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Outcomes of pulmonary MDR-TB: impacts of fluoroquinolone resistance and linezolid treatment

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Objectives: Fluoroquinolones (FQs) are the most important second-line drugs for MDR-TB treatment. Therapeutic options for FQ-resistant (FQ-R) MDR/XDR-TB are very limited. The purpose of the present study was to determine treatment outcomes and risk factors associated with unfavourable outcomes of MDR/XDR-TB, focusing on the impacts of FQ-R status and linezolid treatment.

Methods: This was a retrospective cohort study of 337 MDR-TB patients, including 144 (42.7%) FQ-R MDR/XDR-TB cases. Treatment outcomes were evaluated according to WHO 2013 recommendations.

Results: Later-generation FQs such as levofloxacin or moxifloxacin were given to 331 (98.2%) patients. Overall, favourable outcomes were achieved in 272 (80.7%) patients. FQ-R second-line injectable drug-susceptible MDR [adjusted OR (aOR) 4.299, 95% CI 1.239–14.916, $P=0.015$] and XDR status (aOR 6.294, 95% CI 1.204–32.909, $P=0.024$) were independently associated with unfavourable outcomes. However, FQ-susceptible (FQ-S) second-line injectable drug-resistant MDR status was not associated with unfavourable outcomes (aOR 1.814, 95% CI 0.314–10.485, $P=0.999$). Favourable treatment outcomes were more frequent in FQ-R MDR/XDR-TB patients who received linezolid (82.8%) compared with those who did not receive linezolid (58.1%, $P=0.002$). When FQ-R MDR/XDR-TB treatment without linezolid was used as a reference, the addition of linezolid was associated with favourable outcomes (aOR 4.081, 95% CI 1.237–13.460, $P=0.017$), comparable to those for FQ-S MDR-TB (aOR 4.341, 95% CI 1.470–12.822, $P=0.005$).

Conclusions: Later-generation FQs could improve treatment outcomes of patients with MDR-TB. Linezolid should be considered for inclusion in FQ-R MDR/XDR-TB treatment regimens.

Introduction

Globally, 3.5% of new cases and 20.5% of previously treated cases of TB are MDR, which is defined as having resistance to both rifampin and isoniazid.[1] In addition, XDR-TB, which is defined as MDR-TB with additional resistance to any fluoroquinolone (FQ) and at least one second-line injectable drug (SLID; kanamycin, amikacin or capreomycin), represents an average of 9.0% of MDR-TB cases.[1] Treatment outcomes are poor for MDR-TB compared with drug-susceptible TB and are substantially poorer for XDR-TB.[2–6] According to a meta-analysis of individual patient data, the frequency of treatment success is only ~60% for MDR-TB and 40% for XDR-TB.[7–9]

One of the major problems with MDR-TB treatment is the limited availability of effective drugs.[10,11] Current WHO treatment guidelines for MDR-TB recommend the use of pyrazinamide along with at least four second-line TB medications, including a later-generation FQ (levofloxacin or moxifloxacin).[12] Although FQs are the most important second-line drugs for MDR-TB treatment,[7,8] information regarding the clinical efficacy of later-generation FQs in the treatment of MDR-TB is very limited.[13]

In patients with FQ-resistant (FQ-R) MDR-TB, including XDR-TB, the development of a treatment regimen of four effective second-line drugs is very difficult, and it is often necessary to include WHO group-5 drugs such as clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin or imipenem.[14,15] Although many WHO group-5 drugs have uncertain activity against TB, linezolid has great promise for the treatment of MDR-TB. Recent meta-analyses and one randomized controlled trial suggest that linezolid has efficacy in the treatment of FQ-R MDR-TB and

even chronic XDR-TB, although the frequency of adverse effects was high and the optimal dose and duration were uncertain.[15–18]

We previously reported treatment outcomes of a cohort of MDR/XDR-TB patients who were diagnosed between 1995 and 2004.[19] In our institution, linezolid has been used since 2005 for the treatment of MDR/XDR-TB.[20–22] The purpose of the present study was to determine the treatment outcomes and risk factors associated with unfavourable outcomes in our most recent cohort of MDR/XDR-TB patients, focusing on the impact of FQ-R and linezolid on treatment outcomes.

Patients and methods

Study populations

The study cohort consisted of 406 consecutive MDR-TB patients who were treated between January 2005 and December 2011 at Samsung Medical Center, a 1961 bed referral hospital in Seoul, Korea. Of these patients, 69 were excluded for the following reasons: (i) 37 were transferred to our hospital after negative conversion of sputum culture with >3 months of treatment with second-line drugs; (ii) 25 were transferred to a national TB hospital after <3 months of treatment in our hospital; and (iii) 7 were treated for extra-pulmonary MDR-TB. Thus, 337 patients with pulmonary MDR-TB were eligible for this study.

This study was approved by the Institutional Review Board of Samsung Medical Center for the review and publication of information obtained from patient records (IRB number 2014-03-007). Informed consent was waived because of the retrospective nature of this study, and patient information was anonymized and de-identified prior to analysis.

Drug susceptibility testing (DST) and management of MDR-TB

DST was performed using the absolute concentration method with Löwenstein–Jensen medium at the Korean Institute of Tuberculosis (Table S1, available as Supplementary data at *JAC* Online).[19] In our hospital, all first isolates of *Mycobacterium tuberculosis* in each culture-confirmed TB patient were referred for DST in the study period. DST for group-1 drugs (isoniazid, rifampin, ethambutol and pyrazinamide), group-2 drugs (streptomycin, kanamycin and capreomycin), a group-3 drug (ofloxacin) and group-4 drugs (prothionamide, cycloserine and *para*-aminosalicylic acid) was routinely performed during the study period. DST for rifabutin and moxifloxacin began in 2006 and DST for amikacin and levofloxacin was available starting in 2007 and 2009, respectively. The drugs to which isolates were susceptible were defined as effective drugs in this study. There were 20 patients with ofloxacin-susceptible MDR-TB who received moxifloxacin or levofloxacin without available DST results of moxifloxacin or levofloxacin. We considered that moxifloxacin or levofloxacin was an effective drug in these patients. DST for linezolid, amoxicillin/clavulanate or clarithromycin was not performed during the study period.

All patients were treated with individualized regimens with at least four effective drugs, in accordance with previously published WHO guidelines.[23,24] If four effective drugs were not available, WHO group-5 drugs, such as linezolid, amoxicillin/clavulanate and clarithromycin, were included in the treatment regimen. The addition of linezolid to the treatment regimen was decided by the attending physician. Treatment was given for 18–24 months, including at least 12 months after culture conversion. In general, an injectable agent was used for a minimum of 6 months and at least 4 months after culture conversion for the intensive phase treatment. Sputum smear examinations and cultures were performed monthly for the first 6 months and then at 2 to 3 month intervals until the end of treatment.[19]

Although the decision to perform surgical resection was made by the attending physicians, the general indication was MDR-TB refractory to or deemed likely to be unresponsive to medical treatment on the basis of resistance patterns. All candidates for surgery were required to have sufficient pulmonary function to tolerate resection and a localized lesion with a high bacterial burden, such as a cavity (or cavities).[19]

Treatment outcomes

Treatment outcomes were defined as cured, treatment completed, treatment failed, died, lost to follow-up and not evaluated, in accordance with the 2013 revised WHO recommendations.[25]

A patient was classified as cured if the patient completed treatment without evidence of treatment failure and three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase. Patients who completed treatment without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase were considered to have completed treatment. Treatment failure was defined as a permanent regimen change of at least two anti-TB drugs because of: (i) lack of conversion by the end of the intensive phase; (ii) bacteriological reversion in the continuation phase after conversion to negative; (iii) evidence of additional acquired resistance to FQs or SLIDs; or (iv) adverse drug reactions. If a case was classified as treatment failed and a different treatment regimen was started, the patient was re-entered in the MDR-TB cohort under a new cohort number and patient category [$n=13$; permanent regimen change of at least two anti-TB drugs because of lack of conversion by the end of the intensive phase ($n=9$), culture reversion in the continuation phase ($n=3$) or additional acquired resistance to FQs ($n=1$)].[25–27] Cure and treatment completion were considered favourable outcomes, whereas other outcome classifications were considered unfavourable.

Statistical analyses

Continuous variables are presented as median and IQR and compared using the Mann–Whitney *U*-test or the Kruskal–Wallis test. Categorical variables are presented as numbers (percentages) and compared using Pearson's χ^2 test or Fisher's exact test. If there were multiple comparisons, we corrected the *P* value and CI using the Bonferroni method.

To evaluate the effect of resistance to FQs and to SLIDs on the treatment of MDR-TB patients, outcomes were evaluated according to the resistance patterns after adjustment for potential confounding factors using multiple logistic regression models. In addition, to evaluate the influences of FQ susceptibility and linezolid on treatment outcomes in patients with FQ-R MDR-TB, we used FQ-R MDR-TB patients who did not receive linezolid as a reference in multiple logistic regression models in which a favourable outcome was the outcome variable of interest, with adjustment for potential confounding factors such as demographics, disease severity and treatment modalities. All tests were two-sided and a *P* value of <0.05 was considered significant. The data were analysed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The baseline characteristics of patients with MDR-TB are presented in Table 1. Of 337 patients, 181 (53.7%) were male and the median age was 34 years (IQR, 28–46 years). None of the patients was positive for HIV infection. One hundred and fifty-one (44.8%) patients had received previous treatment with second-line drug regimens for MDR-TB. Positive sputum smear results and cavitary disease on chest radiography were observed in 209 (62.0%) and 167 (49.6%) patients, respectively.

Table 1. Baseline characteristics of 337 patients with MDR-TB

Characteristic	No. (%) or median (IQR)
Age, years	34 (28–46)
Sex, male	181 (53.7)
BMI, kg/m^2	20.5 (18.8–22.6)
Current smoker	47 (13.9)
Alcoholic	33 (9.8)
Comorbid condition	
diabetes mellitus	44 (13.1)
chronic liver disease	20 (5.9)
chronic heart disease	7 (2.1)
malignancy	6 (1.8)
neurological disease	3 (0.9)
Previous treatment history	
none	44 (13.1)
first-line drugs only	142 (42.1)
second-line drugs	151 (44.8)
Positive sputum smear	209 (62.0)
Radiographic findings	
cavitary disease	167 (49.6)
bilateral disease	149 (44.2)
Drug resistance patterns	
FQ-S SLID-S MDR-TB	170 (50.4)
FQ-S SLID-R MDR-TB	23 (6.8)
FQ-R SLID-S MDR-TB	96 (28.5)
XDR-TB	48 (14.2)

The prevalence of drug resistance at the time of treatment initiation was high (Table S2). The isolates were resistant to a median of 6 drugs (IQR, 4–8 drugs). Based on DST results for FQs and SLIDs, 170 (50.4%) patients had FQ-susceptible (FQ-S) SLID-susceptible (SLID-S) MDR-TB, 23 (6.8%) had FQ-S SLID-resistant (SLID-R) MDR-TB, 96 (28.5%) had FQ-R SLID-S MDR-TB and 48 (14.2%) had XDR-TB. Thus, 144 (42.7%) patients had FQ-R MDR-TB (including XDR-TB).

Treatment modalities

The median treatment duration was 23.1 months (IQR, 18.1–24.2 months). Patients received a median of 6 drugs (IQR, 5–7 drugs) (for details of treatment modalities see Table S3). The median number of effective drugs was 4 (IQR, 3–5 drugs). Injectable agents were administered to 302 (89.6%) patients for a median duration of 7.0 months (IQR, 5.9–11.1 months). FQs were given to 331 (98.2%) patients. Levofloxacin or moxifloxacin was given to 139 (96.5%) of the 144 patients with FQ-R MDR-TB. Ofloxacin was not used during the study period. Linezolid was administered to 62 patients, including 1.8% (3/170) of patients with FQ-S SLID-S MDR-TB, 4.3% (1/23) of patients with FQ-S SLID-R MDR-TB, 29.2% (28/96) of patients with FQ-R SLID-S MDR-TB and 62.5% (30/48) of patients with XDR-TB, for a median of 14.2 months (IQR, 5.9–22.8 months). The dosage of linezolid used was as follows: 53 (85.5%) patients were treated with 300 mg/day; 7 (11.3%) were given 600 mg/day; and 2 (3.2%) were initially administered 600 mg/day, which was subsequently lowered to 300 mg/day. Five patients received bedaquiline for 24 weeks during a clinical trial (ClinicalTrials.gov identifier NCT00980811) and six patients received delamanid for 8 weeks during another clinical trial.[28]

Surgical resection was performed in 60 patients (17.8%), including wedge resection ($n=1$), segmentectomy ($n=9$), lobectomy ($n=26$), lobectomy plus segmentectomy ($n=10$) and pneumonectomy ($n=14$), after a median of 4.2 months (IQR 2.9–8.8 months) of second-line drug treatment. Of these 60 patients, 42 (70.0%) underwent surgery during the intensive phase of their initial MDR-TB treatment.

Treatment outcomes

Favourable outcomes were achieved in 272 (80.7%) patients (Table 2). Treatment outcomes differed significantly according to drug resistance patterns. A favourable outcome was less frequent in patients with FQ-R SLID-S MDR-TB (67.7%, $P<0.001$) and those with XDR-TB (68.8%, $P<0.001$) compared with those with FQ-S SLID-S MDR-TB (90.6%). However, the favourable outcomes in patients with FQ-S SLID-R MDR-TB (87.0%) did not differ from those of patients with FQ-S SLID-S MDR-TB ($P=0.999$).

Baseline characteristics, disease severity, drug resistance patterns and treatment modalities were compared according to treatment outcomes. In univariable analysis, unfavourable outcomes were associated with older age, diabetes mellitus, previous TB treatment, positive sputum smear and cavitary disease. Patients with favourable outcomes received a greater number of effective drugs (Table S4).

Association of treatment outcomes with resistance patterns and linezolid treatment

The results of multivariable analyses assessing the effects of FQ and SLID resistance on MDR-TB treatment outcomes using logistic regression models are presented in Table 3. Whereas FQ-S SLID-R was not associated with unfavourable outcomes [adjusted OR (aOR) 1.814, 95% CI 0.314–10.485, $P=0.999$], FQ-R SILD-S was independently associated with unfavourable outcomes after adjustment for potential confounding factors (aOR 4.299, 95% CI 1.239–14.916, $P=0.015$). Furthermore, XDR-TB was significantly associated with unfavourable outcomes after adjustment for potential confounding factors (aOR 6.294, 95% CI 1.204–32.909, $P=0.024$).

To evaluate the effect of linezolid on the outcomes of patients with FQ-R MDR-TB, including XDR-TB, we divided our cohort into three groups: FQ-S MDR-TB, FQ-R MDR-TB with linezolid treatment and FQ-R MDR-TB without linezolid treatment. Compared with patients with FQ-S MDR-TB, patients with FQ-R MDR-TB who did or did not receive linezolid treatment were more likely to have a previous treatment history for TB, sputum smear positivity, cavitary disease and bilateral disease (Table 4). Although patients with FQ-R MDR-TB had a longer duration of the intensive phase and more frequent surgical resections, the number of effective drugs was lower than for those with FQ-S MDR-TB. Compared with FQ-S MDR-TB patients (90.2%), favourable treatment outcomes were less frequent in FQ-R MDR-TB patients who did not

Table 2. Treatment outcomes of 337 patients with MDR-TB

	FQ-S SLID-S MDR-TB ($n=170$)	FQ-S SLID-R MDR-TB ($n=23$)	FQ-R SLID-S MDR-TB ($n=96$)	XDR-TB ($n=48$)	Total MDR-TB cases ($n=337$)
Favourable outcomes	154 (90.6)	20 (87.0)	65 (67.7)	33 (68.8)	272 (80.7)
cured	142 (83.5)	19 (82.6)	61 (63.5)	31 (64.6)	253 (75.1)
treatment completed	12 (7.1)	1 (4.3)	4 (4.2)	2 (4.2)	19 (5.6)
Unfavourable outcomes	16 (9.4)	3 (13.0)	31 (32.3)	15 (31.3)	65 (19.3)
treatment failed	2 (1.2)	0	10 (10.4)	3 (6.3)	15 (4.5)
died	1 (0.6)	0	2 (2.1)	2 (4.2)	5 (1.5)
lost to follow-up	8 (4.7)	2 (8.7)	9 (9.4)	4 (8.3)	23 (6.8)
not evaluated	5 (2.9)	1 (4.3)	10 (10.4)	6 (12.5)	22 (6.5)

Table 3. Association of SLID and FQ resistance patterns with unfavourable outcomes after adjustment for potential confounding factors

		Univariate			Multivariate[b]		
	Unfavourable outcome[a]	OR	95% CI	*P* value	aOR	95% CI	*P* value
FQ-S SLID-S MDR-TB	16/170 (9.4)	1.000	reference		1.000	reference	
FQ-S SLID-R MDR-TB	3/23 (13.0)	1.444	0.290–7.188	0.999	1.814	0.314–10.485	0.999
FQ-R SLID-S MDR-TB	31/96 (32.3)	4.590	2.032–10.372	<0.001	4.299	1.239–14.916	0.015
XDR-TB	15/48 (31.3)	4.375	1.655–11.568	<0.001	6.294	1.204–32.909	0.024

[a]Includes treatment failed, died, lost to follow-up and not evaluated.
[b]Adjusted for demographics [age, sex, BMI, current smoker, alcoholic, comorbidities (diabetes and chronic liver disease) and previous history of TB treatment], disease severity (positive sputum smear, cavitary disease and bilateral disease) and treatment details [individual drugs used for >3 months (rifabutin, ethambutol, pyrazinamide, injectable drugs, FQs, prothionamide, cycloserine, *para*-aminosalicylic acid and linezolid), number of effective drugs included in the treatment regimen and surgical resection].

receive linezolid (58.1%, $P<0.001$), but they were not different for FQ-R MDR-TB patients who received linezolid (82.8%, $P=0.245$).

The results of multivariable analyses assessing the effects of FQ susceptibility and linezolid on favourable outcomes in patients with FQ-R MDR-TB are presented in Table 5. Linezolid treatment in FQ-R MDR-TB patients was associated with a favourable outcome in crude analyses (OR 3.456, 95% CI 1.377–8.675, $P=0.005$), which was comparable to the probability of a favourable outcome in FQ-S MDR-TB patients (OR 6.594, 95% CI 3.177–13.686, $P<0.001$). After adjusting for confounding variables, such as demographics, disease severity and treatment modalities, linezolid treatment for FQ-R MDR-TB patients was still significantly associated with favourable outcomes (aOR 4.081, 95% CI 1.237–13.460, $P=0.017$), comparable to the probability of a favourable outcome in FQ-S MDR-TB patients (aOR 4.341, 95% CI 1.470–12.822, $P=0.005$).

Discussion

The treatment of MDR-TB is difficult and generally has poor outcomes. Although FQs are the most important second-line anti-TB drugs for MDR-TB treatment, the incidence of FQ-R MDR-TB has increased in many countries.[29] Therapeutic options for FQ-R MDR/XDR-TB are very limited.[10,11] In this study, we found that FQ-S MDR-TB could be successfully treated with currently WHO-recommended antibiotic regimens.[12] Treatment success was high in patients with FQ-S SLID-S MDR-TB (90.6%) or FQ-S SLID-R MDR-TB (87.0%) and low in patients with FQ-R SLID-S MDR-TB (67.7%) or XDR-TB (68.8%). In addition, linezolid increased treatment success in patients with FQ-R MDR/XDR-TB (82.8%) compared with those treated without linezolid (58.1%).

We found that >90% of FQ-S SLID-S MDR-TB patients experienced treatment success. In this cohort, all patients were treated with individualized regimens in accordance with previously published WHO guidelines.[23,24] The regimens typically included at least four effective drugs, including first-line drugs, an injectable agent, a later-generation FQ and then any agent with documented bacteriostatic activity such as prothionamide, cycloserine or *para*-aminosalicylic acid.[30] Current WHO guidelines for the management of MDR-TB recommend that all patients with MDR-TB be treated with later-generation FQs, such as levofloxacin or moxifloxacin, rather than an earlier-generation FQ, such as ofloxacin.[12] However, limited information was provided regarding the clinical efficacy of later-generation FQs in the treatment of MDR-TB.[13] The frequency of treatment success in our cohort was higher than the 64% reported in an individual patient data meta-analysis, in which the currently recommended later-generation FQs were used in only 14% of patients.[7] In recently published studies that evaluated the efficacy of new drugs, such as bedaquiline or delamanid, later-generation FQs were used in 0%[31] or 60%–70%[28] in the background regimen for treatment of MDR-TB. Our study suggests that adherence to current WHO guidelines for the use of later-generation FQs could improve the treatment outcomes of FQ-S SLID-S MDR-TB patients.

Table 4. Comparisons of demographics, disease severity, treatment modalities and treatment outcomes for 337 MDR-TB patients according to FQ resistance and linezolid treatment

	FQ-S MDR-TB ($n=193$)[a]	FQ-R MDR-TB with linezolid[b] ($n=58$)	FQ-R MDR-TB without linezolid[c] ($n=86$)	*P* value
Demographic data				
age, years	33 (28–45)	35 (28–47)	34 (28–48)	0.907
male	105 (54.4)	27 (46.6)	49 (57.0)	0.449
BMI, kg/m^2	20.7 (19.1–22.6)	19.9 (18.4–22.6)	20.3 (18.3–22.8)	0.331
current smoker	30 (15.5)	5 (8.6)	12 (14.0)	0.410
alcoholic	17 (8.8)	5 (8.6)	11 (12.8)	0.555
comorbid condition				
diabetes	20 (10.4)	7 (12.1)	17 (19.8)	0.096
chronic liver disease	15 (7.8)	3 (5.2)	2 (2.3)	0.202
previous treatment history				<0.001
none	39 (20.2)	0	5 (5.8)	
first-line drugs only	113 (58.5)	7 (12.1)	22 (25.6)	
second-line drugs	41 (21.2)	51 (87.9)	59 (68.6)	
Disease severity				
positive sputum smear	103 (53.4)	43 (74.1)	63 (73.3)	0.001
cavitary disease	73 (37.8)	31 (53.4)	63 (73.3)	<0.001
bilateral disease	66 (34.2)	39 (67.2)	44 (51.2)	<0.001
Treatment modalities				
drug used				
rifabutin	25 (13.0)	11 (19.0)	23 (26.7)	0.019
ethambutol	64 (33.2)	8 (13.8)	28 (32.6)	0.014
pyrazinamide	106 (54.9)	9 (15.5)	30 (34.9)	<0.001
injectable drug	174 (90.2)	50 (86.2)	78 (90.7)	0.640
FQ	192 (99.5)	57 (98.3)	82 (95.3)	0.041
prothionamide	162 (83.9)	19 (32.8)	64 (74.4)	<0.001
cycloserine	184 (95.3)	42 (72.4)	80 (93.0)	<0.001
para-aminosalicylic acid	91 (47.2)	23 (39.7)	51 (59.3)	0.051
no. of drugs	6 (5–6)	6 (5–7)	6 (5–7)	<0.001
no. of effective drugs	5 (4–6)	2 (1–3)	3 (3–4)	<0.001
surgical resection	14 (7.3)	22 (37.9)	24 (27.9)	<0.001
duration of the intensive phase, months	6.1 (5.8–7.8)	10.9 (6.0–18.9)	8.6 (6.0–13.2)	<0.001
Treatment outcome				
favourable	174 (90.2)	48 (82.8)	50 (58.1)	<0.001[d]
cured	161 (83.4)	47 (81.0)	45 (52.3)	
treatment completed	13 (6.7)	1 (1.7)	5 (5.8)	
unfavourable	19 (9.8)	10 (17.2)	36 (41.9)	
treatment failed	2 (1.0)	0	13 (15.1)	
died	1 (0.5)	1 (1.7)	3 (3.5)	
lost to follow-up	10 (5.2)	2 (3.4)	11 (12.8)	
not evaluated	6 (3.1)	7 (12.1)	9 (10.5)	

[a]Four patients (2.1%) were treated with linezolid in this group.
[b]Thirty patients (51.7%) had XDR-TB.
[c]Eighteen patients (20.9%) had XDR-TB.
[d]χ^2 test comparing proportions of favourable outcomes.

In our study, FQ-R was a strong predictor of unfavourable outcomes, and this finding was consistent with previous reports that demonstrated the essential role of FQs in MDR-TB treatment.[7,8] One of the most important findings of our study is that the treatment success rate of FQ-R MDR/XDR-TB patients treated with linezolid (82.8%) was much higher than that of those treated without linezolid (58.1%), and was comparable to that observed for FQ-S MDR-TB patients (90.2%). These findings are noteworthy

Table 5. Association of linezolid treatment and favourable outcomes in patients with FQ-R MDR/XDR-TB

Model	Category	OR	95% CI	*P* value
Crude	FQ-R without linezolid	1.000	reference	
	FQ-R with linezolid	3.456	1.377–8.675	0.005
	FQ-S	6.594	3.177–13.686	<0.001
Adjusted[a,b]	FQ-R without linezolid	1.000	reference	
	FQ-R with linezolid	4.081	1.237–13.460	0.017
	FQ-S	4.341	1.470–12.822	0.005

[a]Adjusted for demographics [age, sex, BMI, current smoker, alcoholic, comorbidities (diabetes and chronic liver disease) and previous history of TB treatment], disease severity (positive sputum smear, cavitary disease and bilateral disease) and treatment details [individual drugs used for >3 months (rifabutin, ethambutol, pyrazinamide, injectable drugs, FQs, prothionamide, cycloserine and *para*-aminosalicylic acid), number of effective drugs included in the treatment regimen and surgical resection]. [b]The adjusted model had the following goodness-of-fit test result: $\chi^2=9.926$ ($P=0.270$).

because the effects of linezolid treatment persisted even after accounting for other potential confounding factors, such as demographics, disease severity and treatment modalities.

In patients with FQ-R MDR/XDR-TB, therapeutic options are very limited and group-5 drugs are often required to optimize treatment outcomes.[10–12] Linezolid has been used off-label for the treatment of FQ-R MDR/XDR-TB and appears to be the most promising group-5 drug,[15–18] whereas there does not seem to be any significant add-on benefit from the use of other group-5 drugs among FQ-R MDR/XDR-TB patients treated with linezolid.[15] Although many retrospective case series, some meta-analyses and one randomized controlled trial have suggested the efficacy of linezolid for the treatment of FQ-R MDR/XDR-TB,[32–34] the role of linezolid in an entire MDR/XDR-TB patient cohort has not yet been evaluated. In an individual patient data meta-analysis, linezolid was used in only 3% of patients with FQ-R MDR/XDR-TB.[8] Current WHO guidelines do not include a specific indication for linezolid in MDR/XDR-TB treatment and still categorize linezolid as a group-5 drug.[12] A recent European TBNET consensus statement recommended that linezolid be used as the first option among the group-5 drugs.[35] Our study demonstrates that the treatment success rates of FQ-R MDR/XDR-TB patients could be increased by adding linezolid to the treatment regimen. Therefore, we suggest that linezolid should be reclassified and actively used in FQ-R MDR/XDR-TB patients.

In 2013, the WHO revised the MDR-TB treatment outcome definitions.[25] The aim was to simplify the outcome definitions for MDR-TB cases and to make the treatment outcomes useful for patient care decision-making.[27] To our knowledge, this is the first study using these revised WHO treatment outcome definitions. It was proposed that a regimen change of at least two drugs be required to classify a case as treatment failure.[25,27] To confirm the applicability of the WHO-revised treatment outcome definitions and to make evidence-based adjustments, these new definitions should be tested in diverse settings.

This study has several limitations. First, it was performed at a single referral centre with a retrospective observational design. Second, our study was not a randomized controlled study evaluating the clinical efficacy of linezolid treatment for MDR/XDR-TB. The addition of linezolid to the treatment regimen was decided by the attending physician. Thus, there could be differences in the baseline characteristics and the severity of disease between patients who received linezolid and those who did not. Third, 11 patients received new anti-TB drugs such as delamanid for 8 weeks or bedaquiline for 24 weeks in our cohort. After exclusion of these patients, however, the main results of our study were not changed. Finally, neither DST nor drug exposure assessment was performed for linezolid in this study, making our results difficult to interpret. Although limited information is available on the correlation of results of *in vitro* testing of susceptibility to linezolid with clinical response in MDR-TB patients, patients with linezolid-resistant isolates were reported to be more likely to have an adverse clinical outcome.[36] In addition, although the optimal dosage and best dosing schedule for linezolid remain unclear,[37] our study largely used a daily linezolid dose of 300 mg to limit toxicity while preventing inadequate exposure, and favourable treatment outcomes were not different between patients who received 300 mg/day and those who received 600 mg/day of linezolid [45/53 (84.9%) versus 6/7 (85.7%), $P=1.000$]. However, lowering the dose clearly results in lower exposure to the drug,[38] which may lead to more acquired resistance to this drug. However, we could not confirm the incidence of acquired linezolid resistance in the present study.

In conclusion, this study found that FQ-R MDR/XDR-TB had poor treatment outcomes and that FQ-R was an important predictor of treatment outcomes for MDR-TB patients. The use of linezolid was associated with favourable treatment outcomes in FQ-R MDR/XDR-TB patients. Therefore, linezolid should be considered for inclusion in the treatment regimens of FQ-R MDR/XDR-TB patients until new drugs, such as bedaquiline and delamanid, become available for the programmatic management of this disease. Further studies are required for optimizing the dosage and the duration of administration of linezolid.

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Transparency declarations

None to declare.

Author contributions

Conception and design: B.-H. J., K. J. and W.-J. K. Analysis, interpretation and manuscript writing: B.-H. J., K. J. and W.-J. K. Revision of the manuscript and contribution of intellectual content: B.-H. J., K. J., H. Y. P., O J. K., K. S. L., H. K. K., Y. S. C., J. K., H. J. H., N. Y. L. and W.-J. K.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)

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