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MAJOR ARTICLE

Impact of Fluoroquinolone Use on Mortality Among a Cohort of Patients With Suspected Drug-Resistant Tuberculosis

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Background. Previous retrospective and in vitro studies suggest that use of later-generation fluoroquinolones may reduce mortality risk and improve treatment outcomes for drug-resistant tuberculosis (TB) patients, including individuals resistant to a fluoroquinolone. Meta-analysis results are mixed and few studies have examined this relationship prospectively.

Methods. As part of a comparative diagnostic study, we conducted a prospective cohort study with 834 *Mycobacterium tuberculosis*–infected patients from selected hospitals and clinics with high prevalence of drug-resistant TB in India, Moldova, and South Africa. We used Cox proportional hazards regression models to assess the association between later-generation fluoroquinolone (moxifloxacin or levofloxacin) use and patient mortality, adjusting for risk factors typically associated with poor treatment outcomes.

Results. After adjusting for phenotypic resistance profile, low body mass index (<18.5 kg/m^2), human immunodeficiency virus status, and study site, participants treated with a later-generation fluoroquinolone had half the risk of mortality compared with participants either not treated with any fluoroquinolone or treated only with an earlier-generation fluoroquinolone (adjusted hazard ratio, 0.46 [95% confidence interval, .26–.80]) during follow-up.

Conclusions. Use of later-generation fluoroquinolones significantly reduced patient mortality risk in our cohort, suggesting that removal of a later-generation fluoroquinolone from a treatment regimen because of demonstrated resistance to an earlier-generation fluoroquinolone might increase mortality risk. Further studies should evaluate the effectiveness of later-generation fluoroquinolones among patients with and without resistance to early-generation fluoroquinolones.

Clinical Trials Registration. NCT02170441

Keywords. drug resistance; tuberculosis; mortality; fluoroquinolones.

Although incidence rates of tuberculosis (TB) are decreasing globally, TB remains the leading cause of infectious disease death worldwide [1]. In 2015, the World Health Organization (WHO) estimated that there were 10.4 million new TB cases and 1.4 million TB-related deaths [2]. Drug-resistant disease accounts for a disproportionate number of these deaths [3, 4]. Mortality rates among drug-susceptible patients are typically <10%, while rates among patients with extensively drug-resistant (XDR) TB (ie, bacillary resistance to isoniazid and rifampicin, any fluoroquinolone, and any second-line injectable [kanamycin, capreomycin, or amikacin]) have been reported to be as high as 75%; in the seminal KwaZulu-Natal XDR-TB outbreak, mortality reached 98% [1, 5–7].

Poor treatment outcomes have been associated with prior treatment for TB, history of smoking, diabetes, human immunodeficiency virus (HIV) infection, low body weight, and sputum smear positivity [4, 8–11]. In addition, among drug-resistant TB patients, increased risk of mortality has been attributed to the limited number of potentially effective drugs for patients with resistant strains of *Mycobacterium tuberculosis* (*Mtb*) [12]. The repurposing of fluoroquinolones typically reserved for treating drug-resistant TB for use in newer shorter-course treatments for drug-susceptible TB adds further complexity to treatment options for drug-resistant TB [13, 14].

In vitro analysis has demonstrated that resistance to early-generation fluoroquinolones (ciprofloxacin or ofloxacin) does not always predict cross-resistance to later-generation fluoroquinolones (levofloxacin, moxifloxacin, or gatifloxacin) [15, 16]. Multiple retrospective studies suggest that use of later-generation fluoroquinolones, even among strains that are resistant to an early-generation fluoroquinolone, improve treatment outcomes and reduce mortality risk [4, 8, 17–19]. Additionally, murine models have demonstrated that later-generation fluoroquinolones can be used to successfully treat fluoroquinolone-resistant strains of *Mtb*, specifically those that harbor mutations associated with low minimum inhibitory concentrations (MICs) to early-generation fluoroquinolones

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[20, 21]. Although the WHO currently recommends treatment of drug-resistant TB with later-generation fluoroquinolones [22, 23], few studies have prospectively examined the association between later-generation fluoroquinolone use and risk of mortality [5, 12, 24].

In this prospective cohort study, we evaluated the impact of later-generation fluoroquinolone vs early-generation or no fluoroquinolone use on mortality risk among patients with diverse drug resistance profiles, taking into account risk factors that have been previously associated with poor TB patient outcomes.

METHODS

Data for this analysis were collected as part of a large multisite prospective cohort study (ClinicalTrials.gov registration number: NCT02170441) conducted by the Global Consortium for Drug-Resistant TB Diagnostics, which was designed to compare multiple rapid diagnostic assays for the detection of drug-resistant TB.

Institutional review board approval for this study was received from the University of California, San Diego and from participating institutions at their respective study sites. Participation did not alter the standard of care for participants.

Detailed descriptions of the study protocols have been published previously [25, 26]. In brief, between 2012 and 2013, patients presenting with suspected drug-resistant TB at participating clinic study sites in India, Moldova, and South Africa were screened, consented, and invited to participate. Inclusion criteria for the study were evidence of active TB disease [1], either with acid-fast bacilli (AFB) smear positive, GeneXpert positive, or a high clinical suspicion of TB, and suspected drug resistance [2], defined as having previously received >1 month of treatment for a prior TB episode, failing TB treatment with positive sputum smear or culture after ≥3 months of a standard TB treatment, having close contact with a known drug-resistant TB case, being diagnosed with multidrug-resistant (MDR) TB (defined as resistance to both isoniazid and rifampicin) within the last 30 days, or being previously diagnosed with MDR-TB and failing TB treatment with positive sputum smear or culture after ≥3 months of a standard MDR-TB treatment regimen.

Specimen Collection and Laboratory Methods

Pooled sputum specimens used for analysis were comprised of sputum collected at enrollment and again on the following morning upon waking. Susceptibility testing was performed on all culture-positive sputum specimens using the reference phenotypic assay, MGIT960 (BD Biosciences, Sparks, Maryland). Susceptibility to isoniazid, rifampicin, moxifloxacin, ofloxacin, kanamycin, capreomycin, and amikacin were assessed using WHO critical concentrations of 0.1, 1.0, 0.25, 2.0, 2.5, 2.5, and 1.0 μg/mL, respectively, according to the manufacturer's instructions. Critical concentrations for fluoroquinolones were based on the 2008 WHO guidelines on drug susceptibility testing (DST) of second-line antituberculosis drugs [27]. In 2012, after the initiation of our study, the StopTB Partnership proposed splitting the critical concentration for moxifloxacin into 2 categories (0.5 and 2.0 μg/mL), but this recommendation has not been adopted by the WHO [28].

Data Collection and Variable Construction

Participants were interviewed upon enrollment and again approximately 52 weeks after enrollment. Demographic data, comorbidity data, and other risk factor data were collected at enrollment. Dichotomous variables including HIV status, smoking history, previous TB treatment, and diabetic status were defined as participants with the risk factor being assessed vs participants without risk factor or unknown risk factor status. Drugs used during the initial phase of treatment for the current TB episode were extracted from the medical records at enrollment and approximately 30 days postenrollment. Cases treated with a later-generation fluoroquinolone were defined as individuals who had a record of treatment with either moxifloxacin or levofloxacin (there were no records of treatment with gatifloxacin). The comparison group consisted of individuals not treated with a later-generation fluoroquinolone, which included those treated with an earlier-generation fluoroquinolone (ofloxacin or sparfloxacin) or no fluoroquinolone. Among those with a record of death, follow-up time was calculated from enrollment date to date of death, if recorded. In instances where the date of death included only the month and year, the date of death was calculated to the 15th of the month. Participants classified as deceased without a recorded date of death were excluded from the proportional hazards regression analysis but were included in the overall mortality statistics. Follow-up time for participants not classified as deceased was calculated from enrollment to last date of contact, either the 30-day medical record review or the 52-week follow-up interview. If no data were collected for an individual beyond enrollment, that individual was excluded from all analyses. Drug resistance profile was categorized as follows: susceptible, monoresistant (resistant to either rifampicin or isoniazid), MDR (resistant to rifampicin and isoniazid), pre–XDR (resistant to either a second-line injectable drug or a fluoroquinolone but not both), or XDR (resistant to rifampicin, isoniazid, a second-line injectable drug, and a fluoroquinolone).

Statistical Analysis

Patient demographics and clinical data were described using median and interquartile range (IQR) for continuous variables and frequency and proportion for categorical variables. Statistical significance was set at .05 for all analyses. Kaplan-Meier curves were used to compare mortality by drug resistance category. Cox proportional hazards models were used to determine hazard ratios (HRs) and 95% confidence intervals

(CIs) for all survival analyses. The association between each risk factor and mortality was adjusted for resistance profile in the bivariate analysis initially. All covariates with a $P < .25$ in the bivariate analysis and covariates frequently associated with TB mortality were included in the preliminary multivariable model. The final multivariable model included variables significant at the $P = .05$ level, HIV, and study site. Proportional hazard assumptions were visually assessed using log-log plots and Schoenfeld residuals. All analyses were conducted in Stata software version 13.1 (StataCorp, College Station, Texas).

RESULTS

Of the total 1128 participants enrolled in the parent study, 214 produced culture-negative specimens, 6 yielded invalid DST results, 8 had no record of drug treatment, and 27 lacked any follow-up data. Of the remaining 873 (77%) participants, 101 had a record of death; however, 39 of those participants had no date of death recorded and were excluded from the Cox proportional hazards analysis, resulting in a study sample of 834 (74%) (Figure 1). Participants were followed for a mean of 190 days (median, 91 [IQR, 31–365] days). Forty-two percent of participants completed their final "52 week" visit (range, 32–72 weeks postenrollment).

Of the 834 participants included in this analysis, 65% were male. The median age of the population was 33, and 75% reported being previously treated for a prior episode of TB. Thirty-six percent of participants reported smoking at baseline, 11% were HIV positive, 5% were diabetic, and 54% had a body mass index (BMI) <18.5 kg/m^2.

Overall, 34% (282) were susceptible to all tested drugs, 6% (52) were monoresistant, 18% (153) were MDR, 34% (290) were pre-XDR, and 7% (57) were XDR (Table 1). A total of 279 participants were ofloxacin resistant; of those, 272 (97%) were cross-resistant to moxifloxacin. Of the 379 study participants who had a record of treatment with a later-generation fluoroquinolone (moxifloxacin or levofloxacin), nearly half (48%) were phenotypically resistant to ofloxacin. No patient had a record of treatment with gatifloxacin.

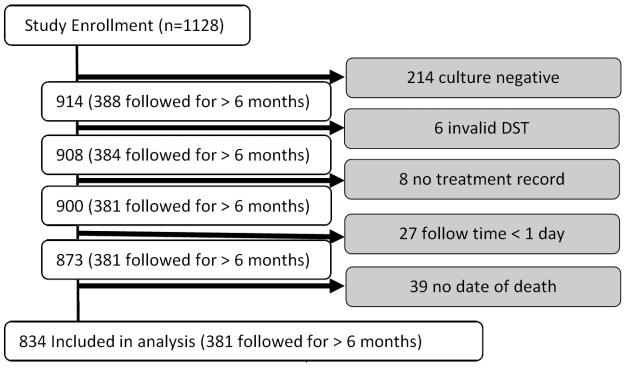

Figure 1. Selection of participants for analysis. Abbreviation: DST, drug susceptibility testing.

If participants without a date of death were included in mortality calculations (n = 873), overall mortality was 11.6% and among participants with XDR-TB mortality was 37.8%. In the study sample used for proportional hazards analysis (N = 834), overall mortality was 7.4%. Mortality rates among participants with susceptible TB, monoresistant TB, and MDR-TB were similar (Figure 2). Participants with XDR-TB had a significantly higher mortality rate than participants with MDR-TB (19.3% vs 6.5%, $P = .02$).

The preliminary main effects model included variables associated with mortality or poor outcomes in previous studies (Table 2). All variables that were not significant in the preliminary model (history of smoking, sputum smear positive, previous treatment, diabetes, age, and sex) were excluded in the final model with the exception of HIV status and study site. Removing these variables together did not significantly reduce the model fit. In the final model, the risk of mortality increased as level of resistance increased, culminating in XDR-TB participants having 9 times greater risk of mortality compared to drug-susceptible participants (adjusted HR, 9.01 [95% CI, 3.11–26.1]) after adjusting for low BMI, HIV status, treatment with later-generation fluoroquinolones, and study site.

Treatment with later-generation fluoroquinolones was associated with >50% reduced risk of mortality (adjusted HR, 0.46 [95% CI, .26–.80]) compared to treatment with an earlier-generation fluoroquinolone or no treatment with any fluoroquinolone regardless of drug resistance profile, HIV status, and study site. Participants with a BMI of <18.5 kg/m^2 had twice the risk of mortality compared to participants with a BMI of ≥18.5 kg/m^2 (adjusted HR, 1.96 [95% CI, 1.15–3.35]) after adjusting for drug resistance profile, HIV status, study site, and treatment with a later-generation fluoroquinolone.

Among XDR-TB participants only (n = 57), use of later-generation fluoroquinolones was not significantly associated with a reduced risk of mortality after controlling for study site, low BMI, and HIV status. Among non-XDR patients however, use of later-generation fluoroquinolones was significantly associated with a reduced risk of mortality (adjusted HR, 0.54 [95% CI, .29–.98]) after adjusting for study site, low BMI, and HIV status. Among fluoroquinolone (ofloxacin and/or moxifloxacin)–resistant participants only, the use of moxifloxacin did not reduce mortality risk (adjusted HR, 1.62 [95% CI, .77–3.40]) after adjusting for study site, low BMI, and HIV status. In addition, the association between the use of levofloxacin and reduced mortality risk was not significant (adjusted HR, 0.49 [95% CI, .22–1.07]) after adjusting for study site, low BMI, and HIV status.

DISCUSSION

This prospective study assessed the impact of later-generation fluoroquinolone use on mortality among a cohort of participants

Table 1. Clinical Characteristics at Baseline and Bivariate Hazard Ratios Adjusted for Resistance Category

Variable	Total (N = 834)	Survived (n = 772)	Died (n = 62)	Adjusted HR (N = 834)	*P* Value	(95% CI)
Resistance category						
Susceptible (reference)	282 (34)	272 (35)	10 (16)	…	…	…
Monoresistance to RIF/INH	52 (6)	49 (6)	3 (5)	…	…	…
MDR	153 (18)	143 (19)	10 (16)	…	…	…
Second-line resistance	290 (34)	262 (34)	28 (45)	…	…	…
XDR	57 (7)	46 (6)	11 (18)	…	…	…
Site						
India (reference)	445 (53)	409 (53)	36 (58)	1.00	…	…
Moldova	225 (27)	208 (27)	17 (27)	1.06	.84	(.59–1.92)
South Africa	164 (20)	155 (20)	9 (15)	2.32	.08	(.90–5.99)
HIV positive (vs negative or unknown)	91 (11)	84 (11)	7 (11)	**3.11**	**.01**	(**1.31–7.37**)
Smear category						
Negative (reference)	134 (16)	128 (17)	6 (10)	1.00	…	…
Rare	70 (8)	64 (8)	6 (10)	2.22	.17	(.71–6.96)
Few	164 (20)	158 (20)	6 (10)	0.89	.85	(.29–2.79)
Many	169 (20)	150 (19)	19 (31)	2.42	.06	(.96–6.11)
Too numerous to count	297 (36)	272 (35)	25 (40)	1.62	.30	(.65–4.01)
Sputum smear positive	700 (84)	644 (83)	56 (90)	1.73	.21	(.74–4.05)
History of smoking (vs no history or unknown)	302 (36)	278 (36)	24 (39)	1.43	.19	(.84–2.46)
Previous treatment	624 (75)	582 (75)	47 (75)	1.05	.88	(.58–1.88)
Low BMI (<18.5 kg/m^2)	448 (54)	406 (53)	42 (68)	**1.96**	**.01**	(**1.15–3.35**)
Diabetes	44 (5)	40 (5)	4 (6)	0.95	.92	(.34–2.62)
Male sex	542 (65)	500 (65)	42 (68)	1.44	.19	(.84–2.47)
Use of a later-generation FQ	379 (45)	352 (46)	27 (44)	**0.48**	**.01**	(**.28–.83**)
Age continuous, median (Q1, Q3)	33 (24, 45)	33 (24, 46)	36 (23, 44)	1.01	.43	(.99–1.02)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CI, confidence interval; FQ, fluoroquinolone; HIV, human immunodeficiency virus; HR, hazard ratio; INH, isoniazid; MDR, multidrug resistant; RIF, rifampin; XDR, extensively drug resistant.

Values in bold indicate significant differences at the $P > .05$ level.

with diverse drug resistance profiles. In our study population, participants with a record of later-generation fluoroquinolone use had half the risk of mortality compared with participants who had a record of earlier-generation fluoroquinolone use or no record of fluoroquinolone use after adjusting for drug resistance profile, HIV status, BMI, and study site.

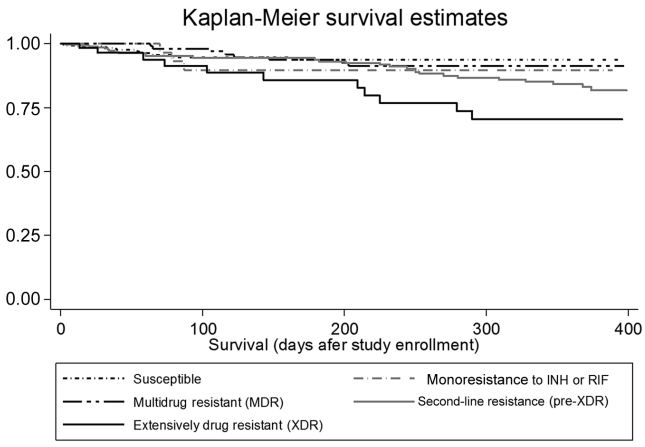

Figure 2. Kaplan-Meier survival analysis estimates of survival stratified by drug resistance category (N = 834). Abbreviations: INH, isoniazid; MDR, multidrug resistant; RIF, rifampin; XDR, extensively drug resistant.

A subanalysis of patients harboring phenotypic early-generation fluoroquinolone resistance revealed that the use of later-generation fluoroquinolones appeared to be protective, although the association was not statistically significant. This may be due to the nearly complete (97%) cross-resistance observed between early- and later-generation fluoroquinolones in our study population. Results may have been more conclusive if there had been less cross-resistance, as demonstrated previously by Jo et al [29].

Our findings confirm what previous retrospective studies have identified: a positive association between later-generation fluoroquinolone use and treatment success [18, 19]. Comparison to results of recent meta-analyses are mixed. Both Jacobson et al and Isaakidis et al demonstrated that the use of fluoroquinolones among XDR-TB and HIV/MDR-TB was associated with improved treatment outcomes and treatment success [8, 17]. In contrast, a large meta-analysis conducted by Falzon et al using patient level resistance and treatment data from a diverse cohort with multiple resistance profiles failed to show any association between treatment with fluoroquinolones and successful outcomes among fluoroquinolone-resistant participants [30]. Lack of consistent results may be due to the infrequent use of later-generation fluoroquinolones in treatment regimens,

Table 2. Preliminary Main Effects Multivariable Regression Model and Final Model

	Preliminary Model		Final Model	
Factor	Hazard Ratio	(95% CI)	Hazard Ratio	(95% CI)
Later-generation FQs	**0.45**	**(.26–.80)**	**0.46**	**(.26–.80)**
Resistance category				
Susceptible (reference)	1.00	…	1.00	…
Monoresistance to RIF or INH	1.57	(.43–5.78)	1.76	(.48–6.45)
MDR	**3.27**	**(1.15–9.30)**	**3.23**	**(1.11–9.41)**
Pre-XDR	**5.42**	**(2.12–13.9)**	**5.31**	**(2.02–12.1)**
XDR	**10.2**	**(3.52–29.8)**	**9.01**	**(3.11–26.1)**
Study site				
India (reference)	1.00	…	1.00	…
Moldova	0.89	(.31–2.51)	1.48	(.79–2.77)
South Africa	1.57	(.45–5.53)	1.68	(.52–5.47)
Smear status	1.91	(.79–4.64)	…	…
BMI <18.5 kg/m^2	**2.21**	**(1.25–3.91)**	**2.10**	**(1.20–3.65)**
HIV positive (vs negative or unknown)	2.41	(.85–6.79)	2.46	(.83–7.32)
Smoker	1.23	(.58–2.59)	…	…
Previous TB treatment	0.66	(.26–1.67)	…	…
Diabetes	0.87	(.28–2.70)	…	…
Age	1.01	(.99–1.03)	…	…
Male (vs female)	1.55	(.84–2.85)	…	…

Abbreviations: BMI, body mass index; CI, confidence interval; FQ, fluoroquinolone; HIV, human immunodeficiency virus; INH, isoniazid; MDR, multidrug resistant; RIF, rifampin; TB, tuberculosis; XDR, extensively drug resistant.

Values in bold indicate significant differences at the $P > .05$ level.

failure to differentiate between early- and later-generation fluoroquinolone use during analysis, or reliance on the results of a single, early-generation drug susceptibility test (ie, ofloxacin) for both early- and later-generation fluoroquinolone resistance determination.

Few prospective studies have assessed fluoroquinolone use, specifically, later-generation fluoroquinolone use among drug-resistant patients, and to our knowledge, our study is one of the first prospective studies to identify an association between later-generation fluoroquinolone use and a reduction in mortality risk. The Preserving Effective Tuberculosis Treatment Study (PETTS), a multicountry prospective cohort study, compared the total number of effective drugs and their association with culture conversion at specified time points, and identified an association between use of any fluoroquinolone and an increased treatment success [12, 31]. In contrast to the current study, the PETTS did not account for typical risk factors associated with poor outcomes or level of drug resistance in their models, and associations were all reported as pairwise comparisons. In a single-country prospective study, Pietersen et al also did not find an association between fluoroquinolone use (either ofloxacin or moxifloxacin) and mortality; however, the study sample included only XDR-TB patients in contrast to the current study which included suspect drug-resistant TB patients with varying levels of drug resistance [5].

The complexity of assessing effectiveness of an entire class of fluoroquinolones in the context of multiple drug regimens cannot be underestimated. Clinical studies designed to assess susceptibility to and effectiveness of individual fluoroquinolones in the context of a multiple drug regimens, including studies investigating the complex relationships between treatment regimens, clinical data, and molecular test results (eg, sequencing data), are needed to confirm these findings.

Resistance Profiles

Notably, and as demonstrated previously, drug resistance profile appeared to be the most significant predictor of mortality; patients with drug-susceptible TB had the lowest risk of mortality and patients with resistance to an increasing number of drugs had an increased risk of mortality, with XDR-TB patients having the highest risk of mortality even after adjusting for risk factors typically associated with mortality [10, 30, 32].

Just over 40% of our study cohort completed their final 52-week follow-up visit. As the Kaplan-Meier plot demonstrates, crude mortality rates in our cohort were not significantly different between participants with drug-susceptible, monoresistant, and MDR-TB, with mortality risk occurring primarily during the first 3 months after enrollment, which is consistent with previous studies [33]. In contrast to participants with MDR-TB, participants with XDR-TB had mortality risks that did not appear to level off after the first 3 months, but instead steadily increased for the duration of the study. This continuing risk of mortality even up to 6 months after diagnosis has been demonstrated previously in patients coinfected with HIV [18].

Although HIV has historically been associated with increased mortality among TB patients, in our study HIV was not significantly associated with an increased risk of mortality in the final model after adjusting for low BMI, resistance profile, and study site [8]. Similar findings have been demonstrated previously, and may be due to increased HIV treatment coverage. Diabetes, history of smoking, AFB smear positivity, and previous treatment were also not significantly associated with mortality in our study.

Patients with low BMI (<18.5 kg/m^2) had twice the risk of mortality compared to patients with normal or higher BMI (≥18.5 kg/m^2) regardless of TB drug resistance profile and comorbidities. Previous studies have suggested that BMI may be a marker of disease severity or lack of treatment response or a proxy for underlying socioeconomic risk factors [34, 35]. Our study confirms that low BMI is associated with poor TB treatment outcomes and underscores the need to aggressively

treat patients presenting with low BMI and also to focus efforts on increasing BMI during treatment [4, 36–38].

Our study was subject to several limitations. Follow-up data collection was limited to 2 time points, reducing our ability to quantify duration of treatment. However, the positive association between reduced mortality risk and patients who had a record of treatment with later-generation fluoroquinolones, regardless of treatment duration, increases our confidence in these findings. Our inability to quantify treatment duration also eliminated possible analysis based on regimen composition or change patterns due to drug toxicity. Additionally, 39 participants classified as deceased did not have a date of death recorded and, therefore, were excluded from the proportional hazards regression analysis, potentially biasing our results toward the null. Although we assessed the impact of both levofloxacin and moxifloxacin (later-generation fluoroquinolones) on clinical outcomes, only moxifloxacin was used to determine phenotypic drug susceptibility. Also, data on fluoroquinolone use during a prior TB episode were not collected; as a result, impact of previous fluoroquinolone exposure could not be assessed. Finally, the proportion of our study cohort with XDR-TB was relatively small, reducing our ability to assess risk factors associated with mortality individually for patients with different drug resistance profiles.

In conclusion, treatment of suspected drug-resistant TB with a later-generation fluoroquinolone appeared to reduce patient mortality risk even after adjusting for resistance profile and risk factors typically associated with poor outcomes. Further studies designed to assess the use of later-generation fluoroquinolones on mortality are needed. In addition, individuals with higher levels of resistance or presenting with low BMI appear to be at significantly increased risk of mortality and should be monitored accordingly.

Notes

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