Journal of Microbiology, Immunology and Infection 57 (2024) 617—628

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Mitigating treatment failure of pulmonary pre-extensively drug-resistant tuberculosis: The role of new and repurposed drugs

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Received 2 February 2024; received in revised form 17 April 2024; accepted 18 April 2024
Available online 26 April 2024

KEYWORDS
Bedaquiline;
Clofazimine;
Carbapenem;
Linezolid;
Delamanid

Abstract *Background:* Pre-extensively drug-resistant tuberculosis (pre-XDR-TB), defined as multidrug-resistant TB (MDR-TB) with additional resistance to any fluoroquinolone (FQ) is difficult to treat. We assessed whether the use of new or repurposed drugs (bedaquiline, delamanid, linezolid, carbapenem, clofazimine, pretomanid) mitigated treatment failure of pre-XDR-TB.
Methods: MDR-TB patients managed in the Taiwan MDR-TB consortium between July 2009—December 2019 were eligible. Treatment outcomes at 30 months were assessed. Logistic regression models were constructed to investigate factors associated with treatment outcomes.
Results: 109 patients with FQ-resistant MDR-TB and 218 patients with FQ-susceptible MDR-TB were included. 60 (55.1%) patients with FQ-resistant MDR-TB and 63 (28.9%) patients with

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https://doi.org/10.1016/j.jmii.2024.04.008

FQ-susceptible MDR-TB have been treated with new or repurposed drugs ($p < 0.01$). Of the 218 patients with FQ-susceptible MDR-TB, 187 (85.8%) had treatment success, 30 (13.8%) died, no treatment failure, and 1 (0.5%) was loss-to-follow-up; of the 109 patients with FQ-resistant MDR-TB, 78 (71.6%) had treatment success, 21 (19.3%) died, 9 (8.3%) had treatment failure, and 1 (0.9%) was loss-to-follow-up ($p < 0.01$). The use of new or repurposed drugs was not associated with treatment outcomes among patients with FQ-susceptible MDR-TB. No patients with FQ-resistant MDR-TB treated with ≥2 new or repurposed drugs within 6 months of treatment initiation had treatment failure ($p = 0.03$). Patients with FQ-resistant MDR-TB treated with 1 new or repurposed drugs was more likely to have treatment failure as compared with patients not treated with new or repurposed drugs (adjOR 7.06, 95% CI 1.72—29.06).
Conclusions: Proper use of new or repurposed anti-TB drugs can mitigate treatment failure in FQ-resistant MDR-TB.

Introduction

Fluoroquinolone is a core drug for the treatment of multidrug-resistant tuberculosis (MDR-TB).[1] Pre-extensively drug-resistant TB (pre-XDR-TB), defined as MDR-TB with additional resistance to fluoroquinolone (FQ) is very difficult to treat. Studies have reported that treatment outcomes of FQ-resistant MDR-TB were worse than FQ-susceptible MDR-TB in part because of a higher proportion of treatment failure.[2] To improve treatment outcomes of MDR-TB, several new and repurposed drugs, including bedaquiline,[3,4] delamanid,[5,6] linezolid,[7,8] meropenem,[9,10] clofazimine,[11,12] and pretomanid,[13] have been increasingly used.

Treatment outcomes of MDR-TB in 1990s in Taiwan was unsatisfactory. The proportion of MDR-TB patients with treatment success was 51.2%, due to a relatively high proportion of loss-to-follow-up (29.1%) and treatment failure (10.4%).[14] To strengthen the management of MDR-TB, the Taiwan MDR-TB consortium (TMTC) funded by the Taiwan Centers for Disease Control (CDC) was established in 2007. The TMTC was a network of hospitals for the management of patients with drug-resistant TB and patients whose TB was difficult to treat due to severe adverse reactions to anti-TB drugs. The TMTC has achieved a high treatment success proportion of MDR-TB through patient-centered care.[15,16] The proportion of patients with MDR-TB enrolled in the TMTC who had treatment success was 82.4% and the proportion of patients who were lost to follow-up was relatively low (2.9%).[15] Although the proportion of treatment failure was relatively low (2.6%), it was 10.4% in patients with FQ-resistant MDR-TB.[15] The TMTC increasingly used new or repurposed anti-TB drugs for the management of MDR-TB in 2010s, especially those with additional resistance to FQ. Whether the use of new or repurposed anti-TB drugs is associated with reduced treatment failure of FQ-resistant MDR-TB in Taiwan has not been evaluated before. We assess treatment outcomes of FQ-resistant MDR-TB managed by the TMTC and report findings of the assessment.

Methods

The study has been approved by the joint Institution Review Board of Taipei Medical University (N202006053).

The primary exposure of interest was new and repurposed anti-TB drugs, such as bedaquiline, delamanid, linezolid, imipenem, meropenem, clofazimine, and combined use of these drugs, in addition to other second line drugs, in the treatment of MDR-TB. Pretomanid has not yet been used during the study period. We hypothesized that the use of new or repurposed anti-TB drugs was associated with reduced risk of treatment failure of FQ-resistant MDR-TB. Therefore, there may not be significant difference in treatment failure between FQ-resistant MDR-TB and FQ-susceptible MDR-TB. We thus included two patients with FQ-susceptible MDR-TB as a comparison group for each patient with FQ-resistant MDR-TB matching on susceptibility to second line injectable agents (amikacin, kanamycin, capreomycin).

All patients with FQ-resistant MDR-TB who were managed in the TMTC between July 2009—December 2019 were eligible for this study, excluding those who (1) had been treated for 3 or more months for their current episode of MDR-TB before being referred to the TMTC, (2) were under 20 years old, (3) were treated with only first-line drugs, or (4) had sole extrapulmonary TB. For each patient with FQ-resistant MDR-TB, two patients with FQ-susceptible MDR-TB were selected as a comparison group. We applied systematic sampling approach for the selection of comparison group at each management group. We selected one FQ-susceptible MDR-TB patient enrolled in the same management group of TMTC right before the FQ-resistant MDR-TB patient, and one FQ-susceptible MDR-TB patient enrolled right after the FQ-resistant MDR-TB patient matching on susceptibility results of second line injectable agents to achieve a 2:1 ratio of FQ-susceptible vs FQ-resistant samples. The exclusion criteria of FQ-resistant MDR-TB were also applied in the selection of FQ-susceptible comparison group.

We reviewed results of drug susceptibility testing at baseline and during treatment (for proper case selections); details of drugs used (dates of start and dates of stop of each drug) and duration of treatment; number of new and repurposed anti-TB drugs used anytime during the treatment course (ever use) and that applied during the initial 6 months of treatment initiation, results of smear and culture at baseline and during treatment; treatment outcomes, as

well as age, sex, history of tuberculosis (new, previously treated), body mass index, smoking, and comorbidities (diabetes, cancer, chronic renal insufficiency, liver cirrhosis, cardiovascular diseases, autoimmune diseases, HIV infection). Drugs added after 6 months of treatment initiation may be added due to unsatisfactory response to treatment or adverse reactions. Therefore, the analysis focused on the use of new and repurposed anti-TB drugs within 6 months of treatment initiation.

Treatment of MDR-TB was individualized, commonly involved the use of 4 or more anti-TB drugs tailored to results of drug susceptibility testing. No patients with FQ-resistant TB were treated with short regimens. Treatment was covered by funding from Taiwan CDC. All service of TB treatment was provided at no cost to patients. Patient-centered directly observed therapy was consistently provided for 5 or more days in a week by trained health workers. Enablers provided to patients to mitigate financial hardship faced by patients and their family were covered by funding from Taiwan CDC.

The primary outcome of interest were treatment outcomes at 30 months (cured, treatment completed, died, failure, loss-to-follow-up). We adapted WHO recommended definitions of outcomes of treatment for MDR-TB treated with second line drugs.[17] Treatment failure was defined as treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of (1) lack of conversion by the end of the intensive phase (8 months), or (2) bacteriological reversion in the continuation phase after conversion to negative, or (3) evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs. Clinicians of the TMTC used to modify treatment regimens for adverse reactions. Therefore, change of two or more drugs because of adverse drug reactions was not classified as treatment failure in this study. Cured and treatment completed were combined as treatment success.

Stata version 15 (Stata Corp LP, College Station, Texas) was used for statistical analysis. Categorical data were analyzed using the Pearson $\chi 2$ test. Logistic regression models were constructed to assess factors associated with treatment success, death, and treatment failure. We used the *logistic* command in Stata to fit the maximum-likelihood logit models. All relevant variables were entered into a multivariate model. $P < 0.05$ was considered statistically significant and applied as threshold value of backward elimination. We kept age groups and sex in the models regardless of the p value as sex and age were essential determinants. A final fitted model was determined by using the likelihood ratio test. The final models were checked by using the goodness-of-fit test to assess the model fit.

No generative artificial intelligence (AI) nor AI-assisted technologies were used in preparing the manuscript.

Results

109 patients with FQ-resistant MDR-TB and 218 patients with FQ-susceptible MDR-TB treated at the TMTC from July 2009—December 2019 were included in this study. Patients characteristics are shown in Table 1. A higher proportion of FQ-resistant MDR-TB were female ($p < 0.01$). Results of susceptibility testing of anti-TB drugs are shown in Table 2. The prevalence of resistance to ethambutol, pyrazinamide, streptomycin, ethionamide/prothionamide, and para-aminosalicylic acid in FQ-resistant TB was significantly higher than that in FQ-susceptible TB (Table 2).

Table 3 shows anti-TB drugs used. Clofazimine was introduced in the treatment of study participants in 2009, linezolid in 2010, carbapenem (imipenem or meropenem) in 2011, bedaquiline in 2013, and delamanid in 2018. The number of patients who have been treated with new or repurposed drugs was 60 (55.1%) among patients with FQ-resistant MDR-TB, and 63 (28.9%) among patients with FQ-susceptible MDR-TB ($p < 0.01$). 27 (24.8%) patients with FQ-resistant MDR-TB and 10 (4.6%) patients with FQ-susceptible MDR-TB have been treated with $\geq$2 new or repurposed drugs. Among the 5 new and repurposed drugs, clofazimine was the most commonly used agent (34.3%), followed by linezolid (14.7%). Bedaquiline has been used for a median of 254 (interquartile range (IQR) 146—462) days; clofazimine for a median of 526 (IQR 316—606) days; linezolid for a median of 315 (IQR 112—635) days; carbapenems or dalamanid for a median of 159 (IQR 46—194) days. Among the 213 patients treated in 2009—2013, the number of new or repurposed drugs used was zero in 183 (85.9%), one in 23 (10.8%) and two or more in 7 (3.3%); and the figures for the 114 patients treated in 2014—2019 was 39 (34.2%), 45 (39.5%) and 30 (26.3%), respectively ($p < 0.01$).

Of the 109 patients with FQ-resistant MDR-TB, 78 (71.6%) had treatment success, 21 (19.3%) died, 9 (8.3%) had treatment failure, and 1 (0.9%) was loss-to-follow-up; of the 218 patients with FQ-susceptible MDR-TB, 187 (85.8%) had treatment success, 30 (13.8%) died, no treatment failure, and 1 (0.5%) was loss-to-follow-up ($p < 0.01$) (Table 4). Among the 51 patients who died during treatment, the cause of death was not TB in 46 (90.2%) patients. The use of new or repurposed drugs was not associated with treatment outcomes among patients with FQ-susceptible MDR-TB, but the use of $\geq$2 new or repurposed drugs had completely mitigated treatment failure in patients with FQ-resistant MDR-TB ($p = 0.03$) (Table 4). Among the 213 patients treated in 2009—2013, 9 (4.2%) patients had treatment failure; among the 114 patients treated in 2014—2019, no patient had treatment failure. Age groups ($p < 0.01$) and comorbidities ($p < 0.01$) were associated with outcomes of treatment, but not positive smear ($p = 0.912$), body mass index ($p = 0.492$), history of TB ($p = 0.15$) and year of treatment ($p = 0.08$).

In univariable analysis, age groups, FQ resistance, and comorbidities were significantly associated with treatment success as compared to other groups (Table 5). The use of new or repurposed drugs, sex, positive smear, history of TB, body mass index, and year of treatment were not significantly associated with treatment success as compared to other groups. In multivariable analysis, patients with FQ-resistant MDR-TB were significantly less likely to have treatment success as compared to patients with FQ-susceptible MDR-TB (adjusted odds ratio (adjOR) 0.38, 95% confidence interval (CI) 0.20—0.70) (Table 5). The elderly (aged $\geq$65 years) were significantly less likely to have treatment success as compared to those aged <45 years (adjOR 0.19, 95% CI 0.08—0.44). Those with

Table 1 Patient characteristics.

	Overall N (%)	Fluoroquinolone susceptible N (%)	Fluoroquinolone resistant N (%)	P value
Total	327 (100)	218	109	
Sex				<0.01
Male	242 (74.0)	173 (79.4)	69 (63.3)	
Female	85 (26.0)	45 (20.6)	40 (36.7)	
Age group (years)				0.52
<45	109 (33.4)	69 (31.7)	40 (36.7)	
45–64	140 (42.8)	98 (45.0)	42 (38.5)	
≥65	78 (23.9)	51 (23.3)	27 (24.8)	0.87
Patient type				
New	210 (64.2)	140 (64.2)	70 (64.2)	
Previously treated	77 (23.6)	55 (25.2)	22 (20.2)	
Body mass index				0.92
<18.5	70 (21.4)	48 (22.0)	22 (20.2)	
18.5–24.9	208 (63.6)	138 (63.3)	70 (64.2)	
≥25	49 (15.0)	32 (14.7)	17 (15.6)	
Smear				0.69
Negative	145 (44.3)	95 (43.6)	50 (45.9)	
Positive	182 (55.7)	123 (56.2)	59 (54.1)	
Year of treatment				0.81
2009–2013	213 (65.1)	143 (65.5)	70 (64.2)	
2014–2019	114 (34.9)	75 (34.4)	39 (35.8)	
Comorbidities				0.87
No	131 (40.1)	88 (40.4)	43 (39.5)	
Yes	169 (59.9)	130 (59.6)	66 (60.6)	
HIV infection	1 (0.3)	1 (0.5)	0	0.32
Hepatitis B	29 (8.9)	19 (8.7)	10 (9.2)	0.46
Hepatitis C	24 (7.3)	15 (6.9)	9 (8.3)	0.42
Alcohol	39 (11.9)	28 (12.8)	11 (10.1)	0.47
Drug abuse	4 (1.2)	3 (1.4)	1 (0.9)	0.72
Diabetes Mellitus	89 (29.4)	57 (26.2)	32 (29.4)	0.54
Hypertension	38 (11.6)	22 (10.1)	16 (14.7)	0.22
Cancer	15 (4.6)	10 (4.6)	5 (4.6)	1.00
COPD	21 (6.4)	15 (6.9)	6 (5.5)	0.63
Renal disease	15 (4.6)	9 (4.1)	6 (5.5)	0.58
Cardiovascular disease	22 (6.7)	13 (6.0)	9 (8.3)	0.44
Autoimmune disease	5 (1.5)	2 (0.9)	3 (2.7)	0.20

comorbidity were significantly less likely to have treatment success as compared to patients without comorbidity (adjOR 0.31, 95% CI 0.15–0.67).

The elderly (aged ≥65 years) had a higher risk of death as compared to those aged <45 years (adjOR 6.76, 95% CI 2.56–17.87). Those with comorbidity had a higher risk of death as compared to patients without comorbidity (adjOR 4.04, 95% CI 1.69–9.67). The use of new or repurposed drugs, sex, FQ resistance, positive smear, history of TB, body mass index, and year of treatment were not significantly associated with death as compared to other groups (Table 6).

No patient with FQ-susceptible MDR-TB had treatment failure, nor patients with FQ-resistant MDR-TB who were treated with ≥2 new or repurposed drugs within 6 months of treatment initiation. In univariable analysis, patients treated with 1 new or repurposed drug within 6 months of treatment initiation was more likely to have treatment failure as compared with patients who were not treated with new or repurposed drug (adjOR 7.06, 95% CI 1.72–29.06). Sex, age group, positive smear, history of TB, body mass index, and year of treatment were not significantly associated with treatment failure in both univariable and multivariable analysis (Table 7).

Discussion

Our assessment revealed that new or repurposed anti-TB drugs have been increasingly used over the study period. The use of new or repurposed drugs was not associated with treatment outcomes in patients with FQ-susceptible MDR-TB, but had an impact on treatment outcomes of FQ-resistant MDR-TB. The use of ≥2 new or repurposed drugs

Table 2 Drug susceptibility testing results.

	Overall N (%)	Fluoroquinolone susceptible N (%)	Fluoroquinolone resistant N (%)	P value
Total	327 (100)	218	109	
Ethambutol				<0.01
Susceptible	130 (39.8)	110 (50.5)	20 (18.3)	
Resistant	195 (59.6)	106 (48.6)	89 (81.7)	
Unknown	2 (0.6)	2 (0.9)	0	
Pyrazinamide				<0.01
Susceptible	137 (41.9)	107 (49.1)	30 (27.5)	
Resistant	81 (24.8)	37 (17.0)	44 (40.4)	
Unknown	109 (33.3)	74 (33.9)	35 (32.1)	
Streptomycin				0.01
Susceptible	146 (44.7)	110 (50.4)	36 (33.0)	
Resistant	172 (52.6)	102 (46.8)	70 (64.2)	
Unknown	9 (2.7)	6 (2.8)	3 (2.8)	
Kanamycin				0.65
Susceptible	292 (89.3)	197 (90.4)	95 (87.2)	
Resistant	32 (9.8)	19 (8.7)	13 (11.9)	
Unknown	3 (0.9)	2 (0.9)	1 (0.9)	
Capreomycin				0.40
Susceptible	298 (91.1)	200 (91.8)	98 (89.9)	
Resistant	17 (5.2)	9 (4.1)	8 (7.3)	
Unknown	12 (3.7)	9 (4.1)	3 (2.7)	
Amikacin				0.78
Susceptible	271 (82.9)	182 (83.5)	89 (81.7)	
Resistant	17 (5.2)	10 (4.6)	7 (6.4)	
Unknown	39 (11.9)	26 (11.9)	13 (11.9)	
Prothionamide				0.02
Susceptible	86 (26.3)	66 (30.3)	20 (18.4)	
Resistant	34 (10.4)	17 (7.8)	17 (15.6)	
Unknown	207 (63.3)	135 (61.9)	72 (66.0)	
Ethionamide				<0.01
Susceptible	172 (52.6)	133 (61.0)	39 (35.8)	
Resistant	77 (23.6)	34 (15.6)	43 (39.5)	
Unknown	78 (23.9)	51 (23.4)	27 (24.8)	
Para-amino salicylic acid				<0.01
Susceptible	289 (88.4)	200 (91.7)	89 (81.6)	
Resistant	32 (9.8)	12 (5.5)	20 (18.4)	
Unknown	6 (1.8)	6 (2.8)	0	
Cycloserine				0.42
Susceptible	217 (66.4)	140 (64.2)	77 (70.6)	
Resistant	1 (0.3)	1 (0.5)	0	
Unknown	109 (33.3)	77 (35.3)	32 (29.4)	

was effective in mitigating treatment failure in FQ-resistant MD-TB. The use of 1 new or repurposed drug was associated with increased risk of treatment failure, likely due to confounding by indication. Difficult cases were treated with only 1 new or repurposed drug when availability of these agents was limited, resulting in unfavourable outcomes. Mortality was relatively high mainly because a relatively high proportion of patients were the elderly with comorbidities, and the cause of death was not TB in the majority. Loss-to-follow-up remained relatively low, confirming the effectiveness of patient-centered management of the TMTC.

Owing to the poor treatment outcomes of FQ-resistant MDR-TB, efforts have been invested in exploring new or repurposed agents that can be used for the treatment of pre-XDR-TB. Clofazimine was synthesized in a drug development project for TB in 1950s,[18] but was not used for TB treatment for decades in part because of the introduction of isoniazid and other anti-TB drugs.[19] Van Deun et al. applied clofazimine in the Bangladesh short regimen, and reported a high proportion of treatment success in MDR-TB patients treated with the Bangladesh short regimen.[20] STREAM stage 1 reported that the Bangladesh short regimen was non inferior to the WHO-recommended long

Table 3 Drug used for treatment of multidrug-resistant tuberculosis.

	Overall N (%)	Fluoroquinolone susceptible N (%)	Fluoroquinolone resistant N (%)	P value
Total	327 (100)	218 (100)	109 (100)	
New/repurposed drugs[a]				
Within 6 months	105 (32.1)	51 (23.4)	54 (49.5)	<0.01
Ever use	123 (37.6)	63 (28.9)	60 (55.1)	<0.01
Linezolid				
Within 6 months	42 (12.8)	12 (5.5)	30 (27.5)	<0.01
Ever use	48 (14.7)	15 (6.9)	33 (30.3)	<0.01
Clofazimine				
Within 6 months	94 (28.8)	47 (21.6)	47 (43.1)	<0.01
Ever use	112 (34.3)	59 (27.1)	53 (48.6)	<0.01
Bedaquiline				
Within 6 months	18 (5.5)	1 (0.5)	17 (15.6)	<0.01
Ever use	18 (5.5)	1 (0.5)	17 (15.6)	<0.01
Meropenam/Impenem				
Within 6 months	14 (4.3)	4 (1.8)	10 (9.2)	<0.01
Ever use	16 (4.9)	4 (4.8)	12 (11.0)	<0.01
Delamanid				
Within 6 months	3 (0.9)	0	3 (2.8)	0.01
Ever use	4 (1.2)	0	4 (3.7)	<0.01
Moxifloxacin				
Within 6 months	290 (88.7)	204 (93.6)	86 (78.9)	<0.01
Ever use	300 (91.7)	208 (95.4)	92 (84.4)	<0.01
Levofloxacin				
Within 6 months	36 (11.0)	23 (10.6)	13 (11.9)	0.55
Ever use	49 (15.0)	30 (13.8)	19 (17.4)	0.51
Kanamycin				
Within 6 months	240 (73.4)	163 (74.8)	77 (70.6)	0.13
Ever use	257 (78.6)	176 (80.7)	81 (74.3)	0.13
Streptomycin				
Within 6 months	49 (15.0)	36 (16.5)	13 (11.9)	0.12
Ever use	63 (19.3)	47 (21.6)	16 (14.7)	0.12
Amikacin				
Within 6 months	10 (3.1)	3 (1.4)	7 (6.4)	0.01
Ever use	14 (4.3)	5 (2.3)	9 (8.3)	0.01
Capreomycin				
Within 6 months	38 (11.6)	19 (8.7)	19 (17.4)	0.01
Ever use	43 (13.2)	20 (9.2)	23 (21.1)	<0.01
Cycloserine/terizidone				
Within 6 months	273 (83.5)	175 (80.3)	98 (89.9)	<0.01
Ever use	284 (86.9)	183 (83.9)	101 (92.7)	<0.01
Prothionamide				
Within 6 months	295 (90.2)	206 (94.5)	89 (81.7)	<0.01
Ever use	296 (90.5)	207 (95.0)	89 (81.7)	<0.01
Para-aminosalicylate				
Within 6 months	172 (52.6)	99 (45.4)	73 (67.0)	<0.01
Ever use	190 (58.1)	112 (51.4)	78 (71.6)	<0.01
Isoniazid				
Within 6 months	52 (15.9)	36 (16.5)	16 (14.7)	0.31
Ever use	61 (18.7)	43 (19.7)	18 (16.5)	0.48
Pyrazinamide				
Within 6 months	236 (72.2)	162 (74.3)	74 (67.9)	0.14
Ever use	266 (81.4)	182 (83.5)	84 (77.1)	0.09
Rifabutin				
Within 6 months	19 (5.8)	16 (7.3)	3 (2.8)	0.10
Ever use	23 (7.0)	18 (8.3)	5 (4.6)	0.22

Table 3 (*continued*)

	Overall N (%)	Fluoroquinolone susceptible N (%)	Fluoroquinolone resistant N (%)	P value
Clarithromycin				
Within 6 months	9 (2.8)	0	9 (8.3)	<0.01
Ever use	12 (3.7)	0	12 (11.0)	<0.01
Amoxicilin/Clavulanate				
Within 6 months	21 (6.4)	3 (1.4)	18 (16.5)	<0.01
Ever use	25 (7.7)	3 (1.4)	22 (20.2)	<0.01
Ethambutol				
Within 6 months	204 (62.4)	151 (69.3)	53 (48.6)	0.01
Ever use	223 (68.2)	158 (72.5)	65 (59.6)	0.01

[a] New/repurposed drugs, bedaquiline, delamanid, linezolid, meropenam/impenem, clofazimine; within 6 months, use within 6 months of treatment initiation; ever use, ever use at anytime during the treatment course.

Table 4 Outcome of treatment of multidrug-resistant tuberculosis.

	Total	Success N (%)	Died N (%)	Failed N (%)	Loss N (%)	P value
Overall	327	265 (81.0)	51 (15.6)	9 (2.8)	2 (0.6)	
Fluoroquinolone (FQ)						<0.01
Susceptible	218	187 (85.8)	30 (13.8)	0	1 (0.5)	
Resistant	109	78 (71.6)	21 (19.3)	9 (8.3)	1 (0.9)	
Number of N/R[a] drugs used						
FQ susceptible						0.74
0	167	142 (85.0)	24 (14.4)	0	1 (0.6)	
1	41	35 (85.4)	6 (14.6)	0	0	
≥2	10	10 (100)	0	0	0	
FQ resistant						0.03
0	55	42 (76.4)	9 (16.4)	3 (5.5)	1 (1.8)	
1	27	18 (66.7)	3 (11.1)	6 (22.2)	0	
≥2	27	18 (66.7)	9 (33.3)	0	0	
Age group (years)						<0.01
<45	109	99 (90.8)	6 (5.5)	3 (2.8)	1 (0.9)	
45—64	140	120 (85.7)	17 (12.1)	3 (2.1)	0	
≥65	78	46 (59.0)	28 (35.9)	3 (3.8)	1 (1.3)	
Sex						0.71
Male	242	195 (80.6)	40 (16.5)	6 (2.5)	1 (0.4)	
Female	85	70 (82.3)	11 (12.9)	3 (3.5)	1 (1.2)	
Smear						0.91
Negative	145	119 (82.1)	22 (15.2)	3 (2.1)	1 (0.7)	
Positive	182	146 (80.2)	29 (15.9)	6 (3.3)	1 (0.6)	
History of TB						0.15
New	209	169 (80.7)	35 (16.8)	3 (1.4)	2 (1.0)	
Previously treated	118	96 (81.4)	16 (13.6)	6 (5.1)	0	
Body mass index						0.49
<18.5	70	53 (75.7)	14 (20.0)	2 (2.9)	1 (1.4)	
18.5—24.9	208	174 (83.7)	29 (13.9)	4 (1.9)	1 (0.5)	
≥25	49	38 (77.6)	8 (16.3)	3 (6.1)	0	
Comorbidities						<0.01
No	131	120 (91.6)	7 (5.3)	3 (2.3)	1 (0.8)	
Yes	196	145 (74.0)	44 (22.5)	6 (3.1)	1 (0.5)	
Year of treatment						0.08
2009—2013	213	172 (80.8)	30 (14.1)	9 (4.2)	2 (0.9)	
2014—2019	114	93 (81.6)	21 (18.4)	0	0	

[a] New/repurposed drugs: bedaquiline, delamanid, linezolid, meropenem/imipenem, clofazimine.

Table 5 Factors associated with treatment success of multidrug-resistant tuberculosis.

	Total	Treatment success N= (%)	OR[b] (95% CI)	P value	Adj OR[b] (95% CI)	P value
Total	327	265 (81.0)				
Sex						
Male	242	195 (80.6)	0.89 (0.47–1.69)	0.72	1.00 (0.48–2.07)	0.99
Female	85	70 (82.3)	1	–	1	–
Age group (years)						
<45	109	99 (90.8)	1	–	1	–
45–64	140	120 (85.7)	0.61 (0.27–1.35)	0.22	0.83 (0.35–1.96)	0.68
≥65	78	46 (59.0)	0.15 (0.07–0.32)	<0.01	0.19 (0.08–0.44)	<0.01
Fluoroquinolone						
Susceptible	218	187 (85.8)	1	–	1	–
Resistant	109	78 (71.6)	0.42 (0.24–0.73)	<0.01	0.38 (0.20–0.70)	<0.01
Number of N/R[a] drugs used						
0	222	184 (82.9)	1	–	–	–
1	68	53 (77.9)	0.73 (0.37–1.43)	0.36	–	–
≥2	37	28 (75.7)	0.64 (0.28–1.47)	0.30	–	–
Smear						
Negative	145	119 (82.1)	1	–		
Positive	182	146 (80.2)	0.89 (0.51–1.55)	0.67	–	–
History of TB						
New	209	169 (80.9)	1	–	–	–
Previously treated	118	96 (81.4)	1.03 (0.58–1.83)	0.91	–	–
Body mass index						
<18.5	70	53 (75.7)	1	–		
18.5–24.9	208	174 (83.7)	1.64 (0.85–3.17)	0.14	–	–
≥25	49	38 (77.6)	1.11 (0.47–2.63)	0.82	–	–
Comorbidities						
No	131	120 (91.6)	1	–	1	–
Yes	196	145 (74.0)	0.26 (0.13–0.52)	<0.01	0.31 (0.15–0.67)	<0.01
Year of treatment						
2009–2013	213	172 (80.8)	1	–	–	–
2014–2019	114	93 (81.6)	1.06 (0.59–1.89)	0.86	–	–

[a] new/repurposed drugs: bedaquiline, delamanid, linezolid, meropenem/imipenem, clofazimine.
[b] OR, odds ratio; Adj OR, adjusted odds ratio.

regimen in the management of rifampicin-resistant TB.[21] Tang et al. reported that MDR-TB patients treated with clofazimine had a treatment success proportion higher than those treated without clofazimine.[12] Linezolid was mainly used for the treatment of Gram-positive bacteria infection, including methicillin-resistant staphylococcus aureus,[22,23] but was also active against *M tuberculosis*.[24] A randomized trial tested linezolid in the treatment of patients with extensively drug-resistant TB who did not had a response to available treatment options and reported that the majority of patients (87%) had a negative sputum culture within 6 months after linezolid had been added.[25] A systematic review and meta-analysis reported a high proportion of sputum culture conversion in MDR-TB patients treated with individualised regimens containing linezolid.[26] However, adverse reactions were frequent. Carbapenem were antibiotics against a broad spectrum of Gram-positive and Gram-negative bacteria, and in combination with clavulanate, also active against *M tuberculosis*.[27,28] Studies have reported outcomes of patients treated with imipenem, meropenem, or ertapenem.[10,29]

Bedaquiline is a first-in-class diarylquinoline that inhibits the proton pump of mycobacterial adenosine triphosphate (ATP) synthase, leading to energy depletion.[30] Bedaquiline has potent bactericidal and sterilizing activity but the onset of activity is delayed for a few days after administration.[31,32] In a phase 2 b randomized placebo-controlled trial, bedaquiline reduced time to culture conversion and achieved a higher proportion of culture conversion as compared with placebo.[33] In a phase 3 randomized trial (STREAM stage 2), a 9-month bedaquiline-containing regimen was superior to a 9-month injectable-containing regimen for the treatment of rifampicin-resistant TB.[34] Delamanid is a nitro-dihydro-imidazooxazole derivative that inhibits mycolic acid biosynthesis. Delamanid is a prodrug requiring activation and has potent bactericidal and sterilizing activity.[35] In a randomized placebo-controlled trial assessing safety and efficacy on the use of delamanid in the treatment of patients with MDR-TB, delamanid was associated with increased sputum-culture conversion at 2 months.[36] However, in a phase 3 randomized placebo-controlled trial, delamanid was not associated

Table 6 Factors associated with death during treatment for multidrug-resistant tuberculosis.

	Total	Death N= (%)	OR[b] (95% CI)	P value	Adj OR[b] (95% CI)	P value
Total	327	51 (15.6)				
Sex						
Male	242	40 (16.5)	1.33 (0.65–2.73)	0.43	1.01 (0.46–2.22)	0.98
Female	85	11 (12.9)	1	–	1	–
Age group (years)						
<45	109	6 (5.5)	1		1	–
45–64	140	17 (12.1)	2.37 (0.90–6.24)	0.08	1.62 (0.60–4.40)	0.34
≥65	78	28 (35.9)	9.61 (3.74–24.71)	<0.01	6.76 (2.56–17.87)	<0.01
Fluoroquinolone						
Susceptible	218	30 (13.8)	1	–	–	–
Resistant	109	21 (19.3)	1.50 (0.81–2.76)	0.20	–	–
Number of N/R[a] drugs used						
0	222	33 (14.9)	1	–	–	–
1	68	9 (13.2)	0.87 (0.40–1.93)	0.74	–	–
≥2	37	9 (24.3)	1.84 (0.80–4.25)	0.15	–	–
Smear						
Negative	145	22 (15.2)	1	–	–	–
Positive	182	29 (15.9)	1.06 (0.58–1.94)	0.85	–	–
History of TB						
New	209	35 (16.8)	1	–	–	–
Previously treated	118	16 (13.6)	0.78 (0.41–1.48)	0.45	–	–
Body mass index						
<18.5	70	14 (20.0)	1	–		
18.5–24.9	208	29 (13.9)	0.65 (0.32–1.31)	0.23	–	–
≥25	49	8 (16.3)	0.78 (0.30–2.03)	0.61	–	–
Comorbidities						
No	131	7 (5.3)	1	–	1	–
Yes	196	44 (22.5)	5.13 (2.23–11.78)	<0.01	4.04 (1.69–9.67)	<0.01
Year of treatment						
2009–2013	213	30 (14.1)	1	–	–	–
2014–2019	114	21 (18.4)	1.38 (0.74–2.54)	0.30	–	–

[a] New/repurposed drugs: bedaquiline, delamanid, linezolid, meropenem/imipenem, clofazimine.
[b] OR, odds ratio, Adj OR, adjusted odds ratio.

with shorter median time to sputum culture conversion over 6 months.[37] An individual patient data meta-analysis on outcomes of pulmonary MDR-TB reported that the use of bedaquiline, levofloxacin, moxifloxacin, linezolid, clofazimine and carbapenems was associated with treatment success, compared with failure or relapse.[38] In 2019, WHO classified bedaquiline, linezolid, levofloxacin/moxifloxacin as group A drugs, clofazimine and cycloserine as group B drugs for designing a longer regimen in the treatment of MDR-TB.[39]

Our study covered a 10-year period during which global experience on the use of new and repurposed anti-TB drugs was accumulating and evidence on the efficacy of these agents in the treatment of MDR-TB emerging. Only a minority of patients in 2009–2013 in the TMTC were treated with new or repurposed anti-TB drugs, and the use of these agents increased in 2014–2019. Our study revealed that proper case management itself was effective in achieving a high treatment success proportion in FQ-susceptible MDR-TB even without the use of new or repurposed drugs because of a relatively low proportion of loss-to-follow-up. However, these agents were crucial for the treatment of FQ-resistant MDR-TB, for which two or more new or repurposed drugs were needed to prevent treatment failure. Adding one new or repurposed drug to a week regimen was inadequate. Mortality was relatively high in our study, mainly due to old age and comorbidities. Similar findings were observed among all types of TB cases in Taiwan. Among all TB cases notified to Taiwan CDC in 2022, 23.1% died, 70.1% had treatment success, 0.3% had treatment failure, 1.7% were lost to follow-up, 4.8% had outcomes not-evaluated at 12 months. Of note is that the majority of patients in the TMTC during the study period was treated with longer regimens lasting about 20 months. The long duration of treatment was detrimental to the quality of life of patients and may impose substantial non-medical cost to patients and their family. WHO has recently recommended all oral short regimens for the treatment of FQ-resistant MDR-TB, such as bedaquiline, pretomanid, and linezolid for 6 months (BPaL).[40] Although the use of short regimens may reduce the duration of suffering of patients and improve their quality of life as

Table 7 Factors associated with treatment failure.

	Total	Treatment failure N= (%)	OR[b] (95% CI)	P value	Adj OR[b] (95% CI)	P value
Total	327	9 (2.8)				
Sex						
Male	242	6 (2.5)	0.69 (0.17–2.84)	0.61	0.68 (0.16–2.91)	0.60
Female	85	3 (3.5)	1	–	1	–
Age group (years)						
<45	109	3 (2.8)	1	–	1	–
45–64	140	3 (2.1)	0.77 (0.15–3.91)	0.76	0.68 (0.12–3.74)	0.65
≥65	78	3 (3.9)	1.41 (0.28–7.19)	0.68	1.29 (0.22–7.37)	0.77
Fluoroquinolone						
Susceptible	218	0	–	–	–	–
Resistant	109	9 (8.3)	–	–	–	–
Number of N/R[a] drugs used						
0	222	3 (1.4)	1	–	–	–
1	68	6 (8.8)	7.06 (1.72–29.06)	0.01	–	–
≥2	37	0	–	–	–	–
Smear						
Negative	145	3 (2.1)	1	–	1	–
Positive	182	6 (3.3)	1.61 (0.40–6.57)	0.50	2.19 (0.51–9.39)	0.29
History of TB						
New	209	3 (1.4)	1	–	1	–
Previously treated	118	6 (5.1)	3.68 (0.90–14.99)	0.07	3.97 (0.93–16.86)	0.06
Body mass index						
<18.5	70	2 (2.9)	1	–	1	–
18.5–24.9	208	4 (1.9)	0.67 (0.12–3.72)	0.64	0.74 (0.13–4.26)	0.74
≥25	49	3 (6.1)	2.22 (0.36–13.79)	0.39	2.37 (0.35–16.21)	0.38
Comorbidities						
No	131	3 (2.3)	1	–	1	–
Yes	196	6 (3.1)	1.35 (0.33–5.49)	0.68	1.39 (0.29–6.60)	0.68
Year of treatment						
2009–2013	213	9 (4.2)	–	–	–	–
2014–2019	114	0	–	–	–	–

[a] New/repurposed drugs: bedaquiline, delamanid, linezolid, meropenem/imipenem, clofazimine.
[b] OR, odds ratio, Adj OR, adjusted odds ratio.

compared to the use of longer regimens, toxicities of short regimens remain a challenge.

The strength of our study was that this was a population-based study because more than 95% of patients with MDR-TB in Taiwan were managed by the TMTC.[15,16] Findings of the study were representative of treatment outcomes of FQ-resistant MDR-TB in Taiwan. Results of second line anti-TB agents were provided by the national mycobacteriology reference laboratory of Taiwan CDC, ensuring its quality.[41] Furthermore, we include FQ-susceptible MDR-TB as a comparison group, enabling assessment of the role of the new and repurposed drugs in the management of both FQ-resistant and FQ-susceptible MDR-TB. The proportion of patients who were lost to follow-up was relatively small, imposing negligible influence in evaluating the contribution of new and repurposed drugs. The limitation of the study was that the TMTC was unique in its structure and operation with proper funding from Taiwan CDC.[15,16] Findings of the TMTC may not be generalizable to other settings.

In conclusion, proper use of ≥2 new and repurposed anti-TB drugs helped mitigate treatment failure in FQ-resistant MDR-TB in the TMTC. Whether the use of short regimen can further improve treatment outcomes of FQ-resistant MDR-TB require further evaluation.

Funding

The study was funded by Wan Fang Hospital (112-wf-eva-05). The funder had no role in the study design, collection, analysis and interpretation of data, writing of the report, and decision to submit the paper for publication.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

CRediT authorship contribution statement

Yi-Wen Huang: Data curation, Investigation, Writing – review & editing, Conceptualization. **Ming-Chih Yu:** Data curation, Investigation, Writing – review & editing. **Chih-**

Bin Lin: Data curation, Investigation, Writing — review & editing. **Jen-Jyh Lee:** Data curation, Investigation, Writing — original draft. **Chou-Jui Lin:** Data curation, Investigation, Writing — review & editing. **Shun-Tien Chien:** Data curation, Investigation, Writing — review & editing. **Chih-Hsin Lee:** Data curation, Investigation, Writing — review & editing. **Chen-Yuan Chiang:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing — original draft.

Declaration of competing interest

None declared.

Acknowledgement

Special thanks go to Taiwan CDC who providing funding for the operation of the TMTC. We thank Chih-Yun Lin and Wei-Hsiang Hsu for data collection and management.

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