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Early View

Original article

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Bedaquiline and Delamanid for the Treatment of Multidrug-resistant Tuberculosis: A Multi-center Cohort Study in Korea

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Take-Home Message: Bedaquiline and delamanid were effective and safe for MDR-TB treatment when combined with WHO-recommended regimens.

Keywords: Bedaquiline; delamanid; tuberculosis; QT prolongation

ABSTRACT

Relatively little is known about the efficacy and safety of the programmatic use of bedaquiline and delamanid in multidrug-resistant tuberculosis (MDR-TB) treatment. This study evaluated 61 patients with MDR-TB treated with bedaquiline (n=39), delamanid (n=11), or both, either sequentially (n=10) or in co-administration (n=1), for more than 1 month, combined with a World Health Organization-recommended regimen. Of these, 49 (80.3%) were men and 12 (19.7%) were women. The median age was 53 years (interquartile range [IQR]=38.5–61.0 years). Forty-two (68.9%) patients had fluoroquinolone-resistant MDR-TB and 16 (26.2%) had extensively drug-resistant TB. The median duration of treatment with bedaquiline and/or delamanid was 168 days (IQR 166.5–196.5 days), with 33 (54.1%) receiving linezolid for median 673 days (IQR 171-736 days). Of the 55 patients with positive sputum cultures at the start of bedaquiline and/or delamanid treatment, 39 (70.9%) achieved sputum culture conversion within a median of 119 days. Treatment was halted in four patients (6.6%) because of prolonged corrected QT interval. In conclusion, bedaquiline and delamanid were effective and safe for treating MDR-TB, with initial evidence of sequential administration of these two drugs as a viable treatment strategy for patients when an adequate treatment regimen cannot be constructed.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is an important public health problem because of a lack of effective and safe anti-TB drugs and regimens. Treatment may entail the administration of many drugs over a long period of time, resulting in low treatment success rates and higher rates of adverse drug reactions (ADRs) [1-6]. Fluoroquinolones and second-line injectable drugs, such as kanamycin, amikacin, and capreomycin, are considered crucial in the treatment of MDR-TB, but resistance to these agents may give rise to extensively drug-resistant TB (XDR-TB). XDR-TB has become an emerging global health concern due the increased resistance to these effective anti-TB drugs [7-9].

Not only clinical trials but also clinical experiences have shown that bedaquiline and delamanid are promising new anti-TB drugs, with good efficacy and safety in the treatment of MDR-TB [10-26]. However, further data regarding their efficacy and safety, including the effects on QT prolongation, in patients with quinolone-resistant MDR-TB and XDR-TB are still required [27-31]. Moreover, sequential or co-administration treatment with bedaquiline and delamanid may improve treatment success in patients with quinolone resistant MDR-TB and XDR-TB [21, 32-36]. This study therefore analyzed the efficacy and safety of bedaquiline and/or delamanid in patients with MDR-TB treated under programmatic conditions.

Methods

Study population

This retrospective cohort study included patients with pulmonary MDR-TB treated between January 2015 and October 2017 at four tertiary referral hospitals and 1 tuberculosis-specific hospital in South Korea, each treating more than 300 patients with TB per year (Figure 1). All enrolled patients underwent treatment with bedaquiline and/or delamanid for more than 1 month, in combination with a background regimen as recommended by the World Health Organization (WHO). Tuberculosis (TB) was diagnosed based on the presence of *Mycobacterium tuberculosis* in sputum cultures. Sputum culture isolates of all patients were subjected to drug susceptibility tests (DST) for 15 anti-TB drugs on Lowenstein-Jensen medium. All DSTs were performed at the National Reference Laboratory of the Korean Institute of Tuberculosis and Green Cross Laboratories using the proportion method. The tested drugs and their critical concentrations for resistance were: isoniazid, 0.2 mg/L; rifampin, 40 mg/L; ethambutol, 2 mg/L; rifabutin, 20 mg/L; streptomycin, 10 mg/L; amikacin, 40 mg/L; kanamycin, 40 mg/L; capreomycin, 40 mg/L; ofloxacin, 2 mg/L; levofloxacin 2 mg/L; moxifloxacin 2 mg/L; prothionamide, 40 mg/L; cycloserine, 30 mg/L; and para-aminosalicylic acid, 1 mg/L. Pyrazinamide susceptibility was determined using the pyrazinamidase test. MDR-TB and XDR-TB were identified based on DST results of individual patients.

Treatment and monitoring

All patients underwent anti-TB treatment regimens as recommended by the WHO, tailored individually to each patient according to previous history of chemotherapy and DST results.

Although the decision to start treatment with bedaquiline and/or delamanid was made by each attending physician, these new anti-TB drugs were prescribed only when an effective treatment regimen could not be provided, because of resistance to a drug, an adverse drug reaction (ADR), poor tolerance, or contraindication to any component of the combination regimen [19, 27-29]. The choice of bedaquiline and/or delamanid was based on the availability of these drugs and on patient condition. In South Korea, the national expert committee reviewed all cases to be treated with bedaquiline and delamanid starting from September 2016 [19]. Accordingly, after this date, individual physicians were required to submit an application form to the national expert committee prior to prescribing the new anti-TB drugs. The national expert committee approved the use of new anti-TB drugs according to patient clinical status and/or when the patient met the criteria for the WHO guidelines.

All enrolled patients were monitored for drug regimen compliance and ADRs during treatment by specially trained nurses who participated in the Public-Private Mix project for TB control in Korea [37]. These nurses were responsible for direct drug administration during hospitalization, and provided support for self-administered drug treatment after discharge from the hospital. Laboratory tests, including sputum smear and culture, complete blood cell count, and liver and renal function tests, were performed every week during hospitalization and at every monthly outpatient hospital visit during the treatment period. Additional laboratory tests were performed if patients manifested symptoms related to ADRs.

Electrocardiograms (EKG) were recorded at baseline, and after 2, 4, 8, 12, and 24 weeks of treatment with bedaquiline and/or delamanid, as recommended by WHO guidelines [28]. Corrected QT interval was calculated as (QT interval)/(RR interval) using Friderica’s Correction

Formula (QTcF) [38]. A significant QTcF prolongation was defined as absolute value > 450 ms in men or > 470 ms in women, or as a > 60 ms increase from baseline [28].

Sputum culture conversion was defined as having at least two consecutive negative cultures, taken at least 30 days apart in patients with a positive sputum specimen at baseline. The day of sputum collection for the first of two consecutive negative results was defined as the time of sputum culture conversion.

Ethics statement

The Institutional Review Board of Chonnam National University Hospital approved the study protocol and provided permission for this study to be reviewed and published, including information obtained from patient records (IRB No. CNUH-1017-168). Informed consent was waived because of the retrospective nature of the study, and patient information was anonymized and de-identified prior to analysis.

Statistical analysis

All data are reported as median and interquartile range (IQR) or as numbers and percentages. Continuous variables were analyzed using the Mann-Whitney U test for two groups or the Kruskal-Wallis test for three groups. Categorical variables were analyzed using Fisher's exact test. Dunn's multiple comparison tests were used for post hoc correction to account for comparisons of three groups. All statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL), with $p < 0.05$ considered statistically significant.

Results

Patient Characteristics

This study enrolled a total of 61 patients with pulmonary MDR-TB treated with bedaquiline and/or delamanid for over 1 month. The median age was 52 years (IQR 38.5–61.0 years), and 49 (80.3%) patients were men. Of these, 39 (64%), 11 (18%), and 11 (18%) were treated with bedaquiline, delamanid, and both drugs, respectively. Patient baseline demographic and clinical characteristics are summarized in Table 1. There were significant differences between the three groups in the number of drugs to which the isolates were resistant and in the percentage of patients resistant to fluoroquinolones, which was significantly higher among patients treated with both drugs than among those treated with bedaquiline alone, as revealed by Dunn's multiple comparison tests.

Isolates from 49 (80.3%), 44 (71.5%), and 28 (45.9%) patients were resistant to ethambutol, pyrazinamide, and streptomycin, respectively. Assessment of resistance to second-line injectable drugs and fluoroquinolones showed that 19 (31.1%) isolates were resistant to kanamycin and 42 (68.9%) were resistant to ofloxacin (Table 2).

Treatment

Of the 11 patients treated with both bedaquiline and delamanid, 10 were treated sequentially and one was treated with co-administration. Of the 10 patients treated sequentially, 9 received bedaquiline followed by delamanid at a median interval of 71 days (IQR 56–78 days), and 1 received delamanid followed by bedaquiline 1 day later. The median duration of treatment with bedaquiline and/or delamanid was 168 days (IQR 166.5–196 days), with no difference between

the groups treated with delamanid and bedaquiline alone. However, length of treatment was significantly longer in patients treated with both drugs than in those treated with one or the other (Table 3). Fifty patients (82.0%) completed 6 months of treatment, including 9 (81.8%) treated with delamanid alone, 34 (87.2%) treated with bedaquiline alone, and 7 (63.6%) treated with both drugs. Of 55 patients who completed 6 months of treatment, 8 patients were treated with bedaquiline (n=6) or delamanid (n=2) for over 190 days. The median duration of bedaquiline therapy was 323 days (IQR 222-394 days) and the duration of delamanid therapy was 210 and 237 days, respectively. Of the 11 patients who did not complete 6 months of treatment, 4 were administered new anti-TB drugs at the end of this study period, while 7 stopped treatment: 5 discontinued the drugs because of ADRs, 1 patient died of an underlying malignancy after treatment with bedaquiline for 126 days, and 1 patient discontinued treatment due to termination of health insurance cover after 119 days of bedaquiline treatment.

There were significant differences in the percentage of patients treated with fluoroquinolones, linezolid, and clofazimine in the three treatment groups. Even after post-test correction using Dunn′s multiple comparison tests, the frequency of fluoroquinolone use was significantly lower in the group treated with both drugs than in the group treated with bedaquiline alone. In contrast, the frequency of clofazimine use was significantly higher in the group treated with both drugs than in the group treated with bedaquiline alone. Moreover, the duration of treatment with bedaquiline and/or delamanid was significantly longer in the group treated with both drugs than in bedaquiline or delamanid alone groups (Table 3). Treatment with other anti-TB drugs did not differ significantly in the three groups, except that clarithromycin and amoxicillin-clavulanic acid frequencies were higher in the group treated with both bedaquiline and delamanid than in the monotherapy groups (Supplementary Table 1).

Efficacy and safety of new drugs

Of the 61 patients with MDR-TB, 55 (90.2%) had positive sputum cultures at the time of starting treatment with bedaquiline and/or delamanid. Of these, 39 (70.9%) achieved culture conversion, although the percentage of patients achieving culture conversion did not differ among the three treatment groups (p=0.160) (Table 3). We evaluated factors potentially associated with culture conversion, including age >45 years, male sex, low BMI, previous TB treatment history, smear positivity, the presence of cavity on chest radiography, XDR-TB, use of linezolid, use of new anti-TB drugs such as bedaquiline and/or delamanid, and treatment duration of new anti-TB drugs. No significant associations were found (Supplementary Table 2).

Regarding the time to culture conversion from the start of treatment with bedaquiline and/or delamanid of patients administered both drugs, all 7 patients who achieved culture conversion received sequential treatment, and the median time to culture conversion was 307.5 (IQR 235.0-346.5), which was significantly longer than that in the groups treated with bedaquiline (p<0.001) or delamanid (p=0.004) alone, even after post hoc analysis (Table 3).

Twenty-eight patients experienced ADRs, resulting in discontinuation of anti-TB drugs. Eight patients experienced optic neuropathy, caused by linezolid in 5 patients and ethambutol in 3 patients; 7 patients experienced peripheral neuropathy caused by linezolid; and in 4 we observed prolonged QTcF caused by bedaquiline and/or delamanid. Furthermore, 2 patients developed gastrointestinal problems, caused by PAS and clarithromycin, respectively; 2 patients developed anemia caused by linezolid; 2 patients developed azotemia, caused by kanamycin and streptomycin, respectively; 1 patient experienced alopecia caused by delamanid; 1 patient

experienced skin eruptions and 1 patient developed hepatotoxicity of unknown cause after stopping delamanid and bedaquiline. Five patients (8.2%) experienced ADRs that resulted in stopping delamanid and/or bedaquiline, including 4 with a significantly prolonged QTcF. Of these 4 patients, 1 was treated with delamanid and bedaquiline sequentially, 1 with both drugs simultaneously, one with bedaquiline, and one with delamanid (Table 4). The frequency of stopping delamanid and/or bedaquiline due to a prolonged QTcF was higher in patients being treated with both drugs than in the other groups, although the differences were not statistically significant (Table 3). QTcF became normalized in all 4 of these patients who stopped delamanid and/or bedaquiline due to prolonged QTcF, and these drugs were not re-introduced. A fifth patient stopped delamanid on day 137 due to severe alopecia, which developed 1 month after commencing treatment and progressively worsened.

Discussion

This cohort study found that treatment of patients with MDR-TB with the new anti-TB drugs delamanid and bedaquiline, individually or sequentially, showed good efficacy and safety in combination with the WHO recommended background regimens. Previous clinical trials showed that treatment with bedaquiline for 24 weeks resulted in sputum culture conversion in 79–81% of patients at week 24 and in 62–72% at week 120 [10, 11, 14]. Moreover, the combination of an optimized background regimen with delamanid for 6–8 months resulted in a sputum culture conversion rate of 65% at 8 weeks and a favorable outcome rate of 75% after 24 months [12, 13]. In a recent large observational cohort study under different settings except experimental conditions, bedaquiline-containing regimens achieved sputum culture conversion rates over 90% at the end of treatment, even with a high proportion of fluoroquinolone-resistant TB (64.5%) and XDR-TB (45.6%) [17]. High culture conversion rates have also been also reported in other recent cohort studies of new anti-TB drugs in patients with MDR-TB [15, 16, 18-26]. In this study, overall culture conversion rate of 71% was achieved, despite 69% of patients having fluoroquinolone-resistant MDR-TB and 26% having XDR-TB. This was relatively high compared to those of previous clinical trials, but not as high as the percentages in observational cohort studies. This difference may be caused by differences in patient conditions, clinical settings, and regimens.

In comparing bedaquiline and delamanid, we found that all patients treated with delamanid achieved culture conversion compared with 67% of patients treated with bedaquiline who achieved sputum culture conversion, although the difference was not statistically significant. Because of the small number of patients treated with delamanid, we could not explain this difference in culture conversion rates. However, patients treated with delamanid tended to be

younger and have higher rates of combined surgery and these factors may account for the differences in culture conversion. Furthermore, over half of patients (51.3%) treated with bedaquiline were prescribed the drug in 2015, whereas the majority of patients (71.4%) treated with delamanid were prescribed the drug in 2016. Physicians may have better knowledge about treating patients with MDR-TB with new anti-TB drugs, especially when they prescribe delamanid, and this may explain the differences in culture conversion between the two drugs.

One of the most important safety issues associated with these new anti-TB drugs is drug-induced QTcF prolongation, which is usually asymptomatic and may cause fatal ventricular tachyarrhythmia [27-30]. The new anti-TB drugs, as well as interactions between these drugs and other anti-TB drugs, can cause QTcF prolongation, and most clinical trials had strict criteria in selecting anti-TB drugs for inclusion in background regimens [10-14]. A recent systematic analysis of cardiac safety with bedaquiline treatment involving 1256 patients and including controlled clinical trials and cohort studies showed that QTc was longer than 500 ms in 3.2% of patients, and 0.6% of patients discontinued treatment due to QTc prolongation [31]. Although the previous study concluded that bedaquiline is a relatively safe drug, this conclusion may be limited due to lack of information regarding cardiac safety and no standardized way to report cardiac safety in most studies [31]. Therefore, more information about cardiac safety of new anti-TB drugs, including with various regimens and settings, is required. However, in our study, 69% of patients experienced significant QTcF prolongation, and only 7% had to discontinue delamanid and/or bedaquiline because of QTcF prolongation, and none experienced drug-induced fatal arrhythmia. This finding was comparable to recent cohort studies testing new anti-TB drugs in patients with MDR-TB [15-19, 23, 24, 26]. Among factors related to QTcF prolongation, co-administration drugs may increase the risk of QTcF prolongation. In our study,

patients treated with clofazimine (28.6% vs 0%, p=0.012) and clarithromycin (33.3% vs. 0%, p=0.003) experienced a significantly higher rate of significant QTcF prolongation. In another factor related to QTcF prolongation, use of both drugs should be considered. Of the 4 patients who discontinued delamanid and/or bedaquiline because of QTcF prolongation in this study, 2 were treated with both drugs.

Although 9 (82%) of the 11 patients treated with both drugs were treated sequentially with bedaquiline followed by delamanid at a median interval of 71 days, treatment was halted only in 1 patient treated initially with delamanid, followed by bedaquiline. This finding is interesting, considering the long half-life of bedaquiline and the potential risk of adverse drug reactions when delamanid is used subsequently before a washout period of bedaquiline. Furthermore, the WHO suggested a delamanid-bedaquiline sequence, and five-day washout period of delamanid is recommended before using bedaquiline due to short half-life of delamanid [28]. However, in Korea, bedaquiline was first approved in April 2014 and Delamanid was approved in October 2015. All patients treated sequentially in this study were commenced on bedaquiline before approval of delamanid in Korea, except for 1 patient undergoing a delamanid-bedaquiline sequence. Patients undergoing the bedaquiline-delamanid sequence had no choice in deciding which the new anti-TB drugs was administered first. Although bedaquiline has a long half-life, the area under the concentration-curve declined rapidly within 2 to 3 weeks of treatment followed by a slow elimination [39]. Therefore, blood concentration of bedaquiline, when patients received delamanid, may not be sufficiently influence QT prolongation. Moreover, as the recent cases of co-administration of the two drugs showed no significant adverse reactions, bedaquiline-delamanid sequential therapy, regardless of the time interval between two drugs, may not be an important factor in serious adverse reactions.

Few studies to date have assessed combinations of delamanid and bedaquiline with WHO recommended background regimens [23, 25, 32-35]. Although most of these studies reported a favorable response, there are still concerns about QTcF prolongation, suggesting the need for additional safety data. One patient in our study was administered both new anti-TB drugs and developed a significant QTcF prolongation, of 521 ms, at 41 days, requiring discontinuation of both delamanid and bedaquiline. This patient failed sputum culture conversion through the end of the study period. These findings suggest that care should be taken in selecting patients for co-administration of both new anti-TB drugs, and that these patients should be carefully monitored for QTcF prolongation.

In the sequential use of both new anti-TB drugs, few cases have been reported without detailed information regarding efficacy and safety [35]. All 10 of our patients treated sequentially had fluoroquinolone resistant MDR-TB, with 7 achieving culture conversion may be higher than that in a previous meta-analysis of individual patient data and a large cohort study in Korea for MDR-TB treatment without using new anti-TB drugs [3, 40]. The time to culture conversion in sequential use of both new anti-TB drugs was significantly longer than those in the groups treated with bedaquiline or delamanid alone and may also be caused by higher drug resistance, as shown in a previous study in patients requiring prolonged use of bedaquiline [18]. However, 1 of these patients experienced significant QTcF prolongation which required discontinuation of both these drugs. Patients treated sequentially with these drugs should be carefully monitored for QTcF prolongation.

Regarding treatment duration of the new anti-TB drugs, 8 patients received prolonged (> 190 days) treatment of bedaquiline or delamanid in this study. The WHO recommends 6 months of treatment for individual drugs, although in some cases this may not be sufficient and a longer

period may be required. Good outcomes with prolonged use of bedaquiline have recently been reported although further data are needed to clarify this issue [18].

One patient (55 year-old male) in this study discontinued bedaquiline treatment due to the termination of health insurance cover and failed to achieve negative sputum conversion until the end of the study period. This could be a public health risk in terms of transmission of high resistant tuberculosis. The decision to discontinue treatment occurred before starting the role of the national expert committee that has approved new anti-TB drugs after a careful review of individual cases in South Korea. Another important issue is the possibility of drug resistance to the new anti-TB drugs in the 16 patients who did not achieve culture conversion at the end of study period. We could not evaluate drug resistance, and this is a limitation of the present study, although this could be of great concern in the TB community. Therefore, appropriate regulatory efforts in approving the prescription of new anti-TB drugs as well as prudent decision-making by physicians when prescribing these drugs, are required to increase the cure rate of MDR-TB and prevent the development of additional drug resistance to these valuable new anti-TB drugs during treatment.

This study has several limitations due to its retrospective design. First, decisions about drug treatment were made by individual attending physicians. Therefore, patients had different treatment regimens. Second, there may have been a selection bias among enrolled patients. Because of the high prices of delamanid and bedaquiline, relatively young and economically well-off patients would likely be candidates for their use. In Korea, however, the costs of all anti-TB drugs, including new drugs, are paid by government-controlled health insurance. Therefore, the decision to treat patients with these new anti-TB drugs may be unrelated to age or economic status. Third, the low number of patients treated with delamanid prevented statistical

comparisons of the efficacy and safety of bedaquiline and delamanid. Bedaquiline was introduced earlier than delamanid, including for compassionate use, resulting in the higher number of patients treated with bedaquiline than with delamanid in this study. Fourth, the efficacy and safety of the reintroduction of new anti-TB drugs after discontinuation due to adverse drug reactions could not be evaluated. The drugs were not administered again once discontinued new anti-TB drugs in this study. Considering the limited number of effective drugs in MDR-TB treatment, reintroduction after discontinuation of new anti-TB drugs could be considered. Fifth, the distribution of treatment groups according to study periods and sites was not even. Bedaquiline was mostly prescribed in the early study period (2015) and over half of delamanid was prescribed in the mid study period (2016). In some study sites there were no cases of delamanid prescription, and most of both drugs (91%) were prescribed in a single center. However, there were no significant differences in culture conversion according to study periods and sites.

In conclusion, treatment of patients with MDR-TB with bedaquiline and/or delamanid, including their sequential use, was generally effective and well-tolerated. However, patients treated with both drugs, whether simultaneously or sequentially, should be carefully monitored for QTcF prolongation.

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Table 1. Baseline demographic and clinical characteristics of 61 patients with multidrug-resistant tuberculosis treated with delamanid and/or bedaquiline

Patient characteristics	Total (n=61)	Delamanid alone (n=11)	Bedaquiline alone (n=39)	Both drugs (n=11)	p value
Sex, male	49 (80.3)	9 (81.8)	32 (82.1)	8 (72.7)	0.893
Age, years	52.0 (40.5-60.0)	48.0 (41.0-64.0)	52.0 (40.0-60.0)	50.0 (39.0-56.0)	0.690
≥45 years	42 (68.9)	7 (63.6)	27 (69.2)	8 (72.7)	0.926
Body mass index, kg/m^2	20.4 (17.6-23.0)	20.9 (18.2-22.9)	20.4 (18.3-23.2)	18.4 (16.3-24.5)	0.519
<18.5 kg/m^2	19 (31.1)	3 (27.3)	10 (25.6)	6 (54.5)	0.246
Ever smoker	29 (47.5)	6 (54.5)	20 (51.3)	3 (27.3)	0.347
Heavy alcohol consumption	17 (27.9)	4 (36.4)	12 (30.8)	1 (9.1)	0.277

Combined extrapulmonary tuberculosis	2 (3.3)	0 (0)	2 (5.1)	0 (0)	1.000
Co-morbid conditions					
Diabetes mellitus	20 (32.8)	4 (36.4)	13 (33.3)	3 (27.3)	1.000
Chronic lung disease	7 (11.5)	0 (0)	5 (12.8)	2 (18.2)	0.451
Chronic kidney disease	3 (4.9)	1 (9.1)	2 (5.1)	0 (0)	0.741
Chronic liver disease	13 (21.3)	3 (27.3)	9 (23.1)	1 (9.1)	0.666
Malignancy	1 (1.6)	0 (0)	1 (2.6)	0 (0)	1.000
Previous treatment history for tuberculosis	51 (83.6)	10 (90.9)	30 (76.9)	11 (100)	0.224
Previously treated for multi-drug resistant tuberculosis	36 (59.0)	6 (54.5)	20 (51.3)	10 (90.9)	0.060
Number of drugs to which the isolates were resistant	9.0 (6.0-11.0)	9.0 (6.0-11.0)	7.0 (5.0-11.0)*	11.0 (9.0-12.0) *	0.025

MDR-TB with SLID resistance	19 (31.1)	3 (27.3)	12 (30.8)	4 (36.4)	0.925
MDR-TB with FQ resistance	42 (68.9)	9 (81.8)	22 (56.4)*	11 (100)*	0.009
XDR-TB	16 (26.2)	3 (27.3)	9 (23.1)	4 (36.4)	0.707
Positive sputum smear	34 (55.7)	6 (54.5)	21 (53.8)	7 (63.6)	0.931
Cavity (or cavities) on chest radiograph	30 (49.2)	5 (45.5)	20 (51.3)	5 (45.5)	1.000
Bilateral disease	45 (73.8)	7 (63.6)	27 (69.2)	11 (100)	0.075
Baseline laboratory tests					
Hemoglobin, g/dL	13.2 (11.7-14.2)	12.9 (11.7-14.6)	12.9 (11.5-14.2)	14.0 (11.8-14.0)	0.846
Albumin, g/L	3.9 (3.6-4.3)	3.7 (3.6-4.1)	3.9 (3.5-4.2)	4.3 (3.9-4.5)	0.065
AST, IU/L	24.0 (18.5-32.5)	28.0 (23.0-35.0)	24.0 (18.0-35.0)	23.0 (17.0-27.0)	0.288

ALT, IU/L	14.0 (8.0-21.5)	18.0 (9.0-21.0)	13.0 (8.0-19.0)	15.0 (8.0-24.0)	0.629
Total bilirubin, g/dL	0.5 (0.4-0.7)	0.4 (0.3-0.7)	0.5 (0.4-0.8)	0.6 (0.4-0.7)	0.749
Baseline QTcF, ms	441.0 (427.0-461.0)	441.0 (427.0-466.0)	438.0 (427.0-460.0)	449.0 (423.0-463.0)	0.660

Data reported as n (%) or median (interquartile range).

*Dunn's post hoc test was performed when the result of the Kruskal-Wallis test was significant: $P < 0.05$

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FQ, fluoroquinolone; MDR-TB, multidrug-resistant tuberculosis; QTcF, corrected QT interval using Friderica's Correction Formula; SLID, second-line injectable drugs; XDR-TB, extensively drug-resistant tuberculosis

Table 2. Drug resistance rates in 61 patients with multidrug-resistant tuberculosis

Drug	Number of patients (%)
Isoniazid	61 (100)
Rifampin	61 (100)
Rifabutin	49 (80.3)
Ethambutol	49 (80.3)
Pyrazinamide	43 (70.5)
Ofloxacin	42 (68.9)
Levofloxacin	41 (67.2)
Moxifloxacin	38 (62.3)
Prothionamide	30 (49.2)
Streptomycin	28 (45.9)
Para-aminosalicylic acid	20 (32.8)
Kanamycin	19 (31.1)
Cycloserine	17 (27.9)
Amikacin	16 (26.2)
Capreomycin (or viomycin)	12 (19.7)

Table 3. Treatment, outcomes, and QT prolongation of patients with multidrug-resistant tuberculosis patients treated with delamanid and/or bedaquiline

Treatment	Total (n=61)	Delamanid alone (n=11)	Bedaquiline alone (n=39)	Both drugs (n=11)	p value
Number of drugs administered, including delamanid and /or bedaquiline	5.0 (4.0-6.0)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	5.0 (3.0-6.0)	0.728
Treatment with any injectable drug	39 (63.9)	6 (54.5)	25 (64.1)	8 (72.7)	0.688
Duration of injectable drug treatment, days	224.0 (188.0-280.0)	229.0 (168.5-268.3)	224.0 (198.5-297.5)	230.0 (166.3-537.3)	0.863
Treatment with any fluoroquinolone	37 (60.7)	7 (63.6)	27 (69.2) +	3 (27.3) +	0.043
Treatment with linezolid*	33 (54.1)	6 (54.5)	17 (43.6)	10 (90.9)	0.017
Treatment with of clofazimine	12 (19.7)	1 (9.1)	5 (12.8) +	6 (54.5) +	0.011

Duration of linezolid treatment, days	673.0 (171.0-736.0)	154.5 (49.0-413.3)	617.0 (136.0-759.0)	729.5 (673.0-874.5)	0.094
Duration of treatment with treated with delamanid and/or bedaquiline, days	168.0 (166.5-196.5)	168.0 (167.0-176.0) ‡	168.0 (165.0-182.0) +	341.0 (230.0-375.0)+ ‡	0.001
Combined surgery*	5 (8.5)	2 (18.2)	1 (2.7)	2 (18.2)	0.102
Culture conversion	39/55 (70.9)	8/8 (100)	24/36 (66.7)	7/11 (63.6)	0.160
Time to culture conversion, days	119.0 (52.5-198.5)	122.0 (53.0-145.3) ‡	84.0 (35.5-174.0) +	307.5 (235.0-346.5)+ ‡	<0.001
Maximum QTcF, ms	469.0 (447.5-486.5)	469.0 (444.0-499.0)	464.0 (448.0-483.0)	475.0 (464.0-535.0)	0.386
Increase in QTcF from baseline, ms	22.0 (12.0-41.0)	25.0 (9.0-42.0)	19.0 (12.0-35.0)	35.0 (18.0-81.0)	0.293

Significant QTcF prolongation	42 (68.9)	7 (63.6)	26 (66.7)	9 (81.8)	0.721
Discontinuation of delamanid and/or bedaquiline because of QTcF prolongation	4 (6.6)	1 (9.1)	1 (2.6)	2 (18.2)	0.129

Data reported as n (%) or median (interquartile range).

*+ ‡ Dunn's post hoc test was performed when the result of the Kruskal-Wallis test was significant: *p>0.05 among groups;

+bedaquiline vs both drugs, P<0.05; ‡ delamanid vs both drugs, P<0.05.

QTcF, corrected QT interval using Friderica’s Correction Formula.

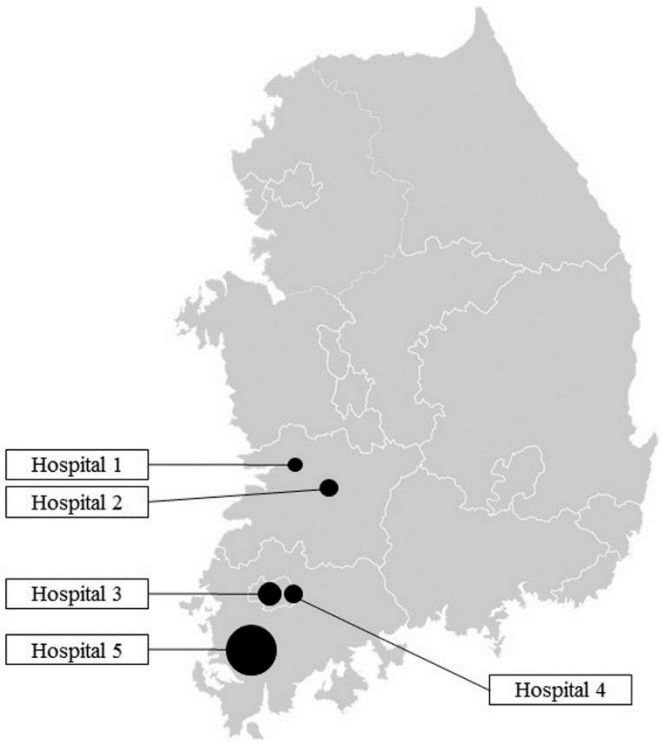
Table 4. Characteristics of four patients who were stopped delamanid and/or bedaquiline due to a prolonged QTcF.

Patient's number	Group	Age, years	Sex	Drug resistance	Duration of delamanid treatment, days	Duration of bedaquiline treatment, days	Baseline QTcF, ms	Maximum QTcF, ms	Concomitant drugs with an increased risk of QTcF prolongation
1	Both drugs (delamanid-bedaquiline sequential treatment)	55	M	XDRTB	168	49	463	572	Clofazimine
2	Delamanid	72	M	XDRTB	103		484	574	No
3	Bedaquiline	85	F	MDRTB		145	446	521	Moxifloxacin, clarithromycin

4	Both drugs (co-administration)	45	F	XDRTB	41	41	476	521	Clarithromycin

MDR-TB, multidrug-resistant tuberculosis; QTcF, corrected QT interval using Friderica's Correction Formula; XDR-TB, extensively drug-resistant tuberculosis

Figure 1. Distribution of five hospitals where patients with MDR-TB were treated with a regimen containing bedaquiline and/or delamanid in Korea. Total number of patients was 61; 3 in hospital 1; 5 in hospital 2; 8 in hospital 3; 5 in hospital 4; 40 in hospital 5.



Supplementary Table 1. Companion tuberculosis drugs administered to patients with multidrug-resistant tuberculosis treated with delamanid and/or bedaquiline

	Total (n=61)	Delamanid alone (n=11)	Bedaquiline alone (n=39)	Both drugs (n=11)	p value
Rifabutin	4 (6.6)	1 (9.1)	2 (5.1)	1 (9.1)	0.615
Ethambutol	9 (14.8)	0 (0)	8 (20.5)	1 (9.1)	0.260
Pyrazinamide	26 (42.6)	5 (45.5)	18 (46.2)	3 (27.3)	0.568
Streptomycin	11 (18.0)	1 (9.1)	9 (23.1)	1 (9.1)	0.435
Kanamycin	17 (28.3)	1 (9.1)	12 (31.6)	4 (36.4)	0.328
Amikacin	13 (21.3)	4 (36.4)	6 (15.4)	3 (27.3)	0.250
Capreomycin (or viomycin)					
Cycloserine	48 (78.7)	9 (81.8)	33 (84.6)	6 (54.5)	0.136
Prothionamide	46 (75.4)	9 (81.8)	31 (79.5)	6 (54.5)	0.236
Para-aminosalicylic acid	27 (44.3)	5 (45.5)	19 (48.7)	3 (27.3)	0.529
Ofloxacin	0	0	0	0	0
Levofloxacin	15 (24.6)	3 (27.3)	10 (25.6)	2 (18.2)	1.000
Moxifloxacin	24 (39.3)	5 (45.5)	18 (46.2)	1 (9.1)	0.087

Clarithromycin*	14 (23.0)	1 (9.1)	7 (17.9)	6 (54.5)	0.019
Amoxicillin-clavulanic acid	18 (29.5)	1 (9.1) ‡	9 (23.1)+	8 (72.7)+ ‡	0.002
Meropenem	4 (6.6)	1 (9.1)	2 (5.1)	1 (9.1)	0.615
Clofazimine*	12 (19.7)	1 (9.1)	5 (12.8)	6 (54.5)	0.011

Results reported as n (%)

*+ ‡ Dunn's post hoc test was performed when the result of the Kruskal-Wallis test was significant: *p>0.05 among groups; +bedaquiline vs both drugs, P<0.05; ‡ delamanid vs both drugs, P<0.05.

Supplementary Table 2. Factors related to culture conversion

Patient characteristic	Culture conversion (n = 39)	Persistently positive (n = 16)	p value
Age ≥45 years	27 (69.2)	11 (68.8)	1.000
Sex, male	31 (79.5)	14 (87.5)	0.706
Body mass index <18.5 kg/m^2	13 (33.3)	6 (37.5)	0.765
Previous treatment history for tuberculosis	31 (79.5)	14 (87.5)	0.706
Previously treated for multi-drug resistant tuberculosis	22 (56.4)	11 (68.8)	0.547
Smear-positive sputum	24 (61.5)	8 (50.0)	0.550
Presence of a cavity (or cavities)	16 (41.0)	11 (68.8)	0.080
Bilateral disease	29 (74.4)	14 (81.3)	0.734
MDR-TB with SLID resistance	9 (23.1)	7 (43.8)	0.191
MDR-TB with FQ resistance	28 (71.8)	12 (75.0)	1.000
XDR-TB	9 (23.1)	5 (31.3)	0.519
Treatment with new drugs			

Delamanid	8 (20.5)	0 (0)	0.162
Bedaquiline	24 (61.5)	12 (75.0)	
Both delamanid and bedaquiline	7 (17.9)	4 (25.0)	
Treatment with linezolid	21 (53.8)	10 (62.5)	0.765
Treatment with fluoroquinolones	21(53.8)	11 (68.6)	0.377
Treatment with levofloxacin	8 (20.5)	5 (31.3)	0.489
Treatment with moxifloxacin	15 (38.5)	6 (37.5)	1.000
Duration of treatment with delamanid and/or bedaquiline, days	173.0 (167.0-190.0)	167.0 (129.5-226.0)	0.168*

Results reported as n (%) or median (interquartile range).

FQ, fluoroquinolone; MDR-TB, multidrug-resistant tuberculosis, SLID, second-line injectable drugs; XDR-TB, extensively drug-resistant tuberculosis