Choice between Levofloxacin and Moxifloxacin and Multidrug-Resistant Tuberculosis Treatment Outcomes

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Abstract

Rationale: We previously showed that the choice of levofloxacin or moxifloxacin for the treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-TB) did not affect sputum culture conversion at 3 months of treatment.

Objectives: To compare final treatment outcomes between patients with MDR-TB randomized to levofloxacin or moxifloxacin.

Methods: A total of 151 participants with MDR-TB who were included for the final analysis in our previous trial were followed through the end of treatment. Treatment outcomes were compared between 77 patients in the levofloxacin group and 74 in the moxifloxacin group, based on the 2008 World Health Organization definitions as well as 2013 revised definitions of treatment outcomes. In addition, the time to culture conversion was compared between the two groups.

Measurements and Main Results: Treatment outcomes were not different between the two groups, based on 2008 World Health Organization definitions as well as 2013 definitions. With 2008 definitions, cure was achieved in 54 patients (70.1%) in the levofloxacin group and 54 (73.0%) in the moxifloxacin group ($P = 0.72$). Treatment success rates, including cure and treatment completed, were not different between the two groups (87.0 vs. 81.1%, $P = 0.38$). With 2013 definitions, cure rates (83.1 vs. 78.4%, $P = 0.54$) and treatment success rates (84.4 vs. 79.7%, $P = 0.53$) were also similar between the levofloxacin and moxifloxacin groups. Time to culture conversion was also not different between the two groups (27.0 vs. 45.0 d, $P = 0.11$ on liquid media; 17.0 vs. 42.0 d, $P = 0.14$ on solid media). Patients in the levofloxacin group had more adverse events than those in the moxifloxacin group (79.2 vs. 63.5%, $P = 0.03$), especially musculoskeletal ones (37.7 vs. 14.9%, $P = 0.001$).

Conclusions: The choice of levofloxacin or moxifloxacin made no difference to the final treatment outcome among patients with fluoroquinolone-sensitive MDR-TB.

Clinical trial registered with www.clinicalrials.gov (NCT01055145).

Keywords: multidrug-resistant tuberculosis; fluoroquinolones; moxifloxacin; levofloxacin

The treatment of multidrug-resistant tuberculosis (MDR-TB) remains difficult because of the high cost (1, 2), need for prolonged treatment, and frequent adverse events (3). With such obstacles, the success rate for treating MDR-TB is less than 70% (4–6).

Fluoroquinolones, which inhibit DNA supercoiling and disrupt DNA replication of *Mycobacterium tuberculosis* through interfering with DNA gyrase (7, 8), are pivotal drugs for the treatment of MDR-TB (6). Current guidelines recommend that later-generation fluoroquinolones should be used for all patients with MDR-TB (9, 10). Among these, levofloxacin and moxifloxacin are the two most commonly prescribed to treat patients with MDR-TB (11, 12). However,

the selection of the best fluoroquinolone has been controversial (12). In this setting, we previously performed a multicenter trial to compare the effectiveness of levofloxacin and moxifloxacin for treating MDR-TB and reported that the choice between levofloxacin or moxifloxacin did not affect sputum culture conversion after 3 months of treatment (13).

Because the impact of the choice between levofloxacin and moxifloxacin on final treatment outcomes among patients with MDR-TB is not known yet, we compared final treatment outcomes among patients with MDR-TB who had participated in our previous clinical trial.

Methods

Patients

The current study included participants in our previous prospective, multicenter, randomized, open-label trial that compared the effectiveness of levofloxacin and moxifloxacin among patients with MDR-TB, conducted between February 2010 and July 2012 at 19 institutions in South Korea (13) (ClinicalTrials.gov identifier: NCT01055145). As previously reported, 182 patients with MDR-TB (sensitive to levofloxacin and moxifloxacin), aged between 20 and 75 years, were randomized to receive either levofloxacin (750 mg/d, 90 patients) or moxifloxacin (400 mg/d, 92 patients) with a background drug regimen.

Of 182 patients initially enrolled for the trial, 27 were excluded: 8 did not have MDR-TB, 14 were resistant to levofloxacin or moxifloxacin, and 5 withdrew their consent. Of the remaining 155 patients, 4 were excluded from the analysis: 3 defaulted before negative conversion of sputum, and 1 could not expectorate sputum before negative conversion. These 4 patients were excluded from primary analysis in the previous study because they defaulted or became free of sputum before 3 months of treatment; they were therefore also excluded from the present study. The primary outcome, the proportion of patients who achieved sputum culture conversion after 3 months of treatment, was not different between the levofloxacin (68/77, 88.3%) and moxifloxacin groups (67/74, 90.5%). The main analysis of the current study was based on these 151 patients with MDR-TB.

Table 1. Baseline demographic and clinical characteristics of 151 participants with multidrug-resistant tuberculosis

	Levofloxacin Group (*n* = 77)	Moxifloxacin Group (*n* = 74)	*P* Value
Age, yr	44 (28–58)	42 (31,56)	0.93*
Male	54 (70.1)	48 (64.9)	0.49†
Body mass index, kg/m^2	19.8 (17.85–21.7)	20.7 (19.13–22.65)	0.03*
Presence of bacilli Calmette–Guérin scar	51 (66.2)	53 (71.6)	0.48†
Past history of tuberculosis treatment	38 (49.4)	36 (48.6)	0.49†
Comorbidities			
Diabetes	1 (1.3)	4 (5.4)	0.20†
Malignancy	3 (3.9)	0 (0)	0.25†
Chronic liver diseases	0 (0)	2 (2.7)	0.24
On immunosuppressant	0 (0)	1 (1.4)	0.49†
Radiographic findings			
Presence of cavity	44 (57.1)	42 (56.8)	0.96†
Size, cm	2.5 (1.7–4.3)	2.8 (1.7–4.5)	0.87*
Degree of acid-fast bacilli stating			0.17†
Negative	33 (42.9)	25 (33.8)	
Trace	6 (7.8)	4 (5.4)	
1+	12 (15.6)	11 (14.3)	
2+	11 (14.3)	10 (13.5)	
3+	12 (15.6)	11 (14.3)	
4+	3 (3.9)	13 (17.6)	
No. of resistant antituberculous drugs	4 (3–5)	4 (4–5)	0.09*
Resistance to pyrazinamide	18 (23.4)	29 (39.2)	0.03†
Extensively drug-resistant tuberculosis	0	1 (1.4)‡	—
Duration of follow-up since initiation of treatment, mo	31.5 (27.1–43.1)	33.65 (25.1–46.6)	0.57*

Data presented as n (%) or median (interquartile range).
*P value from Wilcoxon rank-sum test.
†P value from chi-square test or Fisher exact test.
‡*Mycobacterium tuberculosis* isolated from this patient resistant to ofloxacin but sensitive to levofloxacin and moxifloxacin.

Treatment and Follow-Up

After 3 months' participation, all patients were treated according to the World Health

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Organization (WHO) guidelines for MDR-TB treatment (9). The patients visited an outpatient clinic monthly during the intensive phase of treatment and monthly or bimonthly during the continuation phase of treatment. Submission of morning sputum was required on each visit. Sputum samples were cultured in solid mycobacterial culture medium (Ogawa medium) at all institutions as well as in liquid broth medium (MGIT tube; Becton, Dickinson and Co., Sparks, MD) at 12 institutions.

Analysis Design

The analysis population consisted of 151 participants (77 in the levofloxacin group and 74 in the moxifloxacin group, classified based on modified intention-to-treat analysis) who were included for the final analysis in the previous trial. We compared the final treatment outcomes between the two groups. Treatment outcomes were classified based on 2008 WHO definitions (9) as well as the 2013 WHO revised definitions for treatment outcomes (14). In addition, the time to conversion to negative culture on solid media as well as liquid media was compared between two groups. Negative sputum culture conversion was defined as two or more consecutive negative sputum cultures tested at least 4 weeks apart. The time point of the first negative culture was regarded as the time of culture conversion. In addition, the proportions of any adverse drug reactions were also compared.

Final treatment outcomes were also compared based on per-protocol analysis. Because 10 patients stopped the trial drug in the levofloxacin group and 4 stopped in the moxifloxacin group before the completion of treatment, a total of 67 in the levofloxacin group and 70 in the moxifloxacin group were included for per-protocol analysis.

The study protocol was approved by the institutional review boards at all sites.

Statistical Analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics, such as median and interquartile range. Those variables were compared between the levofloxacin and moxifloxacin groups using the chi-square test, Fisher exact test, independent *t* test, or Wilcoxon rank-sum test, as appropriate.

Treatment outcomes and development of adverse drug events were compared between the two groups using the chi-square test or Fisher exact test. We adjusted for body mass index (BMI) and resistance to pyrazinamide by including

Table 2. Treatment duration and use of antituberculous drugs among 151 participants with multidrug-resistant tuberculosis

	Levofloxacin Group (*n* = 77)	Moxifloxacin Group (*n* = 74)	*P* Value
Duration of treatment, mo	19.9 (18.0–23.9)	19.7 (18.0–22.5)	0.34
Duration of fluoroquinolone use, mo	19.6 (17.9–23.8)	19.7 (17.9–22.6)	0.69
No. of drug used	5 (5–6)	5 (5–6)	0.41
Rifabutin	6 (7.8)	6 (8.1)	0.94
Ethambutol	17 (22.1)	19 (25.7)	0.61
Pyrazinamide	64 (83.1)	50 (67.6)	0.03
Injectable agents	70 (90.9)	71 (95.9)	0.33
Streptomycin	29 (37.7)	18 (24.3)	
Kanamycin	41 (53.2)	53 (71.6)	
Amikacin	1 (1.3)	2 (2.7)	
Prothionamide	66 (85.7)	64 (86.5)	0.89
Cycloserine	74 (96.1)	72 (97.3)	1.00
P-aminosalicylic acid	40 (51.9)	43 (58.1)	0.45
Linezolid	2 (2.6)	4 (5.4)	0.44

Data presented as n (%) or median (interquartile range). *P* values are using chi-square test or Fisher exact test. Antituberculous drugs used more than 4 weeks were included and analyzed.

Table 3. Treatment outcomes of 151 participants with multidrug-resistant tuberculosis, using World Health Organization definitions of 2008 and 2013

	Levofloxacin (*n* = 77)	Moxifloxacin (*n* = 74)	Difference, Moxifloxacin − Levofloxacin Percentage Points (95% CI)
Definitions proposed in 2008 by World Health Organization			
Cure	54 (70.1)	54 (73.0)	2.9 (−11.5 to 16.9)
Completion	13 (16.9)	6 (8.1)	−8.8 (−19.6 to 2.1)
Failure	1 (1.3)	4 (5.4)	4.1 (−2.5 to 11.9)
Death	2 (2.6)	0 (0)	−2.6 (−9.0 to 2.7)
Default	4 (5.2)	7 (9.5)	4.3 (−4.6 to 13.6)
Transfer out	3 (3.9)	3 (4.1)	0.2 (−7.3 to 7.8)
Treatment success*	67 (87.0)	60 (81.1)	−5.9 (−17.8 to 5.9)
Failure†	3 (3.9)	4 (5.4)	1.5 (−6.2 to 9.6)
Others‡	7 (9.1)	10 (13.5)	4.4 (−6.0 to 15.1)
Revised definitions on 2013 by World Health Organization			
Cure	64 (83.1)	58 (78.4)	−4.7 (−17.3 to 7.9)
Completion	1 (1.3)	1 (1.4)	0.1 (−5.8 to 6.1)
Failure	4 (5.2)	5 (6.8)	1.6 (−6.8 to 10.3)
Death	2 (2.6)	0 (0)	−2.6 (−9.0 to 2.7)
Lost to follow-up	3 (3.9)	7 (9.5)	5.6 (−2.9 to 14.7)
Not evaluated	3 (3.9)	3 (4.1)	0.2 (−7.3 to 7.8)
Treatment success*	65 (84.4)	59 (79.7)	−4.7 (−17.0 to 7.6)
Failure†	6 (7.8)	5 (6.8)	−1.0 (−10.1 to 8.1)
Others‡	6 (7.8)	10 (13.5)	5.7 (−4.4 to 16.2)

Definition of abbreviation: CI = confidence interval.
Data presented as n (%).
*Treatment success was defined as the sum of "cure" and "completion."
†Failure was defined as the sum of "failure" and "death."
‡Others was defined as the sum of "default" and "transfer out" for 2008 outcomes, and "lost to follow up" and "not evaluated" for 2013 outcomes.

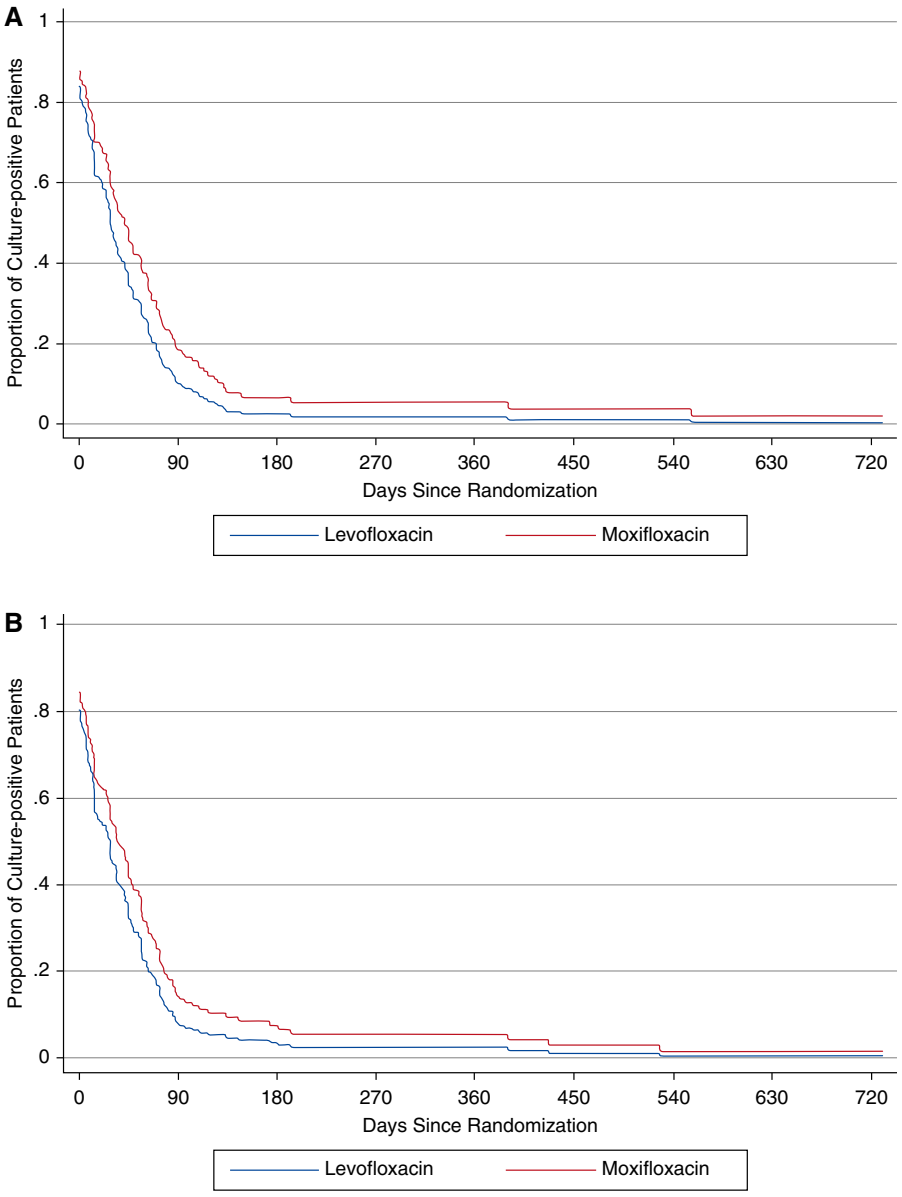

Figure 1. Comparison of time to culture conversion between levofloxacin and moxifloxacin groups, adjusting for body mass index and pyrazinamide use. (*A*) Liquid culture media. (*B*) Solid culture media.

those variables as covariates in the multivariate logistic regression model. To compare the time to culture conversion between the two groups, Cox proportional hazard regression was performed, including BMI and pyrazinamide resistance as covariates. All reported *P* values were two sided and were not adjusted for multiple testing. All analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

The median age of patients in the levofloxacin group was 44 years and that of patients in the moxifloxacin group was 42 years. A total of 54 patients (70.1%) in the levofloxacin group and 48 (64.9%) in the moxifloxacin group were men. BMI was lower among participants in the levofloxacin group than in the moxifloxacin group (median, 19.8 vs. 20.7 kg/m^2; $P = 0.03$). The radiographic findings, degree of acid-fast staining, and number of antituberculous drugs to which patients were resistant were similar between the two groups. Resistance to pyrazinamide was more common among patients in the moxifloxacin group than those in the levofloxacin group (39.2 vs. 23.4%, $P = 0.03$) (Table 1).

Treatment

Treatment duration was not different between participants in the levofloxacin and moxifloxacin groups (median, 19.9 vs. 19.7 mo; $P = 0.34$). Duration of fluoroquinolones (levofloxacin or moxifloxacin) use was also similar (median, 19.6 vs. 19.7 mo; $P = 0.69$).

A median of five drugs was used for both groups of patients. Pyrazinamide was used more frequently among the levofloxacin group than the moxifloxacin group (83.1 vs. 67.6%, $P = 0.03$). Injectable agents were not used in 10 patients (7 in the levofloxacin group and 3 in the moxifloxacin group). Four patients had resistance to all injectable agents, four refused to use injectable drugs, and the remaining two patients experienced adverse reactions (Table 2).

Treatment Outcomes

Treatment outcomes were not different between the two groups, based on 2008 WHO definitions as well as 2013 definitions. With 2008 definitions, cure was achieved in 54 (70.1%) participants in the levofloxacin group and 54 (73.0%) in the moxifloxacin group. The difference (moxifloxacin group minus levofloxacin group) in the cure rate was 2.9 percentage points (95% confidence interval [CI], −11.5 to 16.9; $P = 0.72$) and was not significant. Similarly, treatment success rates, including cure and treatment completed, were not different between the two groups (87.0 vs. 81.1%; difference rate, −5.9%; 95% CI, −17.8 to 5.9). With the 2013 definitions, cure rates (83.1 vs. 78.4%; difference rate, −4.7%; 95% CI, −17.3 to 7.9) as well as treatment success rates (84.4 vs. 79.7%; difference rate, −4.7%; 95% CI, −17.0 to 7.6) were also not different (Table 3).

After adjustment for BMI and pyrazinamide use between the two groups, cure rates ($P = 0.99$ with 2008 WHO definitions and $P = 0.22$ with 2013 revised definitions) and treatment success rates ($P = 0.52$ with 2008 WHO definitions and

$P = 0.19$ with 2013 definitions) were also not different.

Per-protocol analysis showed similar results. Cure rates were similar using 2008 WHO definitions (67.2 vs. 74.3%, $P = 0.36$) as well as 2013 definitions (83.6 vs. 78.6%, $P = 0.46$) between the levofloxacin and moxifloxacin groups.

Time to Culture Conversion

Time to culture conversion on liquid media was 27.0 days (interquartile range [IQR], 7.25–55.5) in the levofloxacin group and 45.0 days (IQR, 10.0–71.5) in the moxifloxacin group. After adjusting for BMI and pyrazinamide use, there was no difference ($P = 0.11$) between the groups. On solid media, time to culture conversion was 17.0 days (IQR, 4.25–52.8) in the levofloxacin group and 42.0 days (IQR, 8.00–67.0) in the moxifloxacin group. After adjusting for BMI and pyrazinamide use, there was no difference ($P = 0.14$) between two groups (Figure 1).

Adverse Drug Events

A total of 61 (79.2%) patients in the levofloxacin group and 47 (63.5%) in the moxifloxacin group reported adverse drug reactions. Musculoskeletal symptoms were more common among patients in the levofloxacin group than those in the moxifloxacin group (37.7 vs. 14.9%, $P = 0.001$), but other adverse reactions were similarly reported (Table 4). No definite cardiac adverse events were reported in either group.

Discussion

Current guidelines recommend that later-generation fluoroquinolones should be used for all patients with MDR-TB (9, 10). In fact, use of later-generation fluoroquinolones is associated with better treatment outcomes among patients with MDR-TB (15, 16).

The results of previous experimental and animal studies have supported moxifloxacin rather than levofloxacin for the treatment of tuberculosis, based on lower minimum inhibitory concentrations (17, 18) and better bactericidal activity (19–21). Based on these observations and others, recent clinical trials aimed at shortening treatment among patients with drug-susceptible pulmonary tuberculosis adopted moxifloxacin instead of levofloxacin (22, 23). However, the results of our previous trial (13) and the current follow-up analysis show that levofloxacin is as effective as moxifloxacin in the treatment of MDR-TB, although adverse events were more frequent in the levofloxacin group.

Our observation of similar effectiveness between levofloxacin and moxifloxacin on final treatment outcomes has another implication for MDR-TB treatment in the era of new antituberculous drugs such as bedaquiline and delamanid. Despite the proven efficacies, both bedaquiline (24) and delamanid (25) have the worrisome adverse event of QT prolongation. Unfortunately, fluoroquinolones, including levofloxacin (26) and moxifloxacin (27), also potentially cause QT prolongation, with moxifloxacin more likely to cause QT prolongation than levofloxacin (28). Based on these reports and the results of our study, levofloxacin rather than moxifloxacin can be recommended based on its safety and effectiveness, when fluoroquinolone use is needed simultaneously with bedaquiline or delamanid in patients with MDR-TB. In fact, levofloxacin has been used in the South African bedaquiline Clinical Access Program (29).

WHO revised its definitions of the treatment outcome for MDR-TB in 2013 (14). In these definitions, cure is defined for a patient who has completed treatment with no evidence of failure and three or more consecutive negative cultures taken at least 30 days apart after the intensive phase. This definition of cure is easier to achieve and more practical than the 2008 definition, which mandates at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment (30). On the contrary, the criteria for failure are expanded; when treatment is terminated or if there is a need for a permanent regimen change of at least two antituberculous drugs because of lack of conversion by the end of the intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions. As a result, in our analysis, the cure rate increased with 2013 definitions (80.8%) from 2008 ones (71.5%), although statistical significance could not be achieved. Likewise, the failure rate increased slightly, from 3.3% with 2008 definitions to 6.0% with 2013 definitions. This increment was accompanied by a decreased portion of patients with treatment completed (12.6% with 2008 definitions to 1.3% with 2013 definitions).

These changes in treatment outcomes contrast from the results of a previous study that showed a decrement in the number patients classified as treatment completed, but a high increment in those classified as treatment failure, using 2013 revised WHO definitions (31). The difference between this study and ours might result from the close monitoring and higher adherence to treatment by patients who participated in our previous trial. In fact, the rate of lost to follow up in

Table 4. Any adverse drug reactions among 151 participants with multidrug-resistant tuberculosis

	Levofloxacin Group ($n = 77$)	Moxifloxacin Group ($n = 74$)	*P* Value
Any adverse events	61 (79.2)	47 (63.5)	0.03
Dermatologic abnormalities	12 (15.6)	7 (9.5)	0.26
Gastrointestinal trouble	30 (39.0)	28 (37.8)	0.89
Hepatotoxicity	14 (18.2)	11 (14.9)	0.58
Hematologic abnormalities	2 (2.6)	3 (4.1)	0.68
Ototoxicity	12 (15.6)	12 (16.2)	0.92
Endocrine abnormalities	6 (7.8)	2 (2.7)	0.28
Peripheral neuropathy	4 (5.2)	1 (1.4)	0.37
Musculoskeletal abnormalities	29 (37.7)	11 (14.9)	0.001
Eye toxicity	4 (5.2)	2 (2.7)	0.68
Psychotic problems	7 (9.1)	4 (5.4)	0.53
Other*	7 (9.1)	9 (12.2)	0.38

Data presented as n (%). *P* values are using chi-square test or Fisher exact test.
*Other includes general weakness, fatigue, sweating, and chills.

the previous study (31) was 14.5%, but it was 6.6% in our analysis.

To interpret the results of this study correctly, several points should be taken into consideration. First of all, the previous trial was designed to compare culture conversion rates at 3 months of treatment, not to compare final treatment outcomes. The calculated number of participants based on 20% difference of culture conversion rates at 3 months might not provide a sufficient power to compare treatment outcomes as well as time to culture conversion between the two groups. Furthermore, our previous trial was stopped prematurely by recommendation of the data and safety monitoring board. Second, as we pointed out in our previous report (13), the results could be different if 1,000 mg/d instead of 750 mg/d of levofloxacin were used in this trial, given that levofloxacin has the best early bactericidal activity at the dose of 1,000 mg/d (32). In fact, the recent treatment guideline by TBNET recommends the use of 1,000 mg/d of levofloxacin (10).

In conclusion, the choice of levofloxacin or moxifloxacin for treatment of patients with MDR-TB made no difference to final treatment outcomes among patients with fluoroquinolones-sensitive MDR-TB. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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