Original Article

Impact of Anti-Tuberculosis Drug Use on Treatment Outcomes in Patients with Pulmonary Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: A Nationwide Retrospective Cohort Study with Propensity Score Matching

Hongjo Choi, M.D., Ph.D.[1] ⓘ, Dawoon Jeong, M.P.H.[2],*, Young Ae Kang, M.D., Ph.D.[3], Doosoo Jeon, M.D., Ph.D.[4], Hee-Yeon Kang, Ph.D.[5],†, Hee Jin Kim, M.D.[6], Hee-Sun Kim, Ph.D.[7] and Jeongha Mok, M.D., Ph.D.[8,9] ⓘ

[1]Department of Preventive Medicine, Konyang University College of Medicine, Daejeon, [2]Research and Development Center, The Korean Institute of Tuberculosis, Korean National Tuberculosis Association, Cheongju, [3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, [4]Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, [5]Department of Health Policy and Management, Seoul National University College of Medicine, Seoul, [6]Central Training Institute, Korean National Tuberculosis Association, Seoul, [7]Department of Health Policy Research, National Evidence-based Healthcare Collaborating Agency, Seoul, [8]Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, Busan, [9]Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea

Abstract

Background: Effective treatment of fluoroquinolone-resistant multidrug-resistant tuberculosis (FQr-MDR-TB) is difficult because of the limited number of available core anti-TB drugs and high rates of resistance to anti-TB drugs other than FQs. However, few studies have examined anti-TB drugs that are effective in treating patients with FQr-MDR-TB in a real-world setting.

Methods: The impact of anti-TB drug use on treatment outcomes in patients with pulmonary FQr-MDR-TB was retrospectively evaluated using a nationwide integrated TB database (Korean Tuberculosis and Post-Tuberculosis). Data from 2011 to 2017 were included.

Results: The study population consisted of 1,082 patients with FQr-MDR-TB. The overall treatment outcomes were as follows: treatment success (69.7%), death (13.7%), lost to follow-up or not evaluated (12.8%), and treatment failure (3.9%). On a propensity-score-matched multivariate logistic regression analysis, the use of bedaquiline (BDQ), linezolid (LZD), levofloxacin (LFX), cycloserine (CS), ethambutol (EMB), pyrazinamide, kanamycin (KM), prothionamide (PTO), and para-aminosalicylic acid against susceptible strains increased the treatment success rate (vs. unfavorable outcomes). The use of LFX, CS, EMB, and PTO against susceptible strains decreased the mortality (vs. treatment success).

Conclusion: A therapeutic regimen guided by drug-susceptibility testing can improve the treatment of patients with pulmonary FQr-MDR-TB. In addition to core anti-TB drugs, such as BDQ and LZD, treatment of susceptible strains with later-generation FQs and KM may be beneficial for FQr-MDR-TB patients with limited treatment options.

Keywords: Fluoroquinolone; Multidrug-Resistant; Outcome; Tuberculosis

Introduction

Multidrug-resistant tuberculosis (MDR-TB) needs lengthy treatment with second-line anti-TB drugs, but these drugs are less effective and more toxic than first-line anti-TB drugs for drug-susceptible TB[1]. As a result, the treatment outcomes of patients with MDR-TB are usually not satisfactory. In 2018, the treatment success rate for MDR- and rifampicin-resistant (RR)-TB was only 59% worldwide[2]. MDR-TB is a significant public health problem and a major global obstacle to the elimination of TB[1].

Rapid diagnosis and an effective treatment regimen are essential for achieving treatment success in patients with MDR-TB[3]. However, in the absence of randomized controlled trials, the prioritization and combination of anti-TB drugs that are required to effectively treat MDR-TB have largely been based on meta-analyses of individual patient data, which in most cases originated from observational studies[1,4]. Although the level of evidence in a meta-analysis may not be sufficient, real-world evidence for the efficacies of core anti-TB drugs and their combinations prescribed based on these studies and treatment guidelines continues to accumulate.

Fluoroquinolones (FQs), such as levofloxacin (LFX) or moxifloxacin (MFX), are the most important core anti-TB drugs for treating MDR-TB, given their excellent bactericidal and sterilizing activities[5]. If FQs are excluded from a treatment regimen due to resistance or intolerance, the treatment success rates for MDR-TB decrease considerably[4,6,7]. Thus, developing an effective treatment regimen for fluoroquinolone-resistant (FQr)-MDR-TB is a difficult clinical problem, given the limited number of available core anti-TB drugs and high rates of resistance to anti-TB drugs other than FQs[8]. The global estimate of the FQ resistance rate among all MDR-TB cases is approximately 20%[9]. However, which anti-TB drugs are effective in patients with FQr-MDR-TB is unclear. Although the guidelines suggest several options for FQr-MDR-TB treatment (e.g., a longer individualized regimen or "bedaquiline, pretomanid, linezolid [BPaL] regimen"), supporting evidence is still lacking[1].

The aim of this study, based on nationwide data from South Korea, was to evaluate the impact of anti-TB drug use on treatment outcomes in patients with pulmonary FQr-MDR-TB. FQr-MDR-TB was defined as TB infection that is resistant to any FQ (ofloxacin [OFX], LFX, or MFX) in addition to MDR-TB.

Materials and Methods

1. Study design and population

This retrospective study was performed in South Korea, where the TB notification rates of new cases were 78.9 and 55.0 per 100,000 population in 2011 and 2017, respectively[10]. In 2017, 3.2% of new patients and 10.0% of previously treated patients had MDR-TB[11]. The population for this study was extracted from the original TB cohort (Korean Tuberculosis and Post-Tuberculosis [Korean TB-POST]) generated by linkage of the Korean National Tuberculosis Surveillance System (KNTSS) with the National Health Information Database (NHID) and the Causes of Death Statistics Database[12]. Among TB patients registered in the TB-POST cohort between 2011 and 2018, the following patients were included: patients with TB resistant to isoniazid (INH), rifampicin (RIF), and any FQ (OFX, LFX, or MFX) as demonstrated on a drug-susceptibility test (DST) from the KNTSS; and patients with extensively drug-resistant (XDR)-TB (as formerly defined by the World Health Organization [WHO][13]; patients with MDR-TB resistant to FQ and at least one of the three second-line injectable drugs [SLIDs] [kanamycin (KM), amikacin, and capreomycin]) according to the KNTSS record of drug resistance; and patients with the Korean Standard Classification Diseases code U84.31 (compatible with XDR-TB, as formerly defined by the WHO[13]) from the NHID. If a patient notified the registries of additional treatment episodes after the end of the first treatment episode, data on the last treatment episode were collected in accordance with the inclusion criteria described above. Patients with extrapulmonary TB only or with missing data among any covariates were excluded from the analysis. Patients who were registered in 2018 were also excluded because of the unknown treatment outcome. The study population comprised the population registered in the KNTSS from January 1, 2011, to December 31, 2017. The study protocol was reviewed and approved by the Institutional Review Board of the National Evidence-based Healthcare Collaborating Agency (NECAIRB19-008-1). The requirement for obtaining informed consent was waived because of the retrospective nature of the study using public de-identified data.

2. Measurement and definition

"Drug given" was defined as prescription of an anti-TB drug for at least 30 days during the treatment period. The following anti-TB drugs were evaluated: bedaquiline (BDQ), linezolid (LZD), OFX, LFX, MFX, cycloserine (CS), delamanid (DLM), ethambutol (EMB), pyrazinamide (PZA), streptomycin (SM), amikacin

(AMK), KM, meropenem (MPM), prothionamide (PTO), and para-aminosalicylic acid (PAS). Drug-resistant *Mycobacterium tuberculosis* was defined when health institutions reported strain resistance to anti-TB drugs based on the DST results; otherwise, the strain was considered susceptible.

The history of TB treatment was defined as follows: New patients were those who had never been treated or who had taken anti-TB drugs for <1 month, and previously treated patients were those who had received anti-TB drugs for ≥1 month[13]. Treatment outcomes at treatment completion were categorized in accordance with the WHO definitions as follows: cured, treatment completed, treatment failed, died (TB-related- and non-TB-related death), lost to follow-up, or not evaluated[13]. Treatment success was defined as the sum of cured and treatment completed. For analyses of the effect of each anti-TB drug on the treatment outcome, an unfavorable outcome was defined as the sum of treatment failed, lost to follow-up, and not evaluated; death was defined as the sum of TB-related and non-TB-related deaths during treatment and within 12 months after treatment completion. The following covariates were included: age, sex, nationality, previous treatment history of TB, sputum acid-fast bacilli (AFB) smear result, comorbidity (diabetes mellitus [DM], malignancy, end-stage renal disease, and human immunodeficiency virus [HIV] infection), number of resistant drugs, and resistance to a SLID.

3. DST and TB treatment

Phenotypic DST was performed using the absolute concentration method and Lowenstein-Jensen medium. The drugs and their critical concentrations for resistance were as follows: INH, 0.2 µg/mL; RIF, 40 µg/mL; EMB, 2.0 µg/mL; OFX, 2.0 µg/mL; LFX, 2.0 µg/mL; MFX, 2.0 µg/mL; SM, 10 µg/mL; AMK, 40 µg/mL; KM, 40 µg/mL; PTO, 40 µg/mL; CS, 30 µg/mL; PAS, 1.0 µg/mL; and LZD, 2.0 µg/mL. PZA susceptibility was determined using the pyrazinamidase test. The critical concentrations for resistance to AMK, KM, and OFX were changed during the study period as follows: AMK and KM, 30 µg/mL in January 2014; and OFX, 4.0 µg/mL in January 2016. Tests for LZD have been available since 2016. Molecular DSTs included line probe assays for first- or second-line anti-TB drugs and the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA); all tests were performed according to the manufacturers'

Figure 1. Flowchart of the study participants. *Former definition by the World Health Organization[13]; multidrug-resistant tuberculosis further resistant to any fluoroquinolone and at least one of the three second-line injectable drugs (kanamycin, amikacin, or capreomycin). TB: tuberculosis; MDR: multidrug-resistant; XDR: extensively drug-resistant.
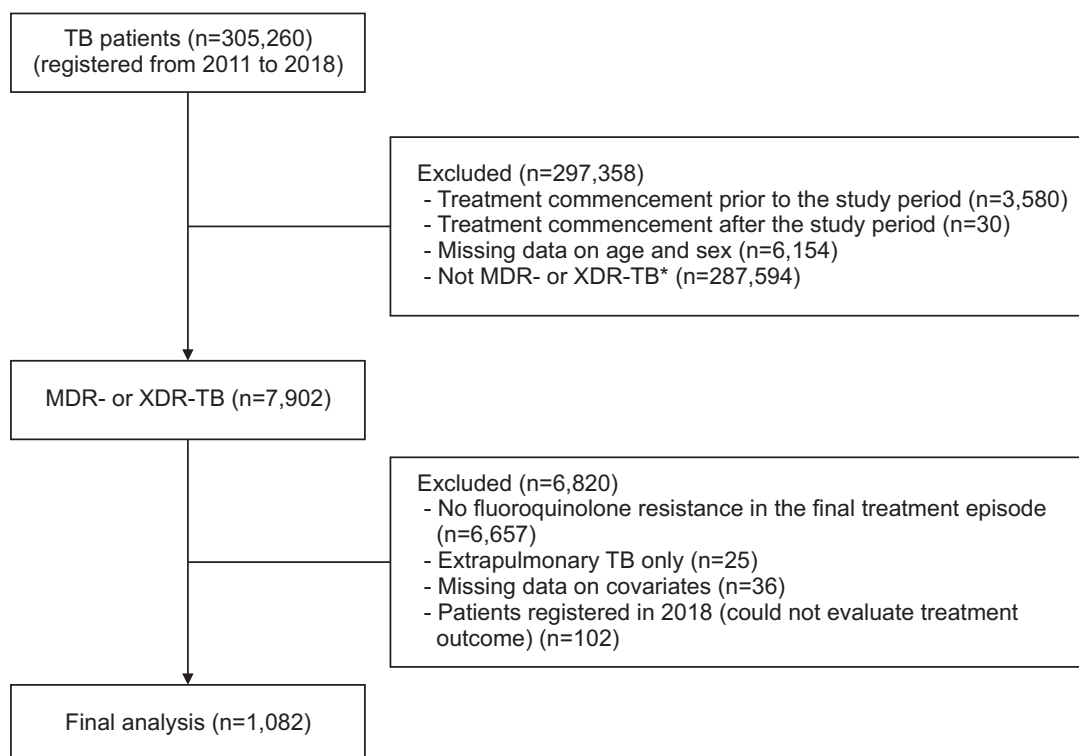
instructions. To determine BDQ resistance, the minimum inhibitory concentration was determined using 7H9 broth and the serial two-fold dilution method. The concentration of BDQ was in the range of 0.03125 to 4.0 mg/L. The interim critical concentration for BDQ resistance was 0.25 mg/L. Tests for BDQ have been available since 2017. Isolates before 2016 and 2017 were considered susceptible to LZD and BDQ, respectively. It was assumed that all isolates were susceptible to DLM and MPM.

The treatment regimen for FQr-MDR-TB was individualized based on the DST result, and it was in line with the Korean guidelines. The regimens and treatment durations recommended by these guidelines are similar to the WHO guidelines: at least four effective second-line anti-TB drugs with or without PZA for at least 20 months[14-16]. In South Korea, BDQ and DLM have been available since March 2014 and October 2014, respectively. Indications for their use were in accordance with the WHO guidelines[16].

4. Statistical analysis

Continuous variables are presented as the median and interquartile range (IQR), and categorical variables are presented as a number with a percent. The distribution by treatment outcomes was analyzed using the Pearson chi-square test or the Cochran-Armitage test for the test of trend. As our study was based on real-world data, propensity score matching (PSM) was used to balance the baseline characteristics of the "drug given" and "drug not given" groups. Drug use (given or not given) was considered as the dependent variable, and the following covariates were included in the PSM: age, sex, AFB smear result, previous treatment history of TB, resistance to SLIDs, number of resistant drugs, DM, and malignancy. The caliper method with a difference of 0.01 and 1:1 matching without replacement were used in the PSM. The impact of anti-TB drug use on the treatment outcome was determined in a multivariate logistic regression model. Treatment success was compared with unfavorable outcomes, and death with treatment success stratified by drug-resistance pattern and including covariates (age, sex, AFB smear result, history of TB treatment, resistance to SLIDs, number of resistant drugs, DM, and malignancy). Although all patients were included in the Pearson chi-square and Cochran-Armitage analyses conducted to assess the epidemiological trends in FQr-MDR-TB in South Korea, one patient with BDQ resistance was excluded from the final logistic regression analysis, as were 24 patients with LZD resistance, due to the small number of cases. All statistical analyses were performed using STATA/

MP4 version 17 (StataCorp LLC, College Station, TX, USA). A p-value <0.05 was considered to indicate statistical significance.

Table 1. Baseline characteristics of patients with fluoroquinolone-resistant multidrug-resistant tuberculosis (n=1,082)

Characteristic	Value
Age, yr	48.0 (35.0–59.0)
Age group, yr	
≤24	76 (7.0)
25–34	182 (16.8)
35–44	192 (17.7)
45–54	250 (23.1)
55–64	192 (17.7)
65–74	109 (10.1)
≥75	81 (7.5)
Male sex	741 (68.5)
Nationality	
Korean	997 (92.1)
Others	85 (7.9)
TB treatment history	
New patient	431 (39.8)
Previously treated patient	651 (60.2)
Sputum AFB smear	
Negative/unknown*	435 (40.2)
Positive	647 (59.8)
Comorbidities	
Diabetes mellitus	240 (22.2)
Malignancy	22 (2.0)
End-stage renal disease	11 (1.0)
HIV	2 (0.2)
Number of resistant drugs[†]	
≤4	227 (21.0)
5–7	276 (25.5)
8–10	371 (34.3)
≥11	208 (19.2)
Resistance to second-line injectable drugs	260 (24.0)

Values are presented as median (interquartile range) or number (%).
*Unknown smear result (n=25). [†]Including isoniazid and rifampin.
TB: tuberculosis; AFB: acid-fast bacilli; HIV: human immunodeficiency virus.

Table 2. Treatment outcomes of patients with fluoroquinolone-resistant multidrug-resistant tuberculosis*

Variable	2011 (n=223)	2012 (n=143)	2013 (n=188)	2014 (n=155)	2015 (n=131)	2016 (n=130)	2017 (n=112)	Total (n=1,082)	p for trend
Treatment success	131 (58.7)	106 (74.1)	133 (70.7)	120 (77.4)	93 (71.0)	89 (68.5)	82 (73.2)	754 (69.7)	0.022
Treatment failed	10 (4.5)	10 (7.0)	6 (3.2)	5 (3.2)	7 (5.3)	3 (2.3)	1 (0.9)	42 (3.9)	0.059
Lost to follow-up/ Not evaluated	55 (24.7)	9 (6.3)	23 (12.2)	11 (7.1)	12 (9.2)	19 (14.6)	9 (8.0)	138 (12.8)	0.001
TB-related death	16 (7.2)	10 (7.0)	15 (8.0)	6 (3.9)	10 (7.6)	8 (6.2)	7 (6.3)	72 (6.7)	0.609
Non-TB-related death	11 (4.9)	8 (5.6)	11 (5.9)	13 (8.4)	9 (6.9)	11 (8.5)	13 (11.6)	76 (7.0)	0.019

Values are presented as number (%).
*Treatment outcome at treatment completion.
TB: tuberculosis.

Table 3. Comparison of patients with treatment success and patients with unfavorable outcomes

Variable	Treatment success (n=754)	Unfavorable outcome* (n=180)	p-value
Age, yr			0.002
≤24	66 (8.8)	9 (5.0)	
25–34	156 (20.7)	18 (10.0)	
35–44	147 (19.5)	32 (17.8)	
45–54	167 (22.2)	46 (25.6)	
55–64	124 (16.5)	38 (21.1)	
65–74	57 (7.6)	24 (13.3)	
≥75	37 (4.9)	13 (7.2)	
Male sex	493 (65.4)	142 (78.9)	<0.001
TB treatment history			<0.001
New	333 (44.2)	53 (29.4)	
Previously treated	421 (55.8)	127 (70.6)	
Sputum AFB smear, positive	450 (59.7)	97 (53.9)	0.156
Comorbidities			
Diabetes mellitus	132 (17.5)	58 (32.2)	<0.001
Malignancy	6 (0.8)	5 (2.8)	0.027
Number of resistant drugs[†]			0.002
≤4	142 (18.8)	54 (30.0)	
5–7	185 (24.5)	47 (26.1)	
8–10	285 (37.8)	46 (25.6)	
≥11	142 (18.8)	33 (18.3)	
Resistance to second-line injectable drugs	176 (23.3)	41 (22.8)	0.872

Values are presented as number (%).
*Sum of treatment failure, loss to follow-up, and not evaluated. [†]Including isoniazid and rifampin.
TB: tuberculosis; AFB: acid-fast bacilli.

Results

1. Baseline characteristics

Among the 305,260 patients with TB registered in the TB-POST cohort from 2011 to 2018, 7,902 were identified as having MDR-TB or XDR-TB. After the pre-defined inclusion and exclusion criteria were applied, 1,082 patients with FQr-MDR-TB were included in the final analysis (Figure 1). Table 1 shows the baseline characteristics of the study population. The patients had a median age of 48.0 years, and 68.5% of patients were male. The majority of the patients (60.2%) had been previously treated for TB. DM was the most common comorbidity (22.2%), and two patients (0.2%) had HIV infection. The median number of resistant drugs, including INH and RIF, was 8.0 (IQR, 5.0 to 10.0), and one-fourth of the patients had resistance to SLIDs. The median treatment duration of all patients and patients with treatment success was 695 days (IQR, 364 to 874) and 755 days (IQR, 626 to 943), respectively.

2. Treatment outcome

The treatment outcomes of patients with FQr-MDR-TB at treatment completion are summarized in Table 2. The overall treatment success rate was 69.7% (n=754). Other treatment outcomes were as follows: death (13.7%; n=148), lost to follow-up or not evaluated (12.8%; n=138), and treatment failure (3.9%; n=42). An analysis of the annual trends in treatment outcomes of all patients showed an increasing trend in the treatment success rates and a decreasing trend in the proportions of patients lost to follow-up or not evaluated. Among all deaths, non-TB-related deaths increased by the year. An additional 46 deaths occurred within 12

Table 4. Comparison of patients with treatment success and patients who died

Variable	Treatment success (n=732)	Death* (n=194)	p-value
Age, yr			<0.001
≤24	66 (9.0)	1 (0.5)	
25–34	153 (20.9)	11 (5.7)	
35–44	146 (20.0)	15 (7.7)	
45–54	164 (22.4)	44 (22.7)	
55–64	121 (16.5)	43 (22.2)	
65–74	51 (7.0)	40 (20.6)	
≥75	31 (4.2)	40 (20.6)	
Male sex	479 (65.4)	140 (72.2)	0.077
Previous treatment history of TB			0.010
New	320 (43.7)	65 (33.5)	
Previously treated	412 (56.3)	129 (66.5)	
Sputum AFB smear, positive	433 (59.2)	130 (67.0)	0.046
Comorbidities			
Diabetes mellitus	126 (17.2)	68 (35.1)	<0.001
Malignancy	6 (0.8)	13 (6.7)	<0.001
Number of resistant drugs[†]			0.024
≤4	136 (18.6)	45 (23.2)	
5–7	180 (24.6)	56 (28.9)	
8–10	279 (38.1)	51 (26.3)	
≥11	137 (18.7)	42 (21.7)	
Resistance to second-line injectable drugs	170 (23.2)	52 (26.8)	0.299

Values are presented as number (%).
*Sum of tuberculosis-related and non-tuberculosis-related deaths during treatment and within 12 months after treatment completion.
[†]Including isoniazid and rifampin.
TB: tuberculosis; AFB: acid-fast bacilli.

months after treatment completion. Thus, a total of 194 patients who died were included in the comparisons of treatment outcomes.

A comparison of patients with treatment success and those with unfavorable outcomes showed a higher proportion of old age, male sex, prior TB treatment, DM, and malignancy in the latter group (Table 3). In a comparison of patients with treatment success and those

Table 5. Association of anti-tuberculosis drug use with treatment success and death in patients with fluoroquinolone-resistant multidrug-resistant tuberculosis

	Variable		Propensity-score-matched multivariate logistic regression		
			No. of pairs	Adjusted OR (95% CI)	p-value
Bedaquiline	Susceptible strain[‡]	Success*	295	2.58 (1.23–5.44)	0.013
		Death[†]	276	1.36 (0.66–2.82)	0.406
Linezolid	Susceptible strain[‡]	Success	430	4.46 (2.25–8.84)	<0.001
		Death	440	0.89 (0.52–1.53)	0.664
Levofloxacin	Susceptible strain	Success	171	3.72 (1.53–9.04)	0.004
		Death	190	0.37 (0.15–0.91)	0.031
Moxifloxacin	Susceptible strain	Success	218	1.94 (0.91–4.13)	0.085
		Death	215	0.80 (0.37–1.72)	0.564
	Resistant strain	Success	448	1.76 (1.07–2.91)	0.026
		Death	429	1.09 (0.65–1.85)	0.738
Cycloserine	Susceptible strain	Success	316	4.12 (2.31–7.34)	<0.001
		Death	301	0.43 (0.24–0.78)	0.005
Delamanid	Susceptible strain[‡]	Success	204	1.26 (0.53–2.95)	0.603
		Death	206	1.67 (0.71–3.92)	0.240
Ethambutol	Susceptible strain	Success	165	3.40 (1.58–7.28)	0.002
		Death	151	0.31 (0.13–0.73)	0.007
	Resistant strain	Success	421	0.98 (0.57–1.66)	0.932
		Death	406	0.73 (0.41–1.32)	0.299
Pyrazinamide	Susceptible strain	Success	222	2.82 (1.47–5.41)	0.002
		Death	206	0.61 (0.32–1.17)	0.134
	Resistant strain	Success	310	1.32 (0.72–2.43)	0.369
		Death	309	0.53 (0.28–1.01)	0.055
Streptomycin	Susceptible strain	Success	238	1.79 (0.87–3.66)	0.112
		Death	232	0.62 (0.29–1.35)	0.231
Amikacin	Susceptible strain	Success	238	1.86 (0.82–4.22)	0.136
		Death	246	1.80 (0.87–3.74)	0.116
Kanamycin	Susceptible strain	Success	404	3.68 (2.00–6.77)	<0.001
		Death	395	0.64 (0.37–1.12)	0.116
Prothionamide	Susceptible strain	Success	328	3.85 (2.20–6.73)	<0.001
		Death	310	0.47 (0.26–0.85)	0.012
Para-aminosalicylic acid	Susceptible strain	Success	433	1.91 (1.15–3.15)	0.012
		Death	413	0.78 (0.46–1.34)	0.372

*The comparator was an unfavorable outcome (sum of treatment failure, loss to follow-up, and not evaluated). [†]Sum of tuberculosis-related and non-tuberculosis-related deaths during treatment and within 12 months after treatment completion; comparator was treatment success. [‡]Probable susceptible strain; isolates before 2016 and 2017 were assumed to be susceptible to linezolid and bedaquiline, respectively, and all isolates were assumed to be susceptible to delamanid.
OR: odds ratio; CI: confidence interval.

who died, similar results were obtained for the latter group, except for sex; the sputum AFB smear positivity rate was higher among patients who died (Table 4).

3. Impact of anti-TB drug use on the treatment outcome

In a univariate analysis of the association of drug use with treatment success (vs. unfavorable outcomes), all drugs except OFX and MPM were associated with higher treatment success rates in patients infected with susceptible strains. Among patients with infections caused by resistant strains, no drug was associated with treatment success except MFX (Supplementary Table S1). In a univariate analysis of the association of drug use with death (vs. treatment success), treatment with LFX, MFX, CS, EMB, PZA, SM, KM, PTO, and PAS for susceptible strains and treatment with EMB and PZA for resistant strains were associated with lower mortality (Supplementary Table S2).

Table 5 shows the results of the PSM multivariate logistic regression analysis of the impact of anti-TB drug use on the treatment outcome. The use of BDQ, LZD, LFX, CS, EMB, PZA, KM, PTO, and PAS against susceptible strains, and the use of MFX against resistant strains increased the treatment success rate (vs. unfavorable outcomes). In terms of death (vs. treatment success), the use of LFX, CS, EMB, and PTO against susceptible strains resulted in lower mortality.

Discussion

In this study, most drugs used against susceptible strains were associated with better outcomes in terms of increased treatment success and decreased mortality. This finding is in line with that of a meta-analysis of patients with RR/MDR-TB[4], and it highlights the importance of DST-guided regimen selection for treating FQr-MDR-TB. Thus, DSTs should be expanded to include not only core anti-TB drugs but also the companion drugs used to treat FQr-MDR-TB. Compared with the treatment outcomes of patients with FQ-susceptible MDR-TB in previous South Korean studies, the treatment outcomes of patients with FQr-MDR-TB in our study were poorer[17,18]. This result demonstrates both the importance of FQs as core anti-TB drugs and the need for rapid detection of FQ resistance.

Not surprisingly, BDQ use and LZD use were associated with increased treatment success in patients with FQr-MDR-TB. However, these drugs did not affect mortality. Although this result may reflect the unique characteristics of FQr-MDR-TB patients or non-TB-related death after treatment completion, it was assumed

that more severe disease in patients treated with BDQ and LZD would in turn increase the mortality. During the study period, BDQ use and LZD use in South Korea were authorized only for patients who could not be treated with conventional anti-TB drugs (e.g., due to high-level resistance). Also, the patients in our cohort who were treated with BDQ were older and had TB that was resistant to a larger number of drugs than patients who did not receive BDQ (Supplementary Table S3). Even if we apply the PSM method to maintain balance between the groups that were given and not given a drug, unmeasured confounders may remain. For example, old age was an independent predictor of more deaths in the group that used BDQ, LZD, DLM, and MFX compared with the group that was not given these drugs (data not shown). However, DLM, another new anti-TB drug, was not associated with treatment success or death. Like BDQ, severe TB in patients treated with DLM might have affected the analysis. The clinical decision to use DLM for FQr-MDR-TB patients may be influenced by disease severity, as indicated by the total number of resistant drugs. For example, DLM was probably administered to patients with high resistance to other drugs (Supplementary Table S3). Similar trends would likely be seen in patients treated with BDQ and LZD. Patients who were resistant to more than nine drugs were likely to be treated with BDQ, LZD, and DLM (Supplementary Table S3). Although we tried to reduce confounding using several statistical methods, these factors may nevertheless have affected the analysis. In a previous study conducted in South Korea that included 131 patients with FQr-MDR-TB, there was no difference in the treatment success rates between the BDQ and DLM groups[19]. The role of DLM in treating FQr-MDR-TB should be further investigated. First-line (e.g., EMB and PZA) and companion second-line (e.g., CS, PTO, and PAS) anti-TB drugs known to have weak or modest efficacies against RR/MDR-TB were beneficial in our study. This may be because these drugs are more efficacious under a "weak" treatment regimen, i.e., in the absence of FQs, a group of strong core anti-TB drugs, as the latter were excluded.

Since the revision of the WHO's guidelines in 2018, SLIDs are no longer considered core anti-TB drugs for treating RR/MDR-TB[20]. This recommendation was mainly based on the side effects, adherence rate, and limited efficacies of SLIDs. However, given their excellent bactericidal activities and their ability to prevent resistance, SLIDs may be beneficial in FQr-MDR-TB patients with limited treatment options. In a previous study, acquired BDQ resistance during treatment was less frequent in patients with FQr-MDR-TB when

SLIDs were included in the regimen[21]. In a recent meta-analysis of individual patient data on SLIDs, SM or AMK use was associated with higher rates of cure in patients with FQr-MDR-TB, whereas neither KM nor capreomycin had any meaningful impact[22]. In our study, among SLIDs, only KM was associated with increased treatment success. Whether this result was due to the characteristics of the patients included in our cohort or due to other factors still remains to be determined. Interestingly, in our patients, the use of LFX against a susceptible strain was associated with increased treatment success and decreased mortality. We speculate that these results might be attributed to OFX-resistant and LFX/MFX-susceptible patients. Although there is controversy regarding the impact of using later-generation FQs in cases where there is a discrepancy in DST results between OFX and LFX/MFX and how it may affect the treatment outcomes[23,24], our results support the use of later-generation FQs against susceptible strains in patients with FQr-MDR-TB. However, in the absence of clear evidence on the efficacy of FQs for treating FQr-MDR-TB, FQs should be used with caution and should not be considered "effective" in patients with FQr-MDR-TB. The use of MFX against resistant strains was also associated with a higher treatment success rate. Low-level MFX resistance and the use of high-dose MFX might have affected the results, but this could not be investigated in our cohort.

The efficacy of an anti-TB drug and DST results are the most important considerations in the choice of a treatment regimen. However, phenotypic DST for several companion drugs may not be reliable and reproducible[1]. Therefore, clinical decision-making should be based on both the DST results and previous treatment history to ensure that effective treatment regimens are prescribed, as well as on factors, such as the severity and site of the disease, comorbidities, risk of adverse events, drug interactions, and patient preference[1]. In our study, the proportion of patients treated successfully increased, while the rates of loss to follow-up and non-evaluation decreased over the study period. In addition to the introduction and widespread use of rapid diagnostic tests for drug-resistant TB, as well as new and repurposed anti-TB drugs, advances in the national TB program (e.g., the implementation of a public–private mix program) might be a factor responsible for the positive outcomes of FQr-MDR-TB patients[7,17,18]. Nevertheless, the rate of patients lost to follow-up was still high and non-TB-related deaths showed an increasing trend. These results emphasize the importance of a comprehensive approach in patients with FQr-MDR-TB, as this population is more vulnerable than those with FQ-susceptible MDR-TB. In addition, while clinicians should monitor the therapy and disease course, patients should be supported by health education, socioeconomic support, emotional/psychosocial assistance, palliative care, and management of adverse drug reactions, all of which would improve treatment adherence[25]. Although these elements are essential components of patient-centered care, they are ignored by many national TB programs.

This study had several limitations. First, it was conducted only in South Korea and almost all patients included were HIV negative. Thus, the results may not be generalizable globally. Second, clinical factors affecting the treatment outcomes of TB patients were not fully investigated. The presence of a cavity, disease extent, body mass index, and nutritional status are well-known factors affecting the outcomes. These factors and other residual confounding factors might have influenced the results. Third, patient adherence to anti-TB drugs could not be considered, which may have caused bias in determining an "effective" anti-TB drug. Fourth, non-TB-related death or death after treatment completion might not be associated with the use of an anti-TB drug. However, we followed the definitions and analytical methods that are commonly used globally. Finally, the impact of clofazimine, another important anti-TB drug in the revised guidelines, was not evaluated because of the small number of patients treated accordingly.

In conclusion, DST-guided regimen selection is important in treating patients with pulmonary FQr-MDR-TB. In addition to core anti-TB drugs, such as BDQ and LZD, the use of later-generation FQs and KM against susceptible strains may be beneficial for patients with limited treatment options. Additional studies are warranted to obtain additional evidence on the efficacies of anti-TB drugs and regimens for treating FQr-MDR-TB, a hard-to-treat disease.

Authors' Contributions

Conceptualization: Choi H, Kim HS, Mok J. Methodology: Choi H, Kim HS, Mok J. Formal analysis: Choi H, Jeong D, Kang YA, Jeon D, Kang HY, Kim HJ, Kim HS, Mok J. Data curation: Choi H, Jeong D, Kang HY, Kim HS. Writing - original draft preparation: Choi H, Mok J. Writing - review and editing: Choi H, Jeong D, Kang YA, Jeon D, Kang HY, Kim HJ, Kim HS, Mok J. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article

was reported.

Acknowledgments

Funding

Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Univariate analysis of the association of each anti-tuberculosis drug use with treatment success.

Supplementary Table S2. Univariate analysis of the association of each anti-tuberculosis drug use with death.

Supplementary Table S3. Numbers of resistant drugs and the association of the use of each drug with the number of resistant drugs.

References

1. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment. Drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020.
2. World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization; 2021.
3. Nathanson E, Nunn P, Uplekar M, Floyd K, Jaramillo E, Lonnroth K, et al. MDR tuberculosis: critical steps for prevention and control. N Engl J Med 2010;363:1050-8.
4. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018;392:821-34.
5. Van Deun A, Decroo T, Piubello A, de Jong BC, Lynen L, Rieder HL. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. Int J Tuberc Lung Dis 2018;22:239-45.
6. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J 2013;42:156-68.
7. Lee M, Han J, Kim YR, Kwak N, Kim JH, Park O, et al. Multidrug-resistant tuberculosis in South Korea: a retrospective analysis of national registry data in 2011-2015. Int J Tuberc Lung Dis 2019;23:850-7.
8. Lee T, Lee SJ, Jeon D, Lee HY, Kim HJ, Kang BH, et al. Additional drug resistance in patients with multidrug-resistant tuberculosis in Korea: a multicenter study from 2010 to 2019. J Korean Med Sci 2021;36:e174.
9. World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020.
10. Korea Disease Control and Prevention Agency. Annual report on the notified tuberculosis in Korea, 2021 [Internet]. Cheongju: KDCA; 2019 [cited 2023 Jun 12]. Available from: https://tbzero.kdca.go.kr/tbzero/board/boardView.do?leftMenuId=3&paramMenuId=34&boardSeq=7528&crudType=R.
11. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018.
12. Jeong D, Kang HY, Kim J, Lee H, Yoo BN, Kim HS, et al. Cohort profile: Korean tuberculosis and post-tuberculosis cohort constructed by linking the Korean National Tuberculosis Surveillance System and National Health Information Database. J Prev Med Public Health 2022;55:253-62.
13. World Health Organization. Definitions and reporting framework for tuberculosis: 2013 revision. Geneva: World Health Organization; 2013.
14. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011.
15. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014.
16. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016.
17. Kwak N, Kim HR, Yoo CG, Kim YW, Han SK, Yim JJ. Multidrug-resistant tuberculosis over 20 years at a referral hospital in South Korea: trends and outcomes. Int J Tuberc Lung Dis 2019;23:174-80.
18. Kang Y, Jo EJ, Eom JS, Kim MH, Lee K, Kim KU, et al. Treatment outcomes of patients with multidrug-resistant tuberculosis: comparison of pre- and post-public-private

mix periods. Tuberc Respir Dis (Seoul) 2021;84:74-83.

19. Hwang H, Kang H, Kwon YS, Jeon D, Shim TS, Yim JJ. Outcomes of multidrug-resistant tuberculosis treated with bedaquiline or delamanid. Clin Infect Dis 2021;73:1362-9.

20. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019.

21. Tahseen S, Van Deun A, de Jong BC, Decroo T. Second-line injectable drugs for rifampicin-resistant tuberculosis: better the devil we know? J Antimicrob Chemother 2021;76:831-5.

22. Cegielski JP, Chan PC, Lan Z, Udwadia ZF, Viiklepp P, Yim JJ, et al. Aminoglycosides and capreomycin in the treatment of multidrug-resistant tuberculosis: individual patient data meta-analysis of 12 030 patients from 25 countries, 2009-2016. Clin Infect Dis 2021;73:e3929-36.

23. Lee H, Ahn S, Hwang NY, Jeon K, Kwon OJ, Huh HJ, et al. Limited effect of later-generation fluoroquinolones in the treatment of ofloxacin-resistant and moxifloxacin-susceptible multidrug-resistant tuberculosis. Antimicrob Agents Chemother 2018;62:e01784-17.

24. Jo KW, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2014;18:39-43.

25. World Health Organization. Framework for the engagement of all health care providers in the management of drug resistant tuberculosis. Geneva: World Health Organization; 2015.