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Original Article

Comparative safety of bedaquiline and delamanid in patients with multidrug resistant tuberculosis: A nationwide retrospective cohort study

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Abstract *Background/Purpose(s):* Bedaquiline and delamanid were recently approved for multidrug resistant tuberculosis (MDR-TB). Bedaquiline carries a black box warning of increased risk of death compared to the placebo arm, and there is a need to establish the risks of QT prolongation and hepatotoxicity for bedaquiline and delamanid.
Methods: We retrospectively analyzed data of MDR-TB patients retrieved from the South Korea national health insurance system database (2014—2020) to assess the risks of all-cause death, long QT-related cardiac event, and acute liver injury associated with bedaquiline or delamanid, compared with conventional regimen. Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI). Stabilized inverse probability of treatment weighting based on propensity score was used to balance characteristics between the treatment groups.
Results: Of 1998 patients, 315 (15.8%) and 292 (14.6%) received bedaquiline and delamanid, respectively. Compared with conventional regimen, bedaquiline and delamanid did not increase risk of all-cause death at 24-month (HR 0.73 [95% CI, 0.42—1.27] and 0.89 [0.50

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—1.60], respectively). Bedaquiline-containing regimen increased risk of acute liver injury (1.76 [1.31—2.36]), while delamanid-containing regimen increased risk of long QT-related cardiac events (2.38 [1.05—3.57]) within 6 months of treatment.
Conclusion: This study adds to the emerging evidence refuting the higher mortality rate observed in the bedaquiline trial population. Association between bedaquiline and acute liver injury needs careful interpretation considering for other background hepatotoxic anti-TB drugs. Our finding on delamanid and long QT-related cardiac events suggest careful risk-benefit assessment in patients with pre-existing cardiovascular disease.

Introduction

Bedaquiline and delamanid were recently approved exclusively for treatment of Multidrug-resistant tuberculosis (MDR-TB). Bedaquiline exerts bactericidal activity against *M. tuberculosis* through inhibition of a mycobacterial ATP synthase, and it shortened time to culture conversion and improved treatment outcomes,[1—4] subsequently receiving Group A recommendation in the recent 2019 WHO consolidated guidelines.[5] Delamanid, bactericidal against *M. tuberculosis* by inhibiting mycolic acid biosynthesis, has yet demonstrated its efficacy over placebo in the most recent phase III trial,[6] and effectiveness data from observational studies have been descriptive in nature.[7,8] Moreover, while generally regarded as safe and less toxic than the second-line injectables (SLI), safety of bedaquiline and delamanid outside the trial population warrants further investigation.

There are safety concerns on the risk of death associated with bedaquiline, and adverse events (AEs) including QT prolongation and elevated liver enzymes reported in the bedaquiline and delamanid arms.[9—11] Bedaquiline carries a black box warning based on the finding of more deaths occurring in the bedaquiline vs. placebo arm (12.7% vs. 2.5%; $p = 0.02$) in the phase II trial.[1] Both bedaquiline and delamanid cause modest QT prolongation, presumably via inhibition of cardiac delayed rectifier potassium channels.[10,12] While the magnitude of QT prolongation has been described, no study to date have explored risk of cardiac events manifesting from prolonged QT interval. Moreover, drug-induced hepatotoxicity is not rare during MDR-TB treatment,[13] yet elevation of liver enzymes observed in bedaquiline and delamanid arms have received relatively little attention.[9] These are certainly an important issue to consider when designing an optimal background regimen given that several other anti-TB drugs are also known to affect QT interval and hepatotoxic.[14,15]

As much research were done in experimental setting, there is a need to explore safety of bedaquiline and delamanid in a broader population with less stringent eligibility criteria and using comparative safety study design. Also, there is scant data on their use in the high-income countries with high-resource setting. It has been previously reported that higher incidences of AEs from MDR-TB treatment were observed in high-resource setting, compared with low-resource setting,[16] thereby making it more suitable to explore rare safety endpoints. South Korea is one of the few countries with high-income, intermediate TB burden, and where both bedaquiline and delamanid are equally accessible. In this regard, we conducted a population-based cohort study to evaluate the risk of all-cause death, long-QT related cardiac event, and acute liver injury in South Korean patients who received bedaquiline-or delamanid-containing regimens.

Methods

Setting

South Korea has considerably high TB burden with the annual incidence of 44.6 cases per 100,000 population in 2021, which is the highest and more than 7 times higher than the average of member countries of the Organization for Economic Cooperation and Development (OECD).[17,18] The 2017 South Korea treatment guidelines for drug-resistant TB is generally in line with the 2016 WHO treatment guidelines; the shorter MDR-TB regimen newly recommended by WHO in 2016 was not endorsed in the South Korean guideline due to high prevalence of the additional drug resistance rate in South Korea.[19,20]

Bedaquiline and delamanid entered national formulary to be covered under the national health insurance plan since May 2015. The use of these drugs requires approval from the national TB expert review committee (NTBERC), launched in September 2016 by the Korea Disease Control and Prevention Agency. NTBERC oversees the appropriate use of these drugs, granting approval for use based on an individual's underlying medical conditions, laboratory data, electrocardiogram, drug susceptibility test (DST), and previous treatment outcomes. Eligible cases include pre-extensively drug resistant (XDR)/XDR-TB, MDR-TB resistant to pyrazinamide, or for whom fluoroquinolones (FQs) or SLIs cannot be tolerated.[21]

Data source

This study was conducted using the South Korea National Health Insurance System (NHIS) database between 2014 and 2020. It contains all administrative medical claims of 97.1% of the population, including demographics, income-based insurance premium tiers as a proxy for income level and socioeconomic status, medical diagnosis, procedure,

prescription, and type of medical institution. Diagnoses are coded using the Korea Standard Classification of Diseases, 7th revision (KCD-7), which is based on the International Classification of Diseases, 10th revision (ICD-10), and information on procedures and drugs are coded using the domestic coding system.

Study design and participants

We conducted a retrospective cohort study of MDR-TB patients identified in the NHIS database between 2016 and 2019. Study population included individuals aged 18 years or older diagnosed with MDR-TB and received a guideline-directed treatment regimen. MDR-TB was identified using diagnosis codes for pulmonary TB (ICD-10: A15-A16) and "resistance to tuberculostatic drugs (KCD-7: U84.3)" recorded in the primary and secondary diagnosis positions, respectively. Guideline-directed treatment regimen comprised of at least 4 second-line anti-TB drugs, ascertained by reviewing drug records on or after date of the diagnosis. The full list of anti-TB drugs included in the analysis is presented in the Supplementary Table 1 in the supplement.

Bedaquiline and delamanid groups included patients treated with bedaquiline or delamanid, respectively, plus at least 3 second-line anti-TB drugs. Those who did not receive either drug was classified as conventional regimen group. Conventional regimen was defined as at least 4 second-line anti-TB drugs including core second-line agents, FQs and/or SLIs (i.e., aminoglycosides), plus other anti-TB drugs. The date patients initiated bedaquiline, delamanid, or core second-line agents were assigned as index date for bedaquiline, delamanid, and conventional regimen groups, respectively. We excluded individuals who had rifampin, less than 4 drugs included in the regimen, received both bedaquiline and delamanid on the same date, or without any core second-line agents among patients who received conventional regimen (Supplementary Figs. 1 and 2 in the Supplement).

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[22]

Outcomes

The outcomes of interest were all-cause death, long QT-related cardiac events, and acute liver injury. The date and cause of death (ICD-10 coded) were obtained through linkage to the national statistics data. Intent-to-treat approach was used to follow patients from index date to date of death or end of study period (31 December 2020).

Long QT-related cardiac events included medical diagnosis or death related to QT prolongation. Acute liver injury was identified using ICD-10 codes adopted from published literature on capturing drug-induced hepatotoxicity in a medical claims data (Supplementary Table 2 in the Supplement). The captured events were restricted to diagnoses during hospitalization or emergency department visit. To ensure captured events were incident outcomes, we excluded patients with any records of these events 6 months preceding the date of MDR-TB diagnosis. As-treated approach was used to follow patients from index date to outcome of interest, censored at discontinuation of index drugs, death, or end of study period, whichever was earlier. For conventional regimen group, the index drug was either FQs or SLIs, whichever was discontinued first. Treatment discontinuation was ascertained with a gap exceeding 14 days between the end date of prescription and start date of subsequent prescription.

Statistical analysis

To account for biases related to non-randomized treatment allocation in real-world population, we used propensity score (PS) method to estimate probability of receiving exposure of interest conditional on the measured confounders.[23] PS for receiving bedaquiline or delamanid was estimated by fitting a multivariable logistic regression model using the baseline covariates. Then, inverse probability of treatment weight (IPTW) based on PS was computed to construct a weighted cohort with balanced distribution of the measured confounders across treatment groups. Moreover, stabilization of IPTW was achieved by multiplying the marginal overall prevalence of treatment in the study cohort to avoid any extreme or unstable weight being assigned to a patient with very low probability of receiving treatment.[24]

Baseline covariates were assessed prior to MDR-TB diagnosis, and included age, sex, household income level, lifestyle factors including smoking status and alcohol consumption, past TB or MDR-TB treatment, Charlson comorbidity index (CCI),[25] comorbidities associated with poor prognosis and prescription records for drugs with potential QT prolongation or hepatotoxicity (Supplementary Table 3 in the Supplement).

Descriptive analyses were conducted to summarize the baseline characteristics and treatment characteristics using mean (SD) for continuous variables, median with interquartile range (IQR) for time duration, and frequencies with percentages for categorical variables. For comparing the balance of baseline characteristics between treatment groups, we computed absolute standardized difference (aSD), with a value less than 0.1 considered balanced.

For each outcome, we calculated incidence per 100 person-year with 95% CI based on Poisson distribution, and plotted Kaplan—Meier cumulative incidence curve with log-rank test between the treatment groups. We used cause-specific Cox proportional hazards models, with death treated as a censoring event, to estimate HR for each outcome, except for all-cause death, in bedaquiline and delamanid groups. Risk of all-cause death was estimated at 12-, 24-, and 36-months after treatment initiation. Details on the post-hoc subgroup and sensitivity analyses can be found in eMethod in the supplement.

Results

Of 1998 patients, 315 (15.8%) and 292 (14.6%) received bedaquiline and delamanid, respectively. The mean ages were 53.2 (SD 17.2), 50.4 (17.0), and 53.3 years (17.8) for bedaquiline, delamanid, and conventional regimen groups, respectively, and there were more men across all groups.

Baseline characteristics that varied across the groups were balanced in the weighted cohort after applying IPTW (Table 1).

Median time from diagnosis to initiation of bedaquiline or delamanid were 47 days (IQR, 4–100) and 36 days (3.5–93), respectively (Table 2). Median treatment duration with bedaquiline and delamanid were 5.7 months (5.2–6.1) and 6.0 months (5.8–6.4), respectively. Most frequently administered background drug in bedaquiline and delamanid groups was cycloserine (87.0% and 91.1%), followed by FQs (73.3% and 72.9%), protionamide (73.0% and 71.9%), and linezolid (50.2% and 43.5%).

Cumulative incidence of all-cause death was non-significantly lower (Fig. 1A), whereas that of long QT-related cardiac events were non-significantly higher in delamanid group, compared with conventional regimen group (Fig. 1B). While the cumulative incidence curves showed a trend toward increased risk of acute liver injury for bedaquiline and delamanid groups, the risk was significantly higher only for bedaquiline group (Fig. 1C).

Table 1 Demographic and clinical characteristics of MDR-TB patients initiating treatment between 2016 and 2019.

Characteristic	Bedaquiline		Delamanid		Conventional regimen		Maximum pairwise aSD[a]	
	N = 315 (%)		N = 292 (%)		N = 1391 (%)		Before IPTW	After IPTW[b]
Age, mean (SD)	53.2	(17.2)	50.4	(17.0)	53.3	(17.8)	0.17	0.03
Male	220	(69.8)	184	(63.0)	950	(68.3)	0.11	0.02
Lifestyle factors								
Smoking (ever)	83	(26.4)	80	(27.4)	369	(26.5)	0.02	0.03
Alcohol (>1 time/week)	75	(23.8)	95	(32.5)	306	(22.0)	0.24	0.04
Household income level							0.19	0.04
Q1 (most deprived)	72	(22.9)	51	(17.5)	289	(20.8)		
Q2	78	(24.8)	72	(24.7)	322	(23.1)		
Q3	70	(22.2)	87	(29.8)	354	(25.4)		
Q4 (most affluent)	59	(18.7)	62	(21.2)	269	(19.3)		
Medicaid	36	(11.4)	20	(6.8)	157	(11.3)		
Treatment year							0.58	0.07
2016	49	(15.6)	55	(18.8)	516	(37.1)		
2017	79	(25.1)	82	(28.1)	359	(25.8)		
2018	74	(23.5)	95	(32.5)	280	(20.1)		
2019	113	(35.9)	60	(20.5)	236	(17.0)		
Previous treatment history								
1st-line anti-TB drugs only	253	(80.3)	237	(81.2)	1093	(78.6)	0.07	0.01
2nd-line anti-TB drugs	38	(12.1)	36	(12.3)	139	(10.0)	0.07	0.04
CCI							0.10	0.08
Mean (SD)	1.1	(1.3)	1.2	(1.3)	1.1	(1.4)		
0-1	226	(71.7)	212	(72.6)	1031	(74.1)		
2-3	86	(27.3)	74	(25.3)	338	(24.3)		
4+	3	(1.0)	6	(2.1)	22	(1.6)		
Comorbidity								
Cardiovascular disease	87	(27.6)	75	(25.7)	345	(24.8)	0.06	0.05
Chronic kidney disease	27	(8.6)	18	(6.2)	53	(3.8)	0.20	0.02
Asthma	46	(14.6)	43	(14.7)	211	(15.2)	0.02	0.03
COPD	80	(25.4)	82	(28.1)	346	(24.9)	0.07	0.04
Diabetes	120	(38.1)	86	(29.5)	459	(33.0)	0.11	0.06
Solid organ transplant	3	(1.0)	4	(1.4)	4	(0.3)	0.12	0.05
Viral hepatitis	28	(8.9)	17	(5.8)	87	(6.3)	0.10	0.04
Cancer	38	(12.1)	35	(12.0)	184	(13.2)	0.04	0.06
AIDS	1	(0.3)	5	(1.7)	8	(0.6)	0.11	0.03
Comedication								
QTc prolonging drugs	60	(19.0)	52	(17.8)	257	(18.5)	0.02	0.03
Hepatotoxic drugs	180	(60.3)	175	(59.9)	854	(61.4)	0.03	0.05

[a] Absolute standardized mean difference less than 0.10 considered balanced.
[b] Stabilized IPTW based on propensity score for receiving bedaquiline or delamanid by fitting multivariable logistic regression model using the covariates measured on or prior to MDR-TB diagnosis (c-statistics: 0.673 for bedaquiline, 0.675 for delamanid vs. conventional regimen).
Abbreviations: MDR-TB, multidrug resistant tuberculosis; aSD, absolute standardized difference; SD, standard deviation; IPTW, inverse probability of treatment weighting; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease.

Table 2 Treatment characteristics of MDR-TB patients receiving treatment between 2016 and 2020.

	Bedaquiline (n = 315)	Delamanid (n = 292)	Conventional regimen (n = 1391)	P-value[a]
Interval from diagnosis to index drug initiation				
Median (IQR), days	47 (4–100)[b]	36 (3.5–93)[c]	0 (0-0)[b,c]	<0.001
Treatment with bedaquiline or delamanid				
Median (IQR), months	5.7 (5.2–6.1)	6.0 (5.8–6.4)	–	<0.001
Number of drugs in initial regimen				
Median (IQR)	5 (4–6)[b]	5 (4–6)[c]	5 (4–5)[a,b]	<0.001
4 drugs, n (%)	88 (27.9)	84 (28.8)	489 (35.2)	
5 drugs, n (%)	110 (34.9)	109 (37.3)	582 (41.8)	
6 drugs or more, n (%)	117 (37.1)	99 (33.9)	320 (23.0)	
Initial regimen composition, n (%)				
Fluoroquinolones	231 (73.3)[b]	213 (72.9)[c]	1369 (98.4)[b,c]	<0.001
Second-line injectables	105 (33.3)[b]	95 (32.5)[c]	663 (47.7)[b,c]	<0.001
Linezolid	158 (50.2)[b]	127 (43.5)[c]	62 (4.5)[b,c]	<0.001
pyrazinamide	137 (43.5)[b]	103 (35.3)[c]	1176 (84.5)[b,c]	<0.001
Cycloserine	274 (87.0)	266 (91.1)	1262 (90.7)	0.112
protionamide	230 (73.0)[b]	210 (71.9)[c]	1204 (86.6)[b,c]	<0.001
p-aminosalicylic acid	77 (24.4)	89 (30.5)[c]	297 (21.4)[c]	0.003
Carbapenems	41 (13.0)[b]	42 (13.3)[c]	50 (15.9)[b,c]	<0.001
Amoxicillin-clavulanate	55 (17.5)[b]	45 (14.3)[c]	31 (9.8)[b,c]	<0.001

[a] Based on chi-square test (or Fisher's exact test) for categorical variables and ANOVA (or Kruskal–Wallis test) for continuous variables. Bonferroni test was performed for post hoc correction to account for comparisons of three groups.
[b] p-value<0.05 for bedaquiline vs. conventional regimen.
[c] p-value<0.05 for delamanid vs. conventional regimen.
Abbreviations: MDR-TB, multidrug resistant tuberculosis; SD, standard deviation; IQR, interquartile range.

Incidence rates (per 100 person-year) of each outcome are available in the Supplementary Table 4 in the supplement.

Risks of all-cause death, long QT-related cardiac events, and acute liver injury in bedaquiline and delamanid groups, compared with conventional regimen group, before and after IPTW, are presented in Table 3. A total of 284 deaths were identified at 36-month, corresponding to 43 (13.7%), 30 (10.3%), and 211 (15.2%) deaths in bedaquiline, delamanid, and conventional regimen groups, respectively. In the weighted cohort, bedaquiline showed a non-significant mortality risk reduction at 12-month (adjusted HR 0.73 [95% CI, 0.48–1.12]), compared with conventional regimen group. The risk estimates shifted toward null association at 24- and 36-months (1.04 [0.75–1.44] and 0.99 [0.72–1.36], respectively). Delamanid showed a non-significant mortality risk reduction at 12-month (0.75 [0.45–1.23]) and 24-month (0.83 [0.55–1.25]), but not at 36-month (1.05 [0.75–1.49]).

Overall, there were few patients with long QT-related cardiac events during treatment (5 in bedaquiline, 8 in delamanid, and 23 in standard regimen groups). Of these events, there were only 2 deaths due to long QT-related cardiac events in conventional regimen group (Supplementary Table 5 in the supplement). Compared with conventional regimen, concerning trends toward increased risk of long QT-related cardiac events were observed for bedaquiline (1.43 [0.57–3.57]) and delamanid (2.38 [1.05–5.37]). There were significantly more patients diagnosed with acute liver injury in bedaquiline group (63; 21.7%), compared with conventional regimen group (195; 15.2%), corresponding to aHR of 1.76 (1.31–2.36). The risk in delamanid group was comparable to that of conventional regimen group with HR of 1.14 (0.81–1.61) (Table 3).

In post-hoc subgroup analyses, effect modification by several covariates were identified (Fig. 2). Bedaquiline demonstrated significant mortality benefit among patients with type 2 diabetes (0.41 [0.18–0.94; $P_{interaction}$ = 0.040]), linezolid in the background regimen (0.16 [0.04–0.66; $P_{interaction}$ = 0.002]) and did not receive SLIs (0.51 [0.27–0.97, $P_{interaction}$ = 0.010]). While a similar trend was observed in patients treated with delamanid and linezolid (0.21 [0.05–0.87; $P_{interaction}$ = 0.279]), the interaction did not reach statistical significance. Moreover, effect modification by these interaction terms on all-cause death were no longer observed at 24-month (Supplementary Fig. 3 in the supplement). The results from sensitivity analyses remained largely consistent with that of main analysis (Supplementary Tables 7-10 in the supplement).

Discussion

In this nationwide retrospective cohort study, addition of bedaquiline or delamanid demonstrated a promising trend towards mortality risk reduction during the early course of MDR-TB treatment. Notably, substantial early mortality benefits were observed among bedaquiline group with type 2 diabetes and linezolid included in their background regimens. While it was reassuring to note that there were only few cases manifesting from potential QT prolongation, the observed trend towards increased risk of cardiac events, especially with the use of delamanid, requires careful risk-

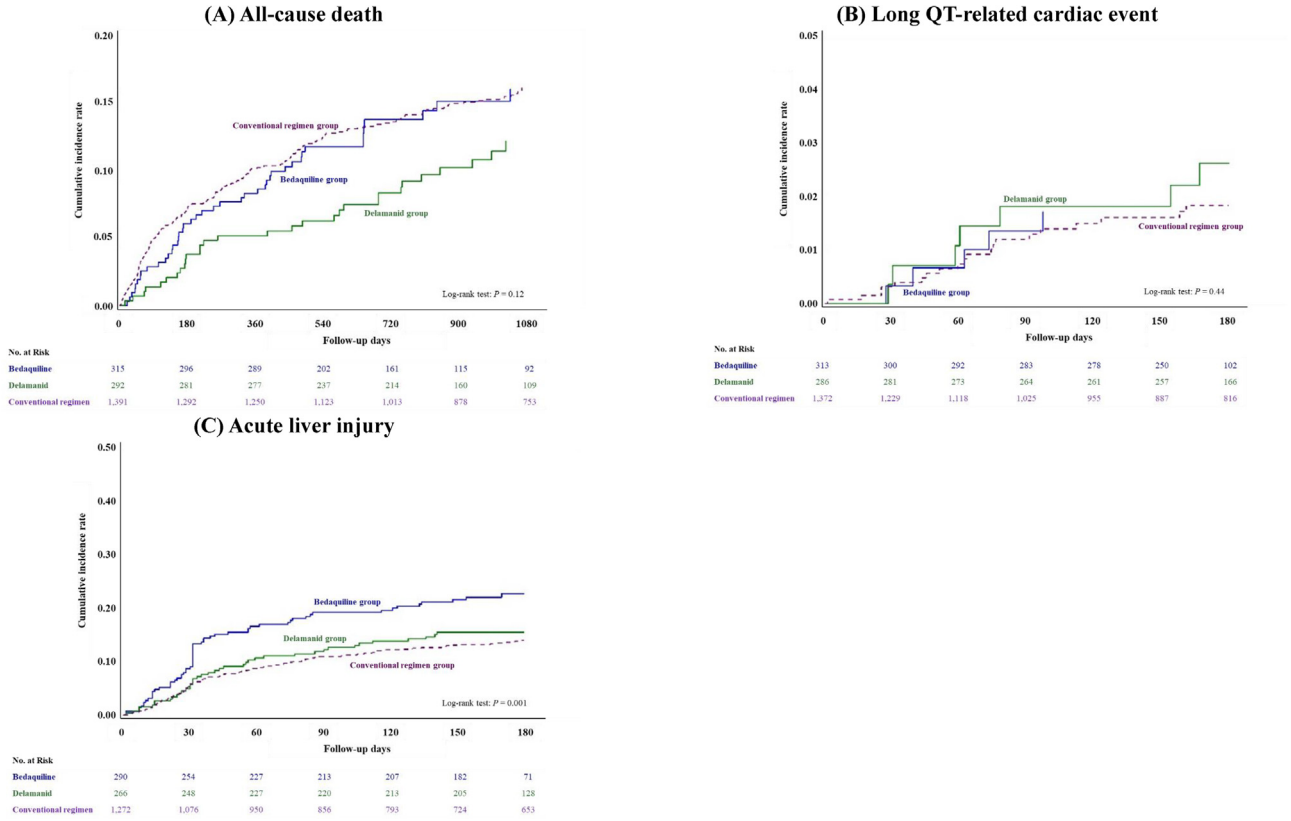


Figure 1. Cumulative incidence curves of (A) all-cause death, (B) long QT-related cardiac event, and (C) acute liver injury in MDR-TB patients receiving bedaquiline, delamanid, and conventional regimen.

benefit assessment in patients with pre-existing cardiovascular disease. Acute liver injuries during intensive treatment phase were not rare, thereby underpinning active monitoring for drug-induced hepatotoxicity.

There has been growing evidence refuting the signal of mortality from the phase 2b bedaquiline trial. Schnippel et al. conducted a retrospective cohort study using the South African TB registry data to evaluate the risk of all-cause death among drug-resistant TB patients receiving bedaquiline. Significantly less patients in bedaquiline group died, compared with the comparator group (12.6% vs. 24.8%), resulting in the HR of 0.35 (95% CI, 0.28–0.46).[26] However, the generalizability of this substantial benefit of bedaquiline was subject to survival and selection biases, subsequently exaggerating the protective effect of bedaquiline.[27] Another study by Zhao et al. found null association of all-cause death among South African patients treated with bedaquiline, compared with those treated with the SLI-based regimen at 12-month after treatment initiation (7.6% vs. 7.5%; p = 0.97).[3]

The significant mortality risk reduction with bedaquiline among patients with diabetes is noteworthy given that diabetes not only increases risk of MDR-TB but also negatively affect the treatment outcome mainly via delayed clearance of *M. tuberculosis*.[28] We believe that the accelerated culture conversion by bedaquiline may have subsequently led to early mortality benefit in this subgroup. Co-treatment with linezolid, a repurposed drug, also led to substantial mortality risk reduction. In a recent meta-analysis, concomitant use of bedaquiline and linezolid in HIV patients with higher CD4+ T-cell count at baseline was associated with a higher treatment success rate,[29] and we add to this evidence by showing the potential for synergistic effect by bedaquiline and linezolid in improving survival in general population.

To our knowledge, this is the first study to generate comparative safety data on delamanid. Unlike bedaquiline, delamanid remains as group C drug in the most recent WHO treatment guidelines due to the finding from phase 3 clinical trial that failed to show significant difference in time to culture conversion, compared with placebo arm.[6] In the most recent non-inferiority trial, treatment success rate at 24-month in delamanid group was non-inferior to that of conventional regimen (75.0% vs. 70.6%; absolute difference 4.4% [97% one-sided CI -9.5% to ∞]).[30] Despite the lack of robust efficacy data on delamanid, bedaquiline and delamanid are being used in parity in South Korea. Hwang et al. recently showed comparable effectiveness between bedaquiline and delamanid by using the NTBERC data in South Korea between 2016 and 2018.[21] Our safety finding on

Table 3 Risk of all-cause death, long QT-related cardiac event, and acute liver injury in MDR-TB patients receiving bedaquiline, delamanid, and conventional regimen.

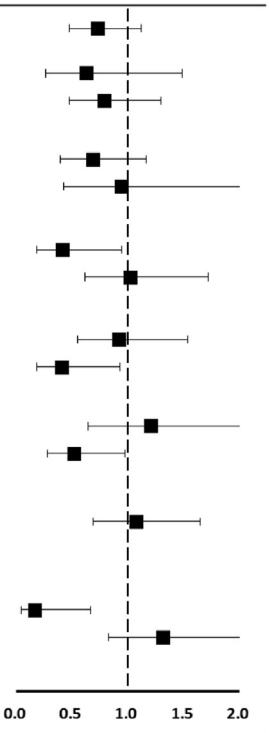
	No. of patient, n	No. of event, n (%)	Unweighted model		Stabilized IPTW model[a]	
			Crude HR (95% CI)	Adjusted HR[b] (95% CI)	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Death (all-cause)[c]						
12-month						
Bedaquiline	315	26 (8.3)	0.81 (0.53–1.23)	0.70 (0.45–1.09)	0.83 (0.55–1.25)	0.73 (0.48–1.12)
Delamanid	292	15 (5.1)	0.50 (0.29–0.84)	0.74 (0.43–1.30)	0.64 (0.39–1.04)	0.75 (0.45–1.23)
Conventional regimen	1391	140 (10.1)	Ref.	Ref.	Ref.	Ref.
24-month						
Bedaquiline	315	40 (12.7)	0.99 (0.70–1.39)	0.89 (0.62–1.28)	1.15 (0.83–1.58)	1.04 (0.75–1.44)
Delamanid	292	23 (7.9)	0.58 (0.38–0.90)	0.83 (0.53–1.31)	0.74 (0.50–1.11)	0.83 (0.55–1.25)
Conventional regimen	1391	184 (13.2)	Ref.	Ref.	Ref.	Ref.
36-month						
Bedaquiline	315	43 (13.7)	0.98 (0.70–1.36)	0.88 (0.62–1.24)	1.07 (0.79–1.46)	0.99 (0.72–1.36)
Delamanid	292	30 (10.3)	0.67 (0.46–0.99)	0.97 (0.65–1.44)	0.97 (0.69–1.35)	1.05 (0.75–1.49)
Conventional regimen	1391	211 (15.2)	Ref.	Ref.	Ref.	Ref.
Long QT-related cardiac event[d]						
Bedaquiline	313	5 (1.6)	1.13 (0.42–3.05)	1.07 (0.38–3.04)	1.39 (0.57–3.41)	1.43 (0.57–3.57)
Delamanid	286	8 (2.8)	1.87 (0.81–4.31)	2.35 (0.98–5.64)	2.24 (1.00–5.01)	2.38 (1.05–5.37)
Conventional regimen	1372	23 (1.7)	Ref.	Ref.	Ref.	Ref.
Acute liver injury[d]						
Bedaquiline	290	63 (21.7)	1.75 (1.31–2.35)	1.68 (1.24–2.29)	1.77 (1.32–2.37)	1.76 (1.31–2.36)
Delamanid	266	42 (15.8)	1.16 (0.82–1.62)	1.11 (0.78–1.58)	1.15 (0.82–1.62)	1.14 (0.81–1.61)
Conventional regimen	1272	195 (15.2)	Ref.	Ref.	Ref.	Ref.

[a] IPTW based on propensity score for receiving bedaquiline or delamanid by fitting multivariable logistic regression model using the covariates measured on or prior to MDR-TB diagnosis.
[b] Adjusted for demographics, life-style factors, previous exposure to 1st or 2nd line anti-TB drugs, CCI, comorbidities, and past use of QT prolonging drugs or hepatotoxic drugs for long QT-related cardiac event and acute liver injury, respectively.
[c] Intention-to-treat analysis with follow-up from index date to date of death, censored at each specified follow-up period.
[d] As-treated analysis with follow-up from index date to date of event, censored at the earliest date of discontinuation of index drugs, death, or end of study period.
Abbreviations: MDR-TB, multidrug-resistant tuberculosis; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity index.

delamanid complements the available data to support a need for reappraisal of the current treatment position of delamanid in the WHO guidelines and expand its access.

QT prolonging effect of bedaquiline and delamanid has been attributed to their inhibitory action on the cardiac delayed rectifier potassium channels, predominantly by their metabolites, M2 for bedaquiline and DM-6705 for delamanid. Cardiac toxicity of bedaquiline is dose-dependent, and delayed QT prolonging effect persisting beyond discontinuation of bedaquiline had been attributed to its long terminal half-life of 5–6 months.[31] Similarly, cardiac toxicity of delamanid was also shown to be dose-dependent, with its QT prolonging effect peaking at around 6–10 weeks of treatment.[32] The magnitude of QT prolongation by bedaquiline and delamanid have been described, yet there is paucity of data on the risk of cardiac events manifesting from QT prolongation. In a retrospective data analysis of bedaquiline treatment episodes from 25 countries, 9.7% experienced QTcF >500msec, but none translated into poor clinical outcomes.[33] Data from WHO active Drug Safety Monitoring project observed 17 (2.6%) cases of QTcF >500msec, of which 8 cases resulted in serious cardiac events (4 cases attributed to bedaquiline and none for delamanid).[34] In the most recent observational study using endTB project data, grade 3 or 4 QT prolongation (QTcF >500msec or Torsade de pointes or polymorphic ventricular tachycardia) were observed in 2.2% of patients exposed to bedaquiline or delamanid.[35] In our study, it is reassuring to find that there were few long QT-related cardiac events and no death from bedaquiline and

All-cause death at 12-month	Bedaquiline		Conventional regimen		sIPTW adjusted HRs (95% CI)
	No. of patients	No. of event (%)	No. of patients	No. of event (%)	
Overall	315	26 (8.3)	1,391	140 (10.1)	0.73 (0.48-1.12)
Age group					
<65 years	240	5 (2.1)	1,022	38 (3.7)	0.62 (0.26-1.48)
≥65 years	75	21 (28.0)	369	102 (27.6)	0.78 (0.47-1.29)
p for interaction					0.864
Sex					
Male	220	16 (7.3)	950	92 (9.7)	0.68 (0.39-1.16)
Female	95	10 (10.5)	441	48 (10.9)	0.94 (0.42-2.09)
p for interaction					0.432
Pre-existing diabetes					
Yes	120	10 (8.3)	459	65 (14.2)	0.41 (0.18-0.94)
No	195	16 (8.2)	932	75 (8.0)	1.02 (0.61-1.72)
p for interaction					0.040
Number of drugs in initial regimen					
4 to 5 drugs	198	14 (7.1)	1,071	99 (9.2)	0.91 (0.54-1.53)
6 or more drugs	117	12 (10.3)	320	41 (12.8)	0.40 (0.18-0.92)
p for interaction					0.484
Co-treatment with SLIs					
Yes	105	13 (12.4)	663	78 (11.8)	1.20 (0.64-2.23)
No	210	13 (6.2)	728	62 (8.5)	0.51 (0.27-0.97)
p for interaction					0.010
Co-treatment with FQs					
Yes	231	24 (10.4)	1,369	135 (9.9)	1.07 (0.69-1.65)
No	84	2 (2.4)	22	5 (22.7)	-
p for interaction					0.010
Co-treatment with linezolid					
Yes	158	7 (4.4)	62	13 (21.0)	0.16 (0.04-0.66)
No	157	19 (12.1)	1,329	127 (9.6)	1.31 (0.82-2.12)
p for interaction					0.002



All-cause death at 12-month	Delamanid		Conventional regimen		sIPTW adjusted HRs (95% CI)
	No. of patients	No. of event (%)	No. of patients	No. of event (%)	
Overall	292	15 (5.1)	1,391	140 (10.1)	0.75 (0.45-1.23)
Age group					
<65 years	231	2 (0.9)	1,022	38 (3.7)	0.35 (0.11-1.17)
≥65 years	61	13 (21.3)	369	102 (27.6)	0.98 (0.55-1.73)
p for interaction					0.018
Sex					
Male	184	9 (4.9)	950	92 (9.7)	0.62 (0.32-1.19)
Female	108	6 (5.6)	441	48 (10.9)	1.63 (0.68-3.89)
p for interaction					0.362
Pre-existing diabetes					
Yes	86	6 (7.0)	459	65 (14.2)	0.76 (0.31-1.86)
No	206	9 (4.4)	932	75 (8.0)	0.81 (0.43-1.52)
p for interaction					0.831
Number of drugs in initial regimen					
4 to 5 drugs	193	10 (5.2)	1,071	99 (9.2)	0.80 (0.44-1.49)
6 or more drugs	99	5 (5.1)	320	41 (12.8)	0.54 (0.21-1.40)
p for interaction					0.829
Co-treatment with SLIs					
Yes	95	3 (3.2)	663	78 (11.8)	0.49 (0.18-1.36)
No	197	12 (6.1)	728	62 (8.5)	0.92 (0.49-1.72)
p for interaction					0.237
Co-treatment with FQs					
Yes	213	12 (5.6)	1,369	135 (9.9)	0.78 (0.44-1.40)
No	79	3 (3.8)	22	5 (22.7)	-
p for interaction					0.946
Co-treatment with linezolid					
Yes	127	7 (5.5)	62	13 (21.0)	0.21 (0.05-0.87)
No	165	8 (4.8)	1,329	127 (9.6)	0.62 (0.32-1.21)
p for interaction					0.279

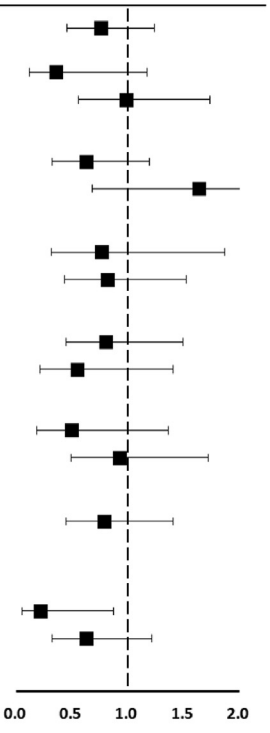


Figure 2. Risk of all-cause death at 12-month in the selected subgroups of MDR-TB patients receiving (A) bedaquiline or (B) delamanid compared with those receiving conventional regimen. MDR-TB, multidrug resistant tuberculosis; sIPTW, standardized inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval; SLI, second-line injectables; FQ, fluoroquinolones.

delamanid groups were attributed to these events. It should also be noted that the observed trends toward increased risk in bedaquiline and delamanid groups may be subject to detection bias as NTBERC requires periodic electrocardiographic monitoring for all approved cases.

Of safety concerns associated with bedaquiline to date, hepatic related AEs have received little attention. Biological plausibility of bedaquiline-induced hepatotoxicity has been attributed to its high lipophilicity, and lipophilic drugs are generally prone to hepatotoxicity. While it has been speculated that this structural characteristic of bedaquiline is responsible for phospholipidosis, an intracellular accumulation of phospholipids, that manifest into hepatotoxicity,[36] clinical implication of this mechanistic link of bedaquiline to hepatic related AEs still remains to be explored. Meanwhile, the proportion of patients with acute liver injury while receiving bedaquiline in our study was considerably higher than the 8.8% reported from pooled safety data of bedaquiline trials.[31] Indeed, our study population were generally older than the trial population, and age >60 years had been shown to increase the risk of drug-induced liver injury by 3.5-fold during TB treatment.[37] Moreover, 2-fold increased risk of drug-induced hepatitis in Asian men during TB treatment also implies a need for future research on genetic susceptibility for bedaquiline-induced hepatotoxicity.[38] Alternatively, it should be noted that diagnosis code-based identification of drug-induced hepatotoxicity in medical claims data only showed modest accuracy,[39] and the captured cases may not reflect true prevalence of acute liver injury manifested by bedaquiline.

With their efficacy in facilitating culture conversion had been explored extensively, optimizing dosing regimen and minimizing side effects of anti-TB drugs remains a next challenge. In Nix-TB trial, a 26-week treatment regimen comprised bedaquiline, pretomanid and high-dose linezolid (BpaL regimen) demonstrated an outstanding treatment success rate of 90% (98 of 109 patients), yet treatment-limiting toxicities including myelosuppression (48%) and peripheral neuropathy (81%) were highly prevalent.[40] Interestingly, a pharmacokinetic data analysis of Nix-TB trial patients revealed no relation between treatment outcome and trough level of BPaL regimen measured up to 16 weeks, suggesting a need for monitoring side effects over therapeutic drug concentration.[41] Hence, healthcare resources should be weighted towards monitoring and managing side effects upon achieving initial culture conversion.

Several limitations must be considered in interpreting our study's findings. First, despite of including all patients treated for MDR-TB in South Korea, our study did not have enough statistical power due to small population size to detect significant differences of the outcomes across the treatment groups. Specifically, the impact of background anti-TB drugs included in the initial regimen on the risk of long QT-related cardiac events could not be analyzed due to very small number of the cases during study period. Further studies using large-scale, multinational data are needed to assess the magnitude of impact of individual background drugs on the potential cardiotoxic effect by bedaquiline and delamanid in a much larger population.

Second, information on the DST patterns were not available. It was not possible to ascertain whether the resistance category differed between treatment groups. However, given the strict eligibility criteria set by NTBERC, patients treated with bedaquiline or delamanid were likely to have harbored more drug resistances. In fact, 62.9% of patients approved for bedaquiline or delamanid by NTBERC had either pre-XDR or XDR-TB between 2016 and 2018,[21] whereas it was only 21.6% in 2015 according to a retrospective analysis of TB registry data of South Korea.[42] Given this, it is worthy to note the trend towards early mortality risk reduction observed for bedaquiline and delamanid despite of this differential risk profiles.

Third, we could not validate whether the captured outcomes were truly drug-induced events. Capturing of AEs in the medical claims data is certainly challenging, especially if the AE does not result in clinically significant event(s). In our case, electrocardiogram and liver function test results were not available, and relied on diagnosis codes for medical conditions manifesting from these signs. Underestimation of the outcomes is possible if the signs of QT interval prolongation and liver enzyme elevation did not manifest into symptomatic episode requiring medical intervention.

Lastly, our findings may not be readily generalizable considering that our study cohort was generally much older and had low prevalence of AIDS, compared with general MDR-TB population.

Notwithstanding these limitations, we addressed the limited data on the comparative safety of bedaquiline and delamanid in hope to expand patient's access to these novel treatment approaches. Given their potential for cardiac toxicity, bedaquiline and delamanid should be used with caution in patients with pre-existing cardiovascular disease, considering for risk vs benefit, until more definitive evidence can be established. Concern on bedaquiline-induced acute liver injury calls for additional research to explore the magnitude of its impact on the MDR-TB treatment outcomes.

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Ethical approval statement

This study was approved by the Institutional Review Board of Sungkyunkwan University (No. 2019-10-030). The need for informed consent was waived as this study was performed using anonymized claims data.

Declaration of competing interest

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Foundation of Korea, and pharmaceutical companies including Daiichi Sankyo, GSK and Pfizer outside the submitted work.

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References

1. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014;**371**:723—32.
2. Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2016;**47**:564—74.
3. Zhao Y, Fox T, Manning K, Stewart A, Tiffin N, Khomo N, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug-resistant tuberculosis: a retrospective cohort study. *Clin Infect Dis* 2019;**68**:1522—9.
4. Ahmad N, Ahuja SD, Akkerman OW, Alffenaar J-WC, Anderson LF, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018;**392**:821—34.
5. WHO guidelines approved by the guidelines review committee. In: *WHO consolidated guidelines on tuberculosis: module 4: treatment - Drug-resistant tuberculosis treatment*. Geneva: World Health Organization © World Health Organization 2020.; 2020.
6. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag Jr V, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019;**7**:249—59.
7. Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. *Eur Respir J* 2017;**50**:1700311.
8. Mohr E, Hughes J, Reuter A, Trivino Duran L, Ferlazzo G, Daniels J, et al. Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa. *Eur Respir J* 2018;**51**:1800017.
9. Patel H, Pawara R, Pawara K, Ahmed F, Shirkhedkar A, Surana S. A structural insight of bedaquiline for the cardiotoxicity and hepatotoxicity. *Tuberculosis* 2019;**117**:79—84.
10. Gupta R, Geiter LJ, Hafkin J, Wells CD. Delamanid and QT prolongation in the treatment of multidrug-resistant tuberculosis. *Int J Tubercul Lung Dis* 2015;**19**:1261—2.
11. Kim CT, Kim TO, Shin HJ, Ko YC, Choe YH, Kim HR, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. *Eur Respir J* 2018;**51**:1702467.
12. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. *Eur Respir J* 2017;**50**:1701462.
13. Keshavjee S, Gelmanova IY, Shin SS, Mishustin SP, Andreev YG, Atwood S, et al. Hepatotoxicity during treatment for multidrug-resistant tuberculosis: occurrence, management and outcome. *Int J Tubercul Lung Dis* 2012;**16**:596—603.
14. Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet* 2015;**385**:1738—47.
15. Younossian AB, Rochat T, Ketterer JP, Wacker J, Janssens JP. High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis. *Eur Respir J* 2005;**26**:462—4.
16. Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2020;**8**:383—94.
17. *Global tuberculosis report 2021*. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
18. Cho KS. Tuberculosis control in the Republic of Korea. *Epidemiol Health* 2018;**40**:e2018036. e2018036.
19. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *Eur Respir J* 2017;**49**:1602308.
20. Joint Committee for the Revision of Korean Guidelines for Tuberculosis. *Korea centers for disease Control and prevention. Korean guidelines for tuberculosis - fourth edition*. 2020.
21. 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.
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007;**18**.
23. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41—55.
24. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med* 2014;**275**:570—80.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chron Dis* 1987;**40**:373—83.
26. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018;**6**:699—706.
27. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;**167**:492—9.
28. Liu Q, Li W, Xue M, Chen Y, Du X, Wang C, et al. Diabetes mellitus and the risk of multidrug resistant tuberculosis: a meta-analysis. *Sci Rep* 2017;**7**:1090.
29. Wu Y, Zhang Y, Wang Y, Wei J, Wang W, Duan W, et al. Bedaquiline and Linezolid improve anti-TB treatment outcome in drug-resistant TB patients with HIV: a systematic review and meta-analysis. *Pharmacol Res* 2022;**182**:106336.
30. Mok J, Lee M, Kim DK, Kim JS, Jhun BW, Jo KW, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. *Lancet* 2022;**400**:1522—30.
31. Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. *Tuberculosis* 2014;**94**:357—62.
32. Szumowski JD, Lynch JB. Profile of delamanid for the treatment of multidrug-resistant tuberculosis. *Drug Des Dev Ther* 2015;**9**:677—82.

33. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017;**49**.
34. Borisov S, Danila E, Maryandyshev A, Dalcolmo M, Miliauskas S, Kuksa L, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. *Eur Respir J* 2019;**54**.
35. Hewison C, Khan U, Bastard M, Lachenal N, Coutisson S, Osso E, et al. Safety of treatment regimens containing bedaquiline and delamanid in the endTB cohort. *Clin Infect Dis* 2022;**75**: 1006—13.
36. Guillemont J, Meyer C, Poncelet A, Bourdrez X, Andries K. Diarylquinolines, synthesis pathways and quantitative structure–activity relationship studies leading to the discovery of TMC207. *Future Med Chem* 2011;**3**:1345—60.
37. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Respir J* 1996;**9**: 2026—30.
38. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest* 2005;**128**:116—23.
39. Billioti de Gage S, Collin C, Le-Tri T, Pariente A, Bégaud B, Verdoux H, et al. Antidepressants and hepatotoxicity: a cohort study among 5 million individuals registered in the French national health insurance database. *CNS Drugs* 2018;**32**:673—84.
40. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020;**382**:893—902.
41. Solans BP, Imperial MZ, Olugbosi M, Savic RM. Analysis of dynamic efficacy endpoints of the Nix-TB trial. *Clin Infect Dis* 2023: ciad051. https://doi.org/10.1093/cid/ciad051.
42. 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 Tubercul Lung Dis* 2019;**23**:850—7.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.04.009.