p=0.005$).

Univariate and multivariate logistic regression analysis with the modified ITT population or with those patients with sputum culture data available at week 8 (as treated) showed similar results; the modified ITT analysis is

shown in table 2. Treatment with moxifloxacin was associated with an increase in the odds of being culture negative at week 8 in the multivariate analysis ($p=0.0009$). Age was associated with culture conversion in the univariate analysis; patients with positive cultures were a mean of 2.5 years older than those who had conversion to negative culture, but this association was not significant in the multivariate analysis. Weight, sex, and cavitation on chest radiograph were not significantly associated with the likelihood of conversion. Patients who had positive sputum cultures at 8 weeks were more likely than those with negative cultures to have had baseline sputum smears with more than ten bacilli per high-power field.

Adverse events did not differ by treatment group. There were 16 serious adverse events (eight in each group) in 12 patients (table 3); one grade 3 cutaneous reaction in the ethambutol group was judged to be related to study drugs by the treating physicians who were not aware of treatment assignment. All other serious adverse events were judged not related to study drugs. Eight patients died during the study, including one in each group still receiving study phase treatment. No death was attributed to study treatment. Only five patients discontinued treatment because of toxic effects; two patients in the moxifloxacin group stopped because of grade 2 nausea and vomiting and one because of grade 2 paraesthesias and ataxia. Two patients in the ethambutol group stopped because of grade 2 rash and pruritis and one because of grade 3 peripheral neuropathy. No clinically or statistically significant changes in the QTc interval were recorded in patients in either group of the trial.

Seven patients (5%) had recurrence of tuberculosis confirmed by positive culture and compatible clinical symptoms: three patients in the moxifloxacin group (at 11, 16, and 27 months after completing treatment) and four in the ethambutol group (at 6, 7, 22, and 32 months after completion). Six of seven isolates were tested for drug resistance, and all remained susceptible to isoniazid

	Univariate analysis				Multivariate analysis	
	Patients with positive culture (n=42)*	Patients with negative culture (n=104)*	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	35.6 (31.9–39.2)	33.1 (30.8–35.4)	0.98 (0.97–1.00)	0.03	0.99 (0.97–1.00)	0.08
Weight (kg)	57.3 (54.2–60.3)	55.5 (53.7–57.4)	0.99 (0.98–1.01)	0.36	1.00 (0.98–1.02)	0.87
Female	14 (33%)	42 (40%)	1.14 (0.81–1.58)	0.45	1.05 (0.74–1.51)	0.77
Cavitation on radiograph	30 (71%)	70 (67%)	1.19 (0.84–1.69)	0.33	1.07 (0.78–1.49)	0.67
Acid-fast bacilli per high-power field on smear						
<1	15 (36%)	58 (56%)
1–10	12 (29%)	14 (13%)	0.75 (0.46–1.25)	0.27	0.90 (0.55–1.46)	0.67
>10	15 (36%)	32 (31%)	0.48 (0.33–0.69)	<0.0001	0.48 (0.33–0.68)	<0.0001
Moxifloxacin group†	15 (36%)	59 (57%)	1.86 (1.35–2.55)	0.0001	1.75 (1.26–2.44)	0.0009

OR=odds ratio. *Data are mean (95% CI) or number (%). †Moxifloxacin versus ethambutol.

Table 2: Univariate and multivariate logistic regression analysis for culture conversion at week 8 in the modified intention-to-treat population

and rifampicin. DNA fingerprinting data on these isolates to distinguish relapse from re-infection are not available.

Discussion

In this phase II clinical trial, we found that compared with ethambutol, moxifloxacin increased the proportion of sputum cultures that converted to negative in patients with pulmonary tuberculosis. More patients in the moxifloxacin group were culture negative after 1 week of treatment than in the ethambutol group, and this difference continued through the 8 weeks of intensive-phase treatment. Compared with the control group, patients assigned to moxifloxacin had an absolute difference in culture conversion after 8 weeks of just under 20%.

The addition of rifampicin to tuberculosis regimens in the 1970s increased culture conversion rates at 2 months by 15–20% and allowed the duration of treatment to be reduced from 18 months to 6–9 months.^{11,12} In subsequent years, the addition of pyrazinamide to regimens containing isoniazid, rifampicin, and ethambutol or streptomycin increased the 8-week sputum conversion rate by 13% and allowed treatment duration to be shortened from 9 months to 6 months.¹³ Our data suggest that the improvement in sterilisation provided by moxifloxacin could shorten tuberculosis treatment by one or several months, on the basis of reductions in treatment duration achieved by similar improvements in 2-month culture conversion with pyrazinamide.¹³ Additionally, in studies published since this trial was initiated, moxifloxacin has shortened treatment to 3 or 4 months in murine models of tuberculosis.^{14,15}

Two other trials done at the same time as this study have shown potency of moxifloxacin. The Tuberculosis Trials Consortium Study 27 compared moxifloxacin with ethambutol and found that culture conversion occurred more rapidly in patients treated with moxifloxacin; however, the proportions of patients with negative cultures were similar in both trial groups after 8 weeks.¹⁶ Study 27 was a multicentre trial and had a factorial design in which half of all patients were treated with a thrice-weekly regimen and the other half with daily treatment. Additionally, the culture methods used were not standardised in the participating laboratories, and more sensitive liquid culture media were used. We used the well-validated Löwenstein-Jensen culture method in our study, and all cultures were done in one laboratory with a standard protocol. Although a single-centre study is more efficient and ensures standardisation of laboratory methods in a phase II trial, the results from one population might not be generalisable to all populations. However, our study was done in a setting with high tuberculosis burden, and previous studies of tuberculosis treatment in similar settings have proved to be broadly relevant to the treatment of patients worldwide.^{11–13}

	Event	Days from enrolment to event	Primary diagnosis	Grade
Ethambutol				
Patient 1	Hospital admission	68	Cutaneous reaction	3
Patient 2	Death	268	Gunshot wound	5
Patient 3	Death	65	Gunshot wound	5
Patient 4	Death	31	Tuberculosis	5
Patient 5	Hospital admission	171	Polyneuropathy	3
Patient 5	Death	240	Unknown	5
Patient 6	Hospital admission	84	Unilateral leg oedema	2
Patient 6	Death	95	Subdural haemorrhage	5
Moxifloxacin				
Patient 7	Hospital admission	31	Community-acquired pneumonia	3
Patient 7	Hospital admission	377	Pulmonary abscess	2
Patient 8	Death	242	Urinary sepsis	5
Patient 9	Hospital admission	57	Spontaneous abortion	NA
Patient 10	Death	372	Gunshot wound	5
Patient 11	Hospital admission	19	Dysphasia	4
Patient 11	Death	61	Oesophageal neoplasm	5
Patient 12	Grade 4 toxicity	69	Proteinuria	4

NA=not applicable. All adverse events were judged as not related to study drugs, apart from the event in patient 1, which was judged as probably related to study drugs.

Table 3: Serious adverse events

The OFLOTUB study, undertaken at several sites in South Africa, found that patients treated with moxifloxacin or gatifloxacin had higher culture conversion rates on solid media after 8 weeks than patients treated with ethambutol, whereas conversion rates for ofloxacin treatment did not differ from those for ethambutol.¹⁷ Modelled data from quantitative cultures also suggested that moxifloxacin resulted in more rapid culture conversion, although solid media data were not reported for earlier timepoints.

In multivariate analysis, assignment to moxifloxacin was associated with culture conversion. Age was associated with culture conversion in the univariate analysis only. Older age has been associated with poorer treatment responses in several trials of tuberculosis treatment.^{16,18} More patients assigned to moxifloxacin had cavities on chest radiograph at baseline, but this feature was not associated with lower efficacy. By contrast, several studies have reported lower culture conversion rates in patients with cavitory lesions on chest radiograph, although results from another large clinical trial did not support these findings.^{16,18–20} If the presence of cavities is truly associated with slower time to culture conversion, the results of this study might underestimate the potency of moxifloxacin. Notably, baseline sputum-smear grade was significantly associated with culture conversion, and heavy smear positivity (more than ten organisms per high-power field) was equally distributed in the two study groups. Both cavitation on radiograph and sputum-smear positivity are semiquantitative measures that are subject

to observer bias and inter-observer variability. The number of patients with HIV infection, which was found to be associated with poorer outcomes in the Tuberculosis Trials Consortium study,¹⁶ was too small for meaningful analysis in this study.

Moxifloxacin was well tolerated and not associated with increased occurrence of adverse reactions or clinical complications compared with ethambutol, a drug generally considered to be very safe. In particular, we found no change in the QTc interval on serial electrocardiograms taken during the trial (data not shown). QTc prolongation is a reported toxic effect of other fluoroquinolone drugs, but has not been noted with moxifloxacin during short durations of treatment. Because tuberculosis treatment lasts longer than treatment of community-acquired pneumonia (the main clinical use for moxifloxacin), the finding of few adverse events is reassuring and suggests that moxifloxacin could be safely used for longer periods; however, this suggestion needs to be confirmed in additional studies that are large enough to detect small but important rates of toxic effects.

The results of our trial have substantial implications for future trials. First, the improved culture conversion rates found after 8 weeks in the experimental group suggest that moxifloxacin, in combination with other first-line antituberculosis drugs, could shorten the time needed to cure tuberculosis by several months. Because treatment default is directly related to the duration of treatment, a reduction in the duration of tuberculosis therapy would substantially improve outcomes. Additionally, shorter regimens for tuberculosis treatment would reduce workloads for overburdened tuberculosis control programmes, especially in high-incidence countries. Second, the demonstration of moxifloxacin's antimycobacterial activity shows that this agent can be used to treat tuberculosis caused by organisms with resistance to first-line antituberculosis agents, such as isoniazid and rifampicin. In view of its clinical effectiveness and superior in-vitro potency against *M tuberculosis* compared with other fluoroquinolone drugs,⁴ moxifloxacin might become the preferred fluoroquinolone for treatment of multidrug-resistant tuberculosis; gatifloxacin might be as active, but is associated with a risk of dysglycaemia when used to treat community-acquired pneumonia in elderly patients.²¹

This phase II trial was intended to test the hypothesis that moxifloxacin would increase the rate of sputum-culture conversion after 8 weeks, and does not prove the efficacy of use of moxifloxacin to shorten tuberculosis treatment. Nevertheless, our data add to a growing body of evidence that suggests that moxifloxacin could shorten tuberculosis treatment by initially eradicating a greater number of organisms and improving the sterilising activity of combination drug regimens.^{14-16,22-25} Trials in animal models also suggest that replacement

of isoniazid with moxifloxacin shortens tuberculosis treatment more than does replacement of ethambutol,¹⁴ but human studies have not yet supported this finding.²⁶ The results of our study support the undertaking of clinical trials to assess whether shorter courses of moxifloxacin-containing regimens can cure tuberculosis as well as or better than the current 6-month regimen. Such trials are under way and their results are eagerly awaited.

Contributors

WRB, ALK, and REC designed the study. MBC, AE, CL, GRMDS, NPG, MCC, ALK, and REC participated in the implementation of the trial. MBC, AE, CL, GRMDS, and ALK participated in administration and MBC and AE in regulatory support. AE, CL, MR, MAC, and REC participated in data management. CL, NPG, and MCC participated in data collection. AE, MR, MAC, and REC contributed to data analysis. REC wrote the report. All authors saw and approved the final report.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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