Infection and Drug Resistance

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ORIGINAL RESEARCH

Explorative Analysis of Treatment Outcomes of Levofloxacin- and Moxifloxacin-Based Regimens and Outcome Predictors in Ethiopian MDR-TB Patients: A Prospective Observational Cohort Study

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Purpose/Background: Although Ethiopia is among the thirty high multi-drug resistant tuberculosis (MDR-TB) burden countries in the world, comparative therapeutic efficacy of moxifloxacin and levofloxacin has not been explored, particularly in MDR-TB patients. We therefore aimed to prospectively compare clinical outcomes and determine potential predictors of the outcomes among patients on moxifloxacin or levofloxacin-based MDR-TB drug regimens.

Methods: We analyzed clinical parameters and laboratory data of eighty MDR-TB patients on moxifloxacin- or levofloxacin-based regimens. The clinical outcomes were compared using the Kaplan–Meier survival functions and the outcome definitions of the 2013 World Health Organization. Monthly sputum culture conversions and a molecular line probe assay results were also assessed. Observed outcomes and patient-related variables between the two groups were compared using chi-square, Wilcoxon Rank and Fisher exact tests. We also determined the potential predictors influencing treatment outcomes of moxifloxacin and levofloxacin using Cox proportional hazard model.

Results: The levofloxacin-based treatment group had a lower failure rate and adverse drug events as well as better treatment success than the moxifloxacin-based group. Overall treatment success was 65%. Disaggregating the data revealed that 53.8% were cured, 11.2% completed treatment, 10.0% died, 11.2% failed, and 13.8% were lost-to-follow-up. The line probe assay result showed that 11.3% of the clinical isolates were resistant to fluoroquinolones and 3.8% were resistant to both fluoroquinolones and injectable anti-TB agents. Treatment regimen type, culture conversion rate, alcohol use, cavity lesion, serum levels of creatinine and alanine aminotransferase were independent predictors of treatment outcome.

Conclusion: The levofloxacin-based regimen group has a better overall treatment success than the moxifloxacin-based group among MDR-TB patients. Clinical parameters and substance use history of the patients influenced treatment outcomes. We recommend further broader clinical studies to substantiate our findings as an input to review MDR-TB treatment guidelines.

Keywords: MDR-TB, moxifloxacin, levofloxacin, line probe assay, treatment outcome, sputum culture conversion, Ethiopia

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Introduction

Drug resistance is a major challenge for tuberculosis (TB) treatment and eradication. It has complicated TB control and undermined the objectives of the World Health Organization (WHO)'s End TB Strategy.[1] The number of new cases of multidrug resistant tuberculosis (MDR-TB), defined as TB resistant at least to

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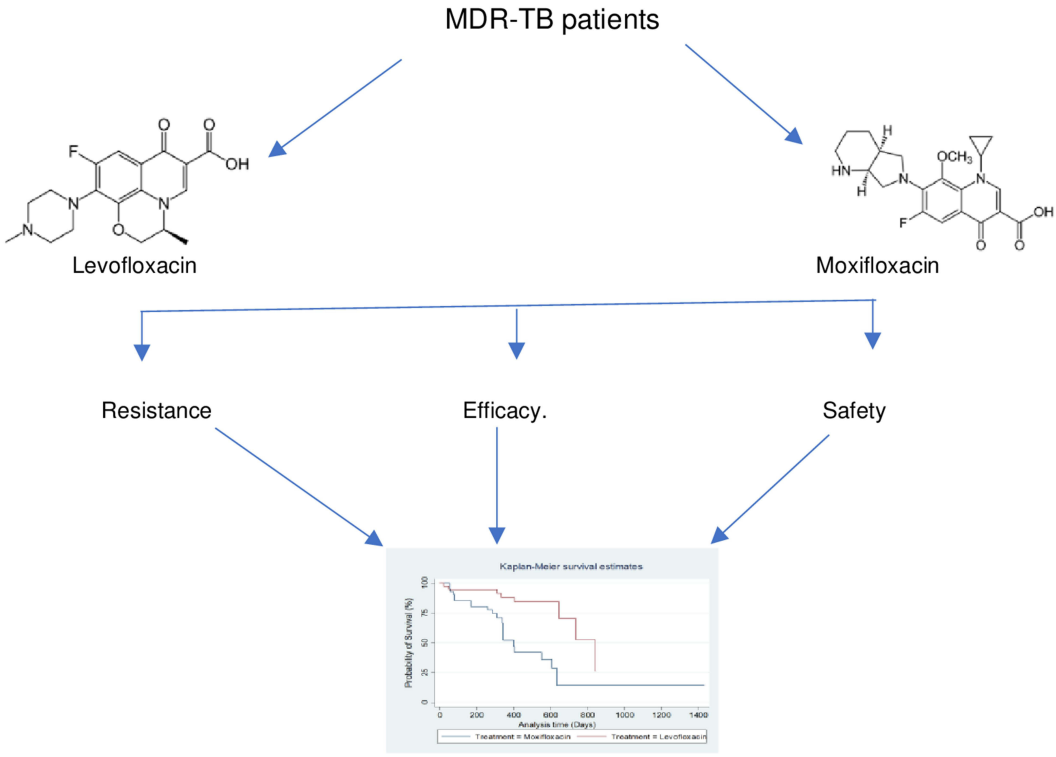
Graphical Abstract



In a prospective observational study, we analyzed clinical parameters and laboratory data of MDR-TB patients and compared the clinical efficacy of moxifloxacin and levofloxacin. Our data showed that levofloxacin-based regimen was associated with greater treatment success and low adverse drug reaction events than moxifloxacin-based regimen.

isoniazid and rifampin, is increasing worldwide.[2] In 2018, there were an estimated 484,000 MDR/RR-TB incident cases worldwide, with an estimated 3.4% of new cases and 18% of previously treated cases.[3] More recently, nearly half a million RR-TB cases occurred in 2019 across the globe.[4]

Treatment outcomes for MDR-TB is poor and its treatment also remains difficult because of high cost,[5,6] long-term treatment, and frequent adverse events (ADRs).[7] The proportion of MDR-TB patients in a 2016 global cohort who successfully completed treatment was only 56%. Only 39% of extensively drug-resistant (XDR)-TB patients successfully completed treatment in 2016.[8] This suggests that the current MDR-TB regimens are suboptimal.

Moxifloxacin and Levofloxacin are the two most potent fluoroquinolones (FQs) currently in use as a core MDR-TB treatment regimens.[9,10] In terms of in-vitro drug susceptibility, moxifloxacin is more potent (critical concentration 0.25 mcg/L) than levofloxacin (critical concentration, 0.5 mcg/mL).[11] Although these drugs have good safety record in long-term administration, their potential to prolong the QT interval (which is more pronounced with moxifloxacin) has raised a concern.[12,13] The injudicious and suboptimal use as well as poor quality of FQs and the accompanying drugs in MDR-TB can also exacerbate the resistance problem.[14–16] Emergence of extensively drug-resistant (XDR) TB has particularly posed a more "complicated" scenario of drug resistance to FQ resistance and MDR-TB and is generally linked with a treatment rate of ≤50%.[17–19]

Inter-individual variabilities among patients and type of drug regimen selected for the treatment of MDR-TB patients can determine the overall treatment success. Important sources of the variabilities may include critical illness, comorbidity, sociodemographic factors, nutritional status, and early bactericidal activity.[20–26] However, in many countries, laboratories are unable to assess drug

resistance and clinical predictors of MDR-TB treatment outcomes, which could have helped tailoring medications use to individual patient needs.[27]

WHO recommends two standardized regimens for treatment of MDR-TB: a short (9–12 months) and a long (18–20 months) regimen. According to the 2016 WHO guideline, the shorter MDR-TB regimen mainly comprised of moxifloxacin, injectable drugs, protionamide, pyrazinamide, clofazimine, and high-dose isoniazid in the intensive phase followed by moxifloxacin, clofazimine, pyrazinamide and ethambutol in the continuation phase. WHO issued a conditional recommendation for the use of this regimen (a no response to extrapulmonary TB, pregnancy, intolerance or risk of potential toxicity, a previous second-line TB medication exposure, or drug resistance to pyrazinamide, ethambutol, kanamycin, moxifloxacin, ethionamide, or clofazimine).[2,28,29] In 2018, the WHO endorsed a fully oral standardized 20-month regimen for MDR-TB, comprising mainly of levofloxacin, bedaquiline, linezolid, clofazimine, cycloserine and others. This later guideline substituted the earlier regimen and excluded the injectable drugs from the regimen. The drugs were selected based on preference of oral above injectable agents, results of drug susceptibility testing (DST), reliability of existing DST methods, population drug resistance levels, history of previous use of medicine in individual patients, drug tolerability and potential drug–drug interactions.[30] However, there are conflicting evidences about preference of either of these regimens in terms of overall treatment success, adverse drug events and the risk of emergence of drug resistance.[31,32]

Recently, the STREAM (Evaluation of a Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis) Stage I trial compared the shorter vs the longer regimen and reported an overall increased occurrence of ADRs and QT interval prolongation in the shorter than the longer regimen.[33] Two randomized clinical trials conducted in the Korean patient-population to compare culture conversion rates and clinical outcomes between levofloxacin-and moxifloxacin-based regimens reported no apparent difference in the therapeutic advantage between the two groups, although a higher occurrence of ADRs was noted in levofloxacin-than moxifloxacin-based regimen.[34,35]

Ethiopia had been among the 30 high-TB and MDR-TB prevalent countries,[4] although it is now out of the high burden countries list due to the recent low TB or MDR-TB incident rates.[36] National data on MDR-TB treatment outcome in Ethiopia are lacking and those available indicate variable treatment success, ranging from 63% to 78.8%. A recent systematic review and meta-analysis revealed that around 18% of MDR/RR-TB patients treated in Ethiopia had a poor treatment outcome.[37–40] Adopting the WHO guidelines, MDR-TB patients in Ethiopia receive either moxifloxacin-or levofloxacin-based MDR-TB regimen. However, studies comparing their treatment advantages and outcome predictors in Ethiopian patients are rare. We therefore aimed to explore the treatment outcomes prospectively between the two regimens using the 2013 WHO definitions[41] and the outcome predicting factors.

Methods

Study Setting and Design

A prospective observational cohort study was conducted in adult MDR-TB patients enrolled at Butajira, Yirgalem, Arbaminch and Nigist Eleni Mohammed Memorial teaching hospitals between November 2017 and May 2020. These hospitals are among the first four hospitals identified by the Ministry of Health of Ethiopia as treatment initiative centers (TICs) for MDR-TB treatment in Southern Ethiopia.

Inclusion and Exclusion Criteria

All adult patients age 18 years and above (new MDR-TB cases and those with prior treatment history with first-line TB drugs) diagnosed either bacteriologically or clinically for MDR-TB and put on either moxifloxacin- or levofloxacin-based treatment regimen since November 2017, and who can provide a written informed consent were included. Patients with no final treatment outcome (transferred out or still on treatment or treatment outcome missed from data sources), critical illness, prior treatment history with FQs, and extra pulmonary TB cases were excluded.

Accordingly, a total 80 GeneXpert confirmed MDR-TB patients and intended for a therapeutic drug monitoring (TDM) were purposively included in this study. Of these patients, 43 were on moxifloxacin- and 37 were on levofloxacin-based MDR-TB regimen. The patients were ambulatory and had been visiting the hospitals every month. They were followed up prospectively over the range of four years (from 2017 to 2020).

Data Collection and Management

Demographic (age and sex), clinical (radiographic, body-mass index, TB treatment experience, comorbidity, and treatment-regimen), and laboratory (AFB and sputum culture) data were collected using a data abstraction form (Supp. 1) by trained TB nurses and public health specialists (Health officers) in each hospital. The data abstraction form was pilot tested prior to the actual data collection and appropriate modifications were made accordingly. The data collectors were trained and oriented about the study design and its objective and patients' follow-up. Most adverse drug reactions (ADRs) experienced were written in patient charts and taken as stated. Hepatotoxicity and nephrotoxicity were inferred from at least three measurements of liver function test (LFT) and Serum creatinine (Scr.) measurements, respectively, during the treatment period. All ADRs were graded as per the DAIDS criteria and summarized as mild (Grade 1), moderate (Grade 2) and severe (Grade 3 and above).[42] At least five consecutive sputum culture results were also recorded for each patient from the routine monthly culture tests since the beginning of the MDR-TB regimen. A molecular line probe assay (LPA) for second-line TB drugs known as Genotype® MTBDRsl VER 2.0 (Hain Life science, Germany)[43] was also conducted on clinical isolates at the end of the intensive phase for the second-line TB drugs. Collected data were checked for accuracy and consistency.

Operational Definitions

In this study, first sputum culture conversion (FSCC) was defined as "the time in days from the date of initiating MDR-TB treatment to the collection date of the first two consecutive negative sputum culture".[44] Treatment outcomes were classified as per the WHO 2013 guideline and compared between the moxifloxacin and levofloxacin treatment groups at the end of treatment follow-up. Cure and treatment completions were defined as treatment success, whereas death, failure/pre-XDR-TB and lost-to-follow-up (LTFU) cases as unsuccessful/unfavorable outcomes. Treatment completion, as recommended by the guidelines, with no evidence of treatment failure and had at least three to five consecutive negative sputum cultures taken at least 30 days apart during the last months of treatment were defined as "Cured", whereas if patients completed the recommended treatment period with improved clinical symptoms but the required number of culture results could not be obtained/unknown, it was defined as "Treatment completed". Treatment outcome of "Death" was assigned to patients who died during the treatment course for any reason. Patients with two or more positive culture results from the recorded five cultures during the final months of treatment or if the treatment was terminated early because of poor clinical or radiological response or adverse event was declared as "Treatment Failure". Patients whose treatment was interrupted for two or more consecutive months for any reason other than medically approved was declared as LTFU.[41]

Data Analysis

Data were entered into excel sheet and then cleaned, coded and entered into the Statistical Software for Social Science (SPSS) version 25.0. Data analysis was carried out using STATA V.14 (StataCorp, College Station, TX, USA). Kaplan–Meier survival functions and FSCC within 90 days were used to evaluate a successful treatment outcome. Log Rank test was used to explore statistically significant difference between moxifloxacin and levofloxacin treatment groups. A Cox proportional hazards model was used to estimate the association between variables and treatment outcome. Variables associated with univariate analysis ($p<0.20$) were considered for backward multivariable analysis. Association between various potential predictors and treatment outcomes was expressed as adjusted hazard ratio (AHR) and 95% confidence intervals (CIs). Observed outcomes between the two groups were also compared in terms of various factors using chi-square, Wilcoxon Rank and Fisher exact tests. For categorical variables, either chi-square (if the number of observations in both groups is more than 5) or Fisher exact test (if the number observations in both or one of the groups are ≤ 5) was used. Wilcoxon rank-sum test was used for continuous variables. Statistical significance was set at $p < 0.05$.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from both the Institutional Review Board of College of Health Sciences, Addis Ababa University (Protocol No. 078/17/Pharma) and the National Ethical Review Committee of the Ministry of Science and Higher Education (Reference No. MoSHE//RD/141/2318/19). Written consent was obtained following provision of information to the participants about the objectives, benefits and risks of the study. Confidentiality and anonymity

were assured by restricting data access and removing identifiers.

Results

Patients' Characteristics

Baseline socio-demographic, laboratory and clinical characteristics of the study participants are presented in Table 1. There was a preponderance of the male gender (53.0%). The patients in both moxifloxacin and levofloxacin groups appeared to be matched for almost all socio-demographic and clinical characteristics, as there were no apparent differences observed using a variety of statistical tests. The new cases of MDR-TB constituted 25% of the total MDR-TB subjects, while the rest were with prior TB treatment history. More than half of the patients (47/80) were moderately or seriously malnourished. The

Table 1 Baseline Socio-Demographic, Laboratory and Clinical Characteristics of the Study Participants in Both Moxifloxacin and Levofloxacin Groups

Patient Characteristics	Moxifloxacin Group (n=43)	Levofloxacin Group (n=37)	P-value
Age (years)	25 (19–37)	26 (20–30)	0.34*
Sex Male	22 (51.2)	22 (59.5)	0.46†
Female	21 (48.8)	15 (40.5)	0.46†
Body mass index (kg/m^2)	17.3 (16.0–19.2)	16.7 (15.6–18.4)	0.40*
Past history of TB treatment	35 (81.4)	25 (67.6)	0.15†
Nutritional status			0.21†
Normal	15 (34.9)	18 (48.6)	
Moderately malnourished	28 (65.1)	19 (51.4)	
Smoking			0.75†
No	37 (86.1)	33 (89.2)	
Yes	6 (13.9)	4 (10.8)	
Khat Chewer			0.29†
No	40 (93.0)	31 (83.8)	
Yes	3 (7.0)	6 (16.2)	
Alcohol consumption			0.39†
No	33 (76.7)	32 (86.5)	
Yes	10 (23.3)	5 (13.5)	
Comorbidities			
Peritonitis	1 (2.3)	1 (2.7)	0.91†
HIV	5 (13.5)	6 (16.2)	0.55†
Typhoid	0 (0.0)	1 (2.7)	0.46†
Hypocalcemic tetany	0 (0.0)	1 (2.7)	0.46†
Dyspepsia	1 (2.3)	0 (0.0)	0.54†
DVT	0 (0.0)	3 (8.1)	0.10†
CHF	1 (2.3)	4 (10.8)	0.18†

(*Continued*)

Table 1 (Continued).

Patient Characteristics	Moxifloxacin Group (n=43)	Levofloxacin Group (n=37)	P-value
PUD and abdominal infection	2 (4.7)	1 (2.7)	0.56†
Pneumonia	2 (4.7)	2 (5.4)	0.63†
Hypertension	0 (0.0)	1 (2.7)	0.46†
Radiographic findings (chest X-ray)			0.11†
No cavitary lesion	28 (65.1)	30 (81.1)	
Cavitary lesion	15 (34.9)	7 (18.9)	
Degree of acid fast bacilli (AFB)			0.07†
Scanty	2 (4.7)	7 (18.9)	
1+	14 (4.7)	5 (13.5)	
2+	20 (46.5)	20 (54.1)	
3+	7 (16.3)	5 (13.5)	
Culture test			0.13†
Positive for MTBC (1+)	27 (62.8)	29 (78.4)	
Positive for MTBC (2+)	16 (37.2)	8 (21.6)	
Biochemistry & Hematological characteristics ‡			
Alanine aminotransferase (AST)			0.17*
Mean ± SD	33.4±13.6	32.0±17.9	
Median (IQR)	33.0 (22–42)	29.0 (20–36.5)	
Alanine transaminase (ALT)			0.27*
Mean ± SD	36.5±25.2	27.8±15.8	
Median (IQR)	29.0 (18–48)	22.0 (14–45)	
Hemoglobin (HG)			0.60*
Mean ± SD	14.7±5.8		
Median (IQR)	13.8 (12.4–14.7)		
Serum albumin (ALB)			0.32*
Mean ± SD	3.3±0.4		
Median (IQR)	3.3 (3.1–3.5)		

Notes: Data presented as n (%) or median (IQR); *P value from Wilcoxon rank-sum test. †P value from chi-square test or Fisher exact test, ‡ these are the average measurement at three different occasions.

Abbreviations: DVT, deep vein thrombosis; CHF, congestive heart failure; HIV, human immunodeficiency virus; IQR, interquartile range; MTBC, *Mycobacterium tuberculosis complex*; PUD, peptic ulcer disease; SD, standard deviation.

proportion of patients with substance use history, including smoking, chewing khat and alcohol consumption was 12.5%, 11.3%, and 18.8%, respectively. The most common comorbidity was HIV in both treatment groups. Congestive heart failure (CHF) tended to be more prevalent in the levofloxacin than the moxifloxacin group, probably to avoid exacerbation of cardiac problems due to moxifloxacin-associated QT interval prolongation.

Treatment Regimens

The moxifloxacin-based regimen consists of Moxifloxacin 600–800 mg, Isoniazid 300–600 mg, Ethambutol 800 mg, Pyrazinamide 1200 mg, Prothionamide 750 mg, Cycloserine 500–750 mg, and Clofazimine 100 mg. The levofloxacin-based regimen, on the other hand, included Levofloxacin 750–1000 mg, Cycloserine 500 mg, Delamanid 500 mg, Bedaquiline 200–400 mg, Clofazimine 100 mg, Linezolid 600 mg, and Prothionamide 750 mg. The medications were administered orally as a single dose except for Delamanid and Bedaquiline. Delamanid was administered twice a day, whereas Bedaquiline was administered 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. Bedaquiline and/or Delamanid were mostly included in the levofloxacin-based regimen, whereas injectable medicines (Amikacin, Kanamycin or capreomycin) were mostly included in the intensive phase in moxifloxacin-based regimen groups (Table 2).

Line Probe Assay

The LPA results performed on clinical isolates obtained from the participants are depicted in Figure 1. The assay revealed that whilst 88.8% of the isolates were sensitive to both FQs and the injectable agents, 3.8% were resistant to both FQs and the injectable second-line drugs (SLDs). The rest (7.5%) were resistant to only FQs, making the overall resistance 11.3%. Chi-square test revealed an association between WHO defined treatment outcome and FQ-resistance ($\chi2=8.18$; $p=0.004$) as well as resistance to both FQ and Injectable agents ($\chi2=5.79$; $p= 0.016$). However, as indicated in Table 3, the overall treatment success rate was higher in levofloxacin-than moxifloxacin-based treatment groups ($p<0.05$).

Treatment Outcome

The detailed description of treatment outcome as per the WHO 2013 guideline is presented in Table 3. Out of the 80 patients, 52 (65.0%) experienced a successful treatment outcome, whereas 28 (35.0%) showed an unfavorable outcome. Disaggregating the data revealed that 43 (53.75%) were cured, 9 (11.25%) completed treatment, 8 (10.0%) died, 9 (11.25%) failed/moved to pre-XDR-TB, and 11 (13.75%) were LTFU. Overall treatment success was

Table 2 Duration of Treatment and Number of Companion Drugs Included in Moxifloxacin-and Levofloxacin-Based Regimens

	Moxifloxacin Group (n=43)	Levofloxacin Group (n=37)	P-value
Duration of treatment, days	297 (169–355)	522 (321–570)	0.007
Duration of fluoroquinolones use, days	297 (169–355)	522 (321–570)	0.007
Drugs used	7 (5–7)	5 (4–6)	0.001
Isoniazid	38 (88.4)	0 (0.0)	0.001
Ethambutol	36 (83.7)	1 (2.7)	0.001
Pyrazinamide	39 (90.7)	23 (62.2)	0.002
Cycloserine	2 (4.7)	36 (97.3)	0.001
Delamanid	1 (2.3)	3 (8.1)	0.331
Clofazimine	41 (95.4)	34 (91.9)	0.524
Bedaquiline	2 (4.7)	17 (45.9)	0.001
Linezolid	2 (4.7)	23 (56.8)	0.001
Prothionamide	35 (81.4)	21 (56.7)	0.055
Injectable agents			
Capreomycin	1 (2.35)	9 (24.3)	0.005
Amikacin	7 (16.3)	0 (0.0)	0.013
Kanamycin	26 (60.5)	2 (5.4)	0.001

Notes: Data presented as n (%) or median (interquartile range). P-values are using chi-square test or Fisher exact test.

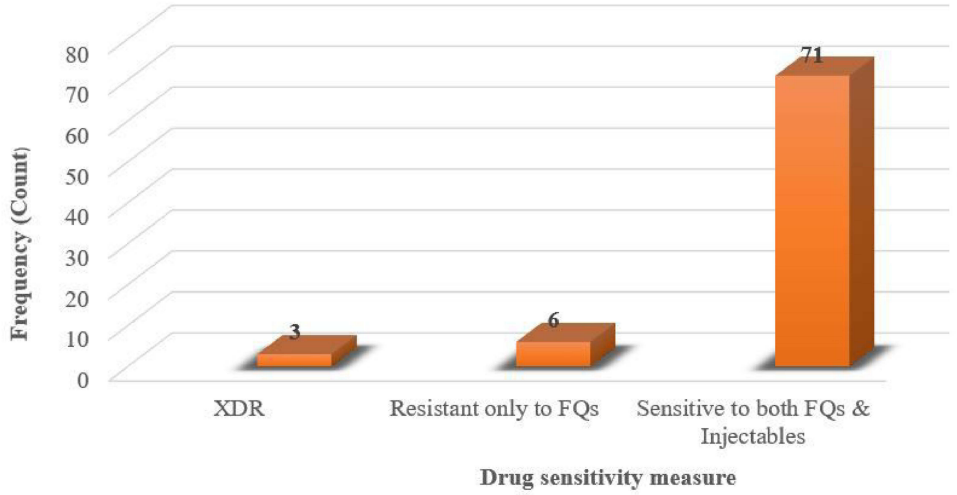


Figure 1 Summary of the Molecular line probe assay for the two core groups of second- line drugs.
Abbreviations: XDR, extremely drug resistant, occurs when there is resistance to both fluoroquinolones and injectable drugs; FQs, fluoroquinolones.

compared between the two treatment groups and found to be higher in levofloxacin- than moxifloxacin-based group ($\chi2$=6.40; p=0.01). However, comparison of each of the WHO defined outcomes between the two treatment groups did not show any statistically significant differences (Table 3).

Nonparametric estimation of the survival distribution comparing the treatment groups using Kaplan–Meier survival analysis is summarized in Figure 2. The overall comparison showed that the risk of unfavorable outcome was lower in the levofloxacin- (Log Rank test ($\chi2$=13.88, P=0.001) than moxifloxacin-based group.

Table 3 Treatment Outcome, Sputum Culture Conversion and Line Probe Assay Results by Treatment Regimen of the Study Subjects with MDR-TB

	Moxifloxacin Group (n=43)	Levofloxacin Group (n=37)	P-value
Treatment outcome			
Cure	19 (44.2)	24 (64.9)	0.06†
Completion	3 (7.0)	6 (16.2)	0.29†
Death	5 (11.6)	3 (8.1)	0.72†
Failed or moved to Pre-XDR-TB	7 (16.3)	2 (5.4)	0.17†
Lost to follow-up	9 (20.9)	2 (5.4)	0.06†
Overall treatment success	22 (51.2)	30 (81.1)	0.01†
First sputum culture conversion			
Within 90 days of treatment started	32 (74.4)	31 (83.8)	0.46†
After 90 days of treatment	11 (25.6)	6 (16.2)	0.41†
Line probe assay result			
Resistance to FQs	7 (16.3)	2 (5.4)	0.17†
Resistance to both FQs and IAs	2 (4.6)	1 (2.7)	0.56†
Duration of follow-up	290 (162–348)	515 (314–563)	0.01*

Notes: n=80; 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.
Abbreviations: FQs, fluoroquinolones; IAs, injectable agents; MDR-TB, multidrug resistant TB; XDR-TB, extremely drug resistant TB.

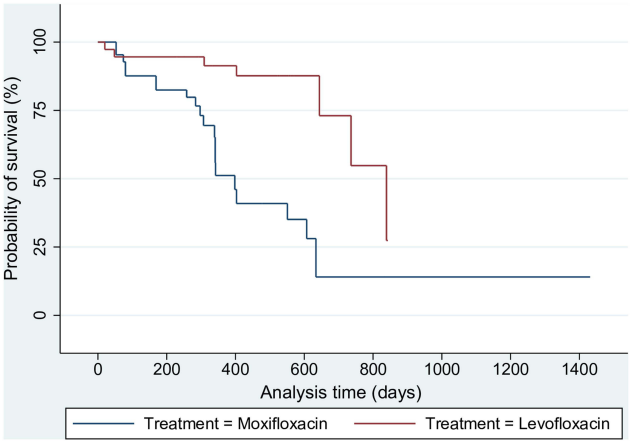


Figure 2 Kaplan–Meier curve showing the probability of survival of MDR-TB patients for moxifloxacin-and levofloxacin-based regimens since commencement to end of treatment follow-up.

Considering treatment group as one of the potential predictor variables, Cox proportional hazard analysis (Table 4) indicated that moxifloxacin treated group had a more risk of (AHR=0.25, 95% CI (0.09–0.71), p<0.05) unfavorable outcome compared to that of levofloxacin group.

The estimated mean survival time ± SE (in days) for moxifloxacin, levofloxacin and overall was 522.73 ±89.90, 716.10±43.80 and 711.05±90.04, respectively. The estimated median survival time ± SE (in days) for moxifloxacin, levofloxacin and overall was 398.00 ± 41.87, 839.00 ± 92.21 and 634.00 ± 20.72, respectively. From the survival plots (Figure 2), it could be observed that the total follow-up time was 1431 days for moxifloxacin and 843 days for levofloxacin. The survival curve for levofloxacin is consistently higher than the curve for moxifloxacin up to 840 days. The median time of survival for levofloxacin treated groups was more than twice that of moxifloxacin treated groups. The probability of survival for moxifloxacin group in the 53rd, 74th, 80th, 169th, 258th, 284th, 297th, 307th, 339th, 341st, 342nd, 398th, 403rd,607th, and 634th days of the follow-up were 95.3%, 92.8%, 87.6%, 82.5%, 79.8%, 76.6%, 73.1, 69.5%, 65.1%, 55.8%, 51.2%, 46.1%, 40.9 and 14.4%, respectively. In the same analysis, the probability of survival for levofloxacin in the 20th, 48th, 309th, 403rd, 644th, 736th, and 839th days of follow-up were 97.3%, 94.6%, 91.3%, 87.7%, 73.1%, 54.8%, and 27.4%, respectively. The cumulative probability of survival at the end of the follow-up period for moxifloxacin treatment group was 14.4%, whereas for that of levofloxacin group was 27.4%. Therefore, the levofloxacin-based regimen had a better survival advantage than that of moxifloxacin-based regimen. The overall treatment success was also better in levofloxacin-than that of moxifloxacin-based regimen as it can be seen from Table 3 (p<0.05). However, there were no statistically significant differences in the WHO defined outcomes such as cure rate (p=0.06), treatment completion (p=0.29), death rate (p=0.72), failure rate (p=0.17) and LTFU (p=0.06).

Culture Conversion Rates

Of the 80 study subjects, 54 (67.5%) had an FSCC within 90 days of treatment. As indicated in Table 4, the FSCC before 90 days of treatment impacted the overall outcome (p<0.05) in both treatment groups. Culture conversion after 90 days was associated with an increased risk of unfavorable outcome. However, the rates of culture conversion between the two treatment groups did not show any significant difference upon time-to-event analysis using the Log Rank (Mantel-Cox) test ($\chi 2$=0.279, P=0.597) (Figure 3). The median (interquartile range) culture conversion estimated days for moxifloxacin, levofloxacin, and the overall were 51 (40–130), 60 (49.5–130) and 60 (49.5–130), respectively. The proportion of culture positivity during the treatment course for moxifloxacin in the 21st, 26th, 30th, 32nd, 33rd, 34th, 35th, 40th, 45th, 47th, 48th, 50th, 51st, 56th, 65th, 66th, 81st, and 85th days was 0.98, 0.95, 0.88, 0.86, 0.81, 0.79, 0.78, 0.74, 0.67, 0.63, 0.56, 0.54, 0.47, 0.44, 0.40, 0.37, 0.35, and 0.33, respectively. On the other hand, it was 0.97, 0.95, 0.92, 0.81, 0.76, 0.70, 0.60, 0.46, 0.43, 0.38, and 0.32 for levofloxacin in the 13th, 14th, 16th, 30th, 48th, 51st, 56th, 60th, 65th, 79th, and 85th days, respectively.

Association Studies

Univariate and multivariate Cox regression analysis was conducted to identify predicting factors for unfavorable treatment outcomes (Table 4). Considering p-value <0.2 as a cut-off point from the univariate regression, potential outcome predicting variables were selected for further multivariate Cox regression analysis. Accordingly, treatment regimen type, prior TB treatment, alcohol consumption, resistance to FQs, FSCC, nutritional status, cavitary lung lesion, Scr., and ALT were selected and the multivariate Cox proportional hazard analysis was carried out (Table 5).

Table 4 Univariate and Backward Multivariate Cox Proportional Hazard Regression to Determine Outcome Predicting Factors in MDR-TB Patients

Univariate Cox Regression					
Patient Variable	**n (%)**	**Outcome**		**P-value**	**HR [95% CI]**
		Success	**Failure**		
Sex, male	44 (55)	28 (53.8)	16 (57.1)	0.38	1.39 [0 0.66–2.97]
Comorbidity	29 (36.3)	18 (34.6)	11 (39.3)	0.88	0.94 [0.62–3.50]
Age (years), >35	15 (18.8)	8 (15.4)	7 (25.0)	0.37	0.94 [0.27–3.22]
Prior TB treatment	60 (75.0)	39 (75.0)	21 (75.0)	0.14*	1.97 [0.80, 4.87]
Body mass index, <18.5	58 (72.5)	38 (73.1)	20 (71.4)	0.55	0.96 [0.83–1.10]
Treatment group, MXF	43 (53.4)	22 (42.3)	21 (75.0)	0.00*	0.22 [0.09–0.53]
Khat consumption	9 (11.3)	3 (5.8)	6 (21.4)	0.29	1.63 [0.46–1.10]
Smoking	10 (12.5)	4 (7.7)	6 (21.4)	0.58	1.30 [0.50–3.38]
Alcohol consumption	16 (20.0)	4 (7.7)	12 (42.9)	0.00*	3.96 [1.83–8.56]
Resistance to FQs	9 (11.3)	3 (5.8)	6 (21.4)	0.09*	3.31 [1.32–6.65]
Resistance to FQs & IAs	3 (3.8)	1 (1.9)	2 (7.1)	0.58	1.42 [0.42–4.83]
FSCC after 90 days	26 (32.5)	5 (9.6)	11 (39.3)	0.01*	2.66 [1.24–5.73]
Malnourished	47 (58.8)	28 (53.8)	19 (67.8)	0.09*	2.07 [0.89–4.81]
Cavitary lung lesion	30 (37.5)	10 (19.2)	20 (71.4)	0.00*	5.11 [2.24–11.65]
Mean AST, ≥32.7†	35 (43.8)	23 (44.2)	12 (42.9)	0.50	2.14 [0.99–1.03]
Mean ALT, ≥32.5†	36 (45.0)	21 (40.4)	15 (53.8)	0.04*	1.58 [0.72–3.49]
Mean ALB, <3.3†	38 (47.5)	24 (46.2)	14 (50.0)	0.57	0.58 [0.58–2.62]
Mean HG, <15.12†	57 (71.3)	37 (71.2)	20 (71.4)	0.69	1.20 [0.96–1.08]
Adverse drug event	60 (75.0)	39 (75.0)	21 (75.0)	0.66	0.82 [0.33–1.99]
Mean Scr. (mg/dL), ≥ 0.87†	31 (38.8)	14 (26.9)	17 (60.7)	0.09*	0.17 [0.030–1.02]

Notes: n=80; *Variables with P-value<0.2.
Abbreviations: CHR, crude hazard ratio; CI, confidence interval; FQs, fluoroquinolones; FSCC, first sputum culture conversion; IAs, injectable agents.

The analysis revealed that the risk of treatment failure was significantly higher in patients with moxifloxacin-based regimen (AHR=0.27, 95% CI=0.10–0.74, p=0.011), FSCC after 90 days (AHR=2.80, 95% CI=1.18–6.66, p=0.02), alcohol consumption (AHR=4.09, 95% CI=1.62–10.34, p=0.003), MDR-TB cases with cavitary lung lesion (AHR=3.09, 95% CI=1.10–8.70, p=0.032), mean Scr ≥0.87 (mg/dL) (AHR=0.27, 95% CI=08–0.88, p=0.029), and mean ALT ≥32.5 (IU/L) (AHR=3.11, 95% CI=1.01–9.54, p=0.019) than their corresponding counterparts.

Adverse Drug Reactions

ADRs noted during the treatment period are summarized in Table 6. Most ADRs occurred were of Grade 1 (mild) or Grade 2 (moderate) and dose or regimen change was not necessary. But in some patients (who were on the moxifloxacin-regimen), ototoxicity with the injectable SLDs was severe (Grade 3) and either doses were reduced or the medications were discontinued. The overall occurrence of ADRs in the study participants was 75.0%. The proportion of ADRs was higher in the moxifloxacin- than the levofloxacin-based group (86.1% vs 62.2%)

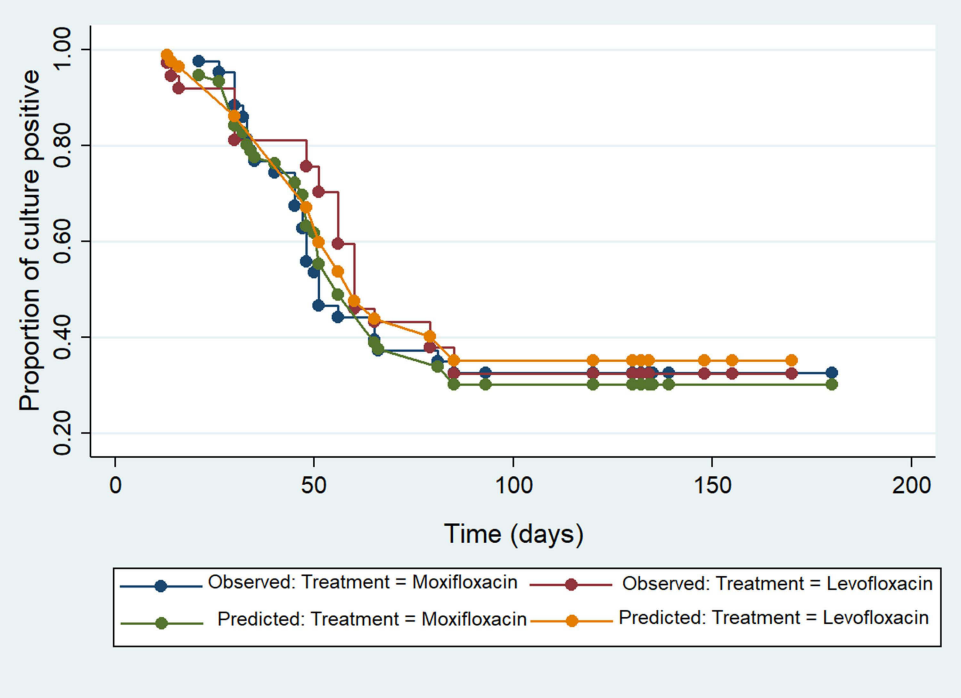


Figure 3 Kaplan–Meier analysis comparing time-to-culture positivity between moxifloxacin- and levofloxacin-based regimens treated MDR-TB patients (n=80).

($\chi2$=6.051; p<0.05). Occurrence of ototoxicity was also higher in the moxifloxacin- than levofloxacin-based group ($\chi2$=6.041; p<0.05). Musculoskeletal abnormalities (myalgia) were the most frequently occurred ADRs in both treatment groups (25.6% versus 29.7%). Occurrence of other ADRs such as myalgia, hematological abnormalities, gastrointestinal upset, hepatotoxicity, psychotic problems, peripheral neuropathy and mild forms of ADRs were not significantly different between the two treatment groups.

Discussion

The results of our study demonstrated a lower risk of treatment failure in levofloxacin- than moxifloxacin-based regimen, as observed in the Kaplan–Meier survival analysis (Log Rank test ($\chi2$=13.88, P=0.001)). Treatment success (cure and treatment completion rates) in the levofloxacin group was also greater than those in the moxifloxacin-group ($\chi2$=7.83; p<0.05). More interestingly, whilst deaths observed in the levofloxacin-based group seemed to be most likely related to the co-existing illnesses (CHF, DVT and pneumonia), deaths were still observed in the moxifloxacin-based group in the absence of other comorbidities and treatment failures. Our finding is concordant with the STREAM Stage I trial, which revealed that shorter regimens were associated with higher risks of treatment failure and relapse compared to longer regimens.[33] This is, however, in contradistinction to the Korean study that reported no apparent difference in treatment outcome between the two groups.[34] On the other hand, time to culture conversion rates between the two groups were not different (Log Rank test $\chi2$=0.279, P=0.597) in our study, which concurs with an earlier Korean study that compared culture conversion rates between the two treatment groups using both liquid and solid media.[35] The overall occurrence of ADRs was also higher in the present study than the Korean study,[34] although no regimen changes were made during the treatment course, as all the ADRs were mild to moderate except for ototoxicity by the injectable agents, which necessitated dose reduction or discontinuation of the offending agents. Moreover, we found more overall ADRs with moxifloxacin- than levofloxacin-based regimen, while the reverse was true for the Korean study. Although musculoskeletal abnormalities were the most frequently cited ADRs in both settings, we did not observe any apparent difference between the two groups, while they were more prevalent in the levofloxacin group in the Korean report.[34] These discrepancies may be due to differences in the background drugs, drug doses, study population and research design. For instance, more proportion of patients in this study received injectable agents as

Table 5 Multivariate Cox Proportional Hazard Regression Analysis of Treatment Outcome Predicting Covariates in MDR-TB Patients

Patient Variable	n (%)	Outcome n (%)		P-value	AHR [95% CI]
		Successful	Unfavorable Outcome		
Treatment group		52 (65.0)	28 (35.0)	0.011*	0.27 [0.10–0.74]
Moxifloxacin	43 (53.8)	22 (42.3)	21 (75.0)		
Levofloxacin	37 (46.2)	30 (57.7)	7 (25.0)		
Prior TB treatment		52 (65.0)	28 (35.0)	0.882	1.08 [0.38–3.08]
None	20 (25)	13 (25.0)	7 (25.0)		
Treated	60 (975)	39 (75.0)	21 (75.0)		
Nutritional Status		52 (65.0)	28 (35.0)	0.652	1.23 [0.50–3.04]
Normal	33 (41.3)	23 (69.7)	10 (30.3)		
Malnourished	47 (58.7)	29 (61.7)	18 (38.3)		
Resistance FQs				0.336	1.75 [0.56–5.46]
FSCC				0.020*	2.80 [1.18–6.66]
Within 90 days	54 (67.5)	42 (77.8)	12 (22.2)		
After 90 days	26 (32.5)	10 (38.5)	16 (61.5)		
Alcohol use				0.003*	4.09 [1.62–10.34]
No	65 (81.2)	51 (78.5)	14 (21.5)		
Yes	15 (18.8)	1 (6.7)	14 (93.3)		
Chest X-ray				0.032*	3.09 [1.10–8.70]
No lesion	58 (72.5)	43 (74.1)	15 (25.9)		
Cavitary lesion	22 (27.5)	9 (40.9)	13 (59.1)		
Mean Scr. (mg/dL)		52 (65.0)	28 (35.0)	0.029*	0.27 [08–0.88]
< 0.87†	49 (61.3)	32 (61.5)	17 (60.7)		
≥ 0.87†	31 (38.7)	20 (38.5)	11 (39.3)		
Mean ALT (IU/L)				0.047 *	3.11 [1.01–9.54]
≤ 32.5†	44 (55)	36 (69.2)	21 (75.0)		
> 32.5†	36 (45)	16 (30.8)	7 (25.0)		

Notes: n=80; *P-value <0.05; †These were the average values considered as a cut-off point below or above which the outcomes were assessed.
Abbreviations: ALT, alanine aminotransferase; IU/L, international units per liter; Scr., serum creatinine; FSCC, first sputum culture conversion (in days); FQs, fluoroquinolones.

companion drugs with the moxifloxacin-regimen, whereas the use of injectable agents in both groups was almost equal in the Korean study.[34] In addition, frequent use of the new drugs (Bedaquiline and Delamanid) with levofloxacin- than moxifloxacin-based regimen might have contributed to the better treatment success and lower risk of treatment failure in the present study. As regards to dose, Korean patients received only 750 mg dose of levofloxacin, whereas patients in the present study received both 750 mg and 1000 mg of levofloxacin. Levofloxacin has the best early bactericidal activity at the dose of 1000 mg/day than at 750 mg/day,[45] which could probably be a reason for the better treatment success observed in the Ethiopian patients. Furthermore, inter-ethnic or inter-individual

Table 6 Adverse Drug Reactions Occurred Among the MDR-TB Patients

	Moxifloxacin Group (n=43)	Levofloxacin Group (n=37)	P-value
Adverse events	37 (86.1)	23 (62.2)	0.014*
Myalgia	11 (25.6)	11 (29.7)	0.679
Hematological abnormalities	7 (16.3)	6 (16.2)	0.994
GI upset	5 (11.6)	2 (5.4)	0.442
Ototoxicity	9 (16.2)	1 (2.7)	0.017*
Hepatotoxicity	9 (20.9)	5 (13.5)	0.556
Psychotic problems	3 (8.1)	1 (2.7)	0.620
Peripheral neuropathy	3 (8.1)	1 (2.7)	0.620
Elevated serum creatinine (nephrotoxicity).	3 (7.0)	2 (5.4)	0.990
Others[†]	9 (11.6)	7 (10.8)	0.823

Notes: n=80, Data presented as n (%). P values are using chi-square test or Fisher exact test. *The P-value is statistically significant (P<0.05); [†]Others refers ADRs like weakness, fatigue, sweating, and chills.

variability, which influence the pharmacokinetics and pharmacodynamics of drugs, maybe a source of variability to the observed drug responses.[46–50] The other probable reason for the observed differences could be the relatively small sample size study sample in the present study. We enrolled a smaller number of patients for the observational follow-up compared to other similar studies and this also might have influenced our study results.

The overall treatment outcome observed in the present study (65%) was relatively lower than a recent national study report (75.7%).[51] Moreover, other studies also indicated a relatively higher treatment success rates in various settings: 82.4% (Taiwan),[52] 75.8% (Pakistan),[53] 72.7% (Korea),[54] 75.7% (Tanzania).[55] However, it is higher than that reported by WHO (57%) in 2017,[56] a meta-analysis (61%)[57] and an Indonesian national (48%) as well as provincial (36%) study.[58] LPA results revealed that 11.3% of the clinical isolates were resistant to FQs, whereas 3.8% were resistant to both FQs and injectable TB drugs. This is much higher than reported recently from a national study (3.4%).[59] A study from Tigray region of Ethiopia reported a rate of FQ resistance much lower (5.3%)[60] than our study. This suggests that the rate of resistance to the essential and most potent MDR-TB drugs (FQs and Injectable agents) may be spreading.

We also determined treatment regimen type, culture conversion rate, alcohol use, cavitary lesion, serum creatinine and ALT levels as predictors of treatment outcome. Late culture conversion was shown to be associated with risk of treatment failure in this study. A negative culture between 2 and 3 months of therapy indicates a successful therapeutic outcome in MDR-TB patients.[61] Outcomes among patients who had a history of alcohol consumption was poor, which concurs with a study report from India.[62] Apart from the probable direct effect of the contemporary and previous alcohol consumption, non-adherence was mentioned to be the main reason for the unfavorable outcome.[62] Cavitary lung lesion was another risk factor related to poor treatment outcome in this study and is in line with a finding of a recent study in Thailand.[63] The possible reason for the association could be related to high bacterial load at the cavities, where drugs may not access and thus unable to eradicate effectively, leading to persistence of the bacteria.[64,65] Patients with a cavity have a bacterial load of up to 10^{11} bacilli/g, making it highly contagious.[66] A study suggested that treatment outcome in TB with cavitary lung lesion may be improved by extending the continuation phase of TB treatment.[67] The other possible reason for poor outcome in cavitary lesion may be due to late stage of the disease which ends in death of the patient.[68]

Mean Scr. level of 0.87 (mg/dL) and above was also associated with unfavorable outcome. The rationale behind this is not very clear. Creatinine, an end product of muscle metabolism, is the most commonly used clinical indicator for renal function.[69,70] It is a frequently used parameter in

hospital wards for the prognosis of diseases and drug dosing. However, it might not be a reliable prognostic parameter in critical illnesses because the pharmacokinetic behavior of drugs in these patients is difficult to predict. Augmented renal clearance is prevalent, even with normal Scr. levels.[71] As a consequence, this results in suboptimal dosing followed by treatment failure and increased mortality.[72] For example, levofloxacin has a linear pharmacokinetics and 80% of it is excreted unchanged via the kidneys. However, renal clearance is 60% higher than creatinine clearance, evidencing the involvement of tubular secretion.[73] In the other scenario, both older and newer FQs are known to elevate Scr. and induce acute interstitial nephritis (AIN), which can cause end stage renal failure that requires hemodialysis.[74] The incidence of elevated Scr. levels is related to FQs range from 0.2 to 1.3%.[75] In the present study, the occurrence of acute elevated Scr. in moxifloxacin- and levofloxacin-based regimen treatment groups was 7.0% and 5.4%, respectively, and is suggestive of AIN. A recent retrospective study of AIN related to FQs use identified that 10% of the study subjects were biopsy-proven AIN cases.[75] Clinicians should be aware of these adverse effects, especially in neutropenic and lymphopenic patients, which might lead to unfavorable outcomes in TB patients.[64–76] Similarly, ALT higher than the mean 32.5 (IU/L) was a predictor of unsuccessful treatment outcome. A study reported that ALT abnormalities were more common in the shorter regimen of 8 weeks.[33] Drug-induced liver injury (DILI) may be the most likely cause of elevated serum ALT.[77] Hepatotoxicity is one of the most frequent and serious ADRs of anti-TB medications like isoniazid and pyrazinamide and may reduce treatment effectiveness by compromising treatment regimens.[78,79] Total occurrence of hepatotoxicity in our evaluation was 17.5%. However, there was no statistically significant difference in the occurrence of hepatotoxicity between the two treatment groups (20.9% verse 13.5%). Early detection of drug-induced elevation of Scr. and ALT levels in MDR-TB patients could help prevent poor treatment outcome due to a possible drug-induced AIN and DILI, respectively.

Limitation of the Study

This study is not a clinical trial but an observational explorative follow-up study on a limited sample of MDR-TB patients in the programmatic treatment course. In addition, the sample size in this study is smaller than related studies. In fact, the total number of patients was expected to be larger than those included in this study. However, difficulties in meeting the eligibility criteria and the COVID-19 pandemic since the beginning of 2020 had significantly affected patients' admission and diagnosis. Nonetheless, the conclusion drawn from this study might be informative for further studies.

Conclusion

Levofloxacin-based MDR-TB regimen with the background new oral drugs seems to be preferable over moxifloxacin-based regimen that includes the injectable SLDs, in terms of better treatment success and lower risk of unfavorable outcomes. Early evaluation of MDR-TB patients for sputum culture conversion rate, history of alcohol use, cavitary lesion, serum Scr. and ALT levels may help tailoring treatment for a better outcome. We recommend further randomized controlled trial in a larger population nationally for a possible MDR-TB treatment program review in the use of these key drugs.

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Disclosure

The authors report no conflicts of interest in this work.

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