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Research letter

Concurrent Use of Bedaquiline and Delamanid for the Treatment of Fluoroquinolone-resistant Multidrug-resistant Tuberculosis: A Nationwide Cohort Study in South Korea

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Title: Concurrent Use of Bedaquiline and Delamanid for the Treatment of Fluoroquinolone-resistant Multidrug-resistant Tuberculosis: A Nationwide Cohort Study in South Korea

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Take-home Message: Concurrent use of bedaquiline and delamanid is safe and effective for the treatment of high-level resistant tuberculosis.

Keywords: bedaquiline; delamanid; tuberculosis; multidrug-resistant tuberculosis; QT prolongation

To the editor:

Multidrug-resistant tuberculosis (MDR-TB), a major global health concern, requires long-term treatment with multiple drugs, which can cause many side effects [1]. Therefore, an effective regimen with a minimum number of drugs is essential to control this disease. Bedaquiline (Bdq) and delamanid (Dlm) are new drugs that exhibit good efficacy and safety for MDR-TB treatment [1]. However, adding only one of the new drugs to a regimen may be insufficient to cure this disease when the infecting strain has a high level of drug resistance, such as fluoroquinolone-resistant MDR-TB or extensively drug-resistant TB (XDR-TB) [1-3]. Therefore, the concurrent use of Bdq and Dlm can effectively strengthen the treatment regimen if the best practices in "off-label" use are followed [4-10]. This study analyzed the efficacy and safety of concurrent use of Bdq and Dlm in patients with MDR-TB and XDR-TB treated under a programmatic condition.

This retrospective cohort study included patients with pulmonary MDR-TB treated between September 2016 and December 2019 at tertiary referral and TB-specific hospitals in South Korea. The National TB Expert Review Committee (NTBERC) of the Korean Centers for Disease Control and Prevention was responsible for reviewing Bdq and Dlm approval since September 2016. In this study, we used the NTBERC database [8]. The process of submitting cases and obtaining permission to report cases has been described in a previous report [8]. Accompanying drugs were used according to the NTBERC's recommendation, which was based on the World Health Organization (WHO) guidelines [11].

MDR-TB was defined as TB resistant to both isoniazid and rifampin, while XDR-TB was defined as TB with additional resistance to any of the fluoroquinolones and to at least one of the three injectable second-line drugs (amikacin, capreomycin, or kanamycin).

Although the decision to initiate treatment with both new TB drugs was made by the attending physicians, these new TB drugs were prescribed only when an effective treatment regimen could not be provided because of drug resistance, adverse drug reactions (ADRs), poor tolerance, or contraindication to any component of the combination regimen. All enrolled patients were monitored for drug compliance and ADRs during treatment by specially trained nurses who participated in the Public-Private Mix project for TB control in South Korea [5].

We analyzed the patients' baseline clinical characteristics, including treatment duration of new drugs, ADRs including QT interval prolongation, sputum culture results at baseline, and sputum culture conversion. The QT interval was corrected using Fridericia's formula (QTcF). Significant QTcF prolongation was defined as any absolute QTcF value ≥ 500 ms or any increase in QTcF value > 60 ms from baseline. The interim treatment outcomes at 12 months, as of August 1, 2020, were analyzed. Interim treatment outcomes were deemed favorable or unfavorable. Favorable outcomes included cure, treatment completion, and culture conversion and maintenance of culture conversion on treatment. Unfavorable outcomes included death, loss to follow-up, and treatment failure, including failed culture conversion. Culture conversion was defined as two consecutive negative results obtained at least 30 days apart in a patient with positive sputum culture results at baseline. The day of sputum collection for the first of the two consecutive negative results was defined as the date of culture conversion.

Twenty-eight patients with MDR-TB were treated concurrently with Bdq and Dlm. Their median age was 49.5 years and most were male (Table 1). All the patients had fluoroquinolone-resistant MDR-TB and 18 (64.3%) patients had XDR-TB. None of the patient tested positive for human immunodeficiency virus. The median (interquartile range [IQR]) duration of the concurrent treatment was 167 (146–168) days. The treatment duration in three patients was >24 weeks (197, 230, and 334 days), whereas that in 22 patients was 24 weeks. However, the remaining three patients were treated for <24 weeks. Of them, one patient died due to bacterial pneumonia after taking 3 days of concurrent treatment. In another patient, Dlm was discontinued after 3 days of concurrent treatment owing to severe gastrointestinal side effects, including nausea and vomiting. In the last patient, although both drugs were administered for 24 weeks, concurrent treatment with both drugs was administered for only 3 weeks. During concurrent treatment, 25 (89.3%) patients received linezolid; however, three patients did not received linezolid due to adverse drug reactions induced by previous linezolid therapy. Common accompanying drugs, other than linezolid, included clofazimine (n=20, 69.0%), meropenem-clavulanate (n=19, 65.5%), cycloserine (n=14, 48.3%), *para*-aminosalicylic acid (n=8, 27.6%), and amikacin (n=7, 24.1%).

Sputum culture conversion was achieved in 18 of 19 (94.7%) patients who had positive culture results at the time of concurrent treatment initiation. The median (IQR) time from the initiation of the concurrent treatment to culture conversion was 32.5 (17.0–51.3) days. Of the 28 patients who had 12-month interim outcomes of MDR-TB treatment available, 23 (82.1%) patients showed favorable outcomes (cure: n=15; complete: n=2; maintenance of culture conversion on treatment; n=6) and five (17.9%) patients showed unfavorable outcomes (failure: n=2; deaths: n=1; lost to follow-up: n=2). One death was not related to TB (bacterial

pneumonia). Among the 22 (78.6%) patients who completed MDR-TB treatment, the median (IQR) duration of the treatment was 624 (508–741) days. Eighteen (64.3%) patients were treated successfully (cure=16, treatment completion=2); treatment failure (n=1), death (n=1), and lost to follow-up (n=2) were reported for the remaining four (14.3%) patients.

Significant QTcF prolongation and QTcF >500 ms were observed in 15 (53.6%) and two (7.1%) patients, respectively. However, there were no clinically significant cardiac events, and the new drugs were used continuously without interruption. Of the two patients with QTcF > 500 ms, one patient who had 504 ms of a maximum QTcF without symptoms recovered to 466 ms without discontinuing the new TB drugs. The other patient who had a maximum QTcF of 518 ms without symptoms was managed by discontinuing the two new TB drugs for 20 days, followed by successful reintroduction.

About the other ADRs except QTcF prolongation, one patient experienced severe nausea and vomiting, resulting in discontinuation of Dlm.

This cohort study revealed that concurrent use of Bdq and Dlm in combination with the WHO-recommended regimens showed good efficacy and safety. Fluoroquinolone-resistant MDR-TB and XDR-TB have poor treatment outcomes [2, 3]. However, in this study, 95% patients achieved culture conversion during concurrent treatment with the two new TB drugs and 82% patients achieved favorable outcomes at the 12-month interim analysis despite fluoroquinolone-resistant MDR-TB in all patients and XDR-TB in 64% patients. Therefore, this study emphasizes the effectiveness of treatment in patients with MDR-TB who have limited treatment options, including those with fluoroquinolone-resistant MDR-TB or XDR-TB. Drug-induced QTcF prolongation is an important safety issue associated with the new TB drugs,

especially under conditions that require additional TB drugs to magnify QTcF prolongation [12, 13]. Additional information regarding the cardiac safety of this treatment in combination with various regimens that may potentiate the side effects is required. In this study, although more than half of patients experienced significant QTcF prolongation, none of the drugs were discontinued. These results are consistent with those of previous studies, including a phase 2 randomized study (DELIBERATE trial) showing the efficacy and safety of sequential and concurrent therapy with the new anti-TB drugs [4-8, 14, 15].

The study limitations include the retrospective study design and a lack of a control arm, long-term treatment outcomes, and data on drug resistance against Bdq and Dlm.

In conclusion, the concurrent use of Bdq and Dlm is effective and well tolerated in MDR-TB patients with fluoroquinolone resistance. This treatment represents an attractive option for patients with fluoroquinolone-resistant MDR-TB or XDR-TB.

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Table 1. Baseline clinical demographics, treatment outcomes, and adverse drug reactions in patients with multidrug-resistant tuberculosis treated concurrently with bedaquiline and delamanid

Total number	28
Age, median years (IQR)	49.5 (45.0–57.8)
≥45 years, n (%)	22 (78.6)
Male patients, n (%)	18 (64.3)
South Korean nationality, n (%)	26 (92.9)
BMI, median kg/m^2 (IQR)	20.2 (19.1–21.3)
<18.5 kg/m^2, n (%)	6 (21.4)
Comorbidity	
Diabetes mellitus, n (%)	7 (25.0)
Hypertension, n (%)	2 (7.1)
Chronic liver disease, n (%)	3 (10.7)
Chronic kidney disease, n (%)	1 (3.6)
Chronic lung disease, n (%)	2 (7.1)
Malignancy (during the preceding 5 years),	1 (3.6)

n (%)	
Psychiatric disease, n (%)	6 (21.4)
Previous tuberculosis treatment history, n (%)	19 (67.9)
Previously treated for MDR-TB, n (%)	13 (46.4)
Number of drugs to which the isolates were resistant, median (IQR)	11 (9–12)
MDR-TB with SLID resistance, n (%)	18 (64.3)
MDR-TB with FQ resistance, n (%)	28 (100.0)
XDR-TB, n (%)	18 (64.3)
Positive sputum smear, n (%)	12 (42.9)
Cavity (or cavities) on chest radiograph or CT, n (%)	14 (50.0)
Bilateral disease on chest radiograph or CT, n (%)	16 (57.1)
Number of drugs administered, including delamanid and bedaquiline, n (%)	5.0 (4.0–5.0)
Treatment with linezolid, n (%)	25 (89.3)

Culture conversion, n (%)	18/19 (94.7)
Time to culture conversion days, median (IQR)	32.5 (17.0–51.3)
Baseline QTcF, median (IQR)	420.0 (410.3-437.0)
Maximum QTcF, median (IQR)	467.0 (452.5–485.5)
Increase between the baseline and the maximum QTcF, median (IQR)	44.0 (25.5–73.5)

BMI, body mass index; FQ, fluoroquinolone; MDR-TB, multidrug-resistant tuberculosis, SLID, second-line injectable drugs; XDR-TB, extensively drug-resistant tuberculosis.