Original Article

Effectiveness and safety of regimen containing bedaquiline and delamanid in patients with drug-resistant tuberculosis

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Abstract

Background: Bedaquiline and delamanid have been included in the individualized treatment regimen (ITR) to treat patients with drug-resistant tuberculosis (DR-TB).

Objective: The objective of this study is to compare the effectiveness of sputum culture conversion and the safety of ITR containing bedaquiline and delamanid.

Methods: Data were collected retrospectively from medical records of DR-TB patients who received ITR between January 2020 and December 2021. Patients were divided into bedaquiline and bedaquiline-delamanid groups. Sputum culture was evaluated until 6 months of treatment. Measurement of QTc interval, renal and liver function test, and serum potassium were evaluated to assess safety during the study period. We used Chi-square to analyze a difference in cumulative culture conversion; meanwhile, Wilcoxon and Mann–Whitney tests were used to analyze differences in laboratory data for each and between the two groups, respectively.

Results: Fifty-one eligible DR-TB patients met the inclusion criteria, 41 in the bedaquiline and 10 in bedaquiline-delamanid group. 43/51 patients had a positive culture at baseline. After 6 months of treatment, 42/43 DR-TB patients (97.6%) had sputum culture conversion and no difference between the two groups ($P \geq 0.05$). QTc interval within normal limit and no patient had a QTc >500 ms during the study period. Creatinine levels significantly differed between the two groups 6 months after treatment ($P < 0.05$).

Conclusion: DR-TB patients who received all oral ITR containing bedaquiline and or delamanid demonstrated favorable sputum conversion with a tolerable safety profile.

Keywords: Bedaquiline, delamanid, effectiveness, individualized treatment regimen, safety

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INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is a serious health problem worldwide. The estimated DR-TB cases in Indonesia are 2.4% of all new TB patients and 13% of those previously treated, with a total case of 24.000 or 8.8 per 100.000 population.[1] The inclusion of bedaquiline in DR-TB therapy significantly increased treatment success.

Bedaquiline and delamanid, two novel antitubercular drugs, resulted in high favorable outcomes, including sputum

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conversion and cure rates.[2] The Indonesia National Tuberculosis Program included bedaquiline and delamanid into programmatic use in the individualized treatment regimen (ITR).

Delamanid, a companion drug, has high early bactericidal and sterilization activity to reduce the bacillary load. In addition, it has an immunomodulatory property by modulating Th1 and Th2 cytokines, thus enhancing the bactericidal activity of macrophages.[3] Data on the concomitant use of bedaquiline with delamanid in Indonesia still need to be available. Two previous studies in Indonesia have reported QTc interval prolongation after the administration of bedaquiline.[4,5] However, these studies did not report QTc prolongation in patients receiving concomitant regimens containing bedaquiline-delamanid. Several studies have demonstrated the effectiveness and safety of a regimen containing bedaquiline-delamanid in Indian[6,7] and African populations.[8] However, in Asian patients, especially Indonesians, the outcome of DR-TB patients related to bedaquiline-delamanid has been poorly studied. Therefore, this study aimed to analyze the effectiveness and safety of ITR containing bedaquiline-delamanid in Indonesian DR-TB patients.

METHODS

Eligibility criteria

This was a retrospective study at the Dr. Soetomo hospital, in Surabaya, Indonesia. This study used medical records of DR-TB patients (MDR, Pre-XDR, and XDR-TB) who received ITR containing bedaquiline and delamanid between January 2020 and December 2021. Patients were divided into the bedaquiline and bedaquiline-delamanid groups. This study was conducted from September to December 2022. This study received approval from the Ethics Committee of Dr. Soetomo Hospital.

The inclusion criteria of this study were as follows: (a) DR-TB patients aged 18 years old or more; (b) completion of 6 months (24 weeks) of treatment; (c) GeneXpert/MTB RIF assay showed rifampicin resistance, and (d) used ITR containing bedaquiline and delamanid together with personalized background therapy. The exclusion criteria were as follows: (a) a QTc interval greater than 500 ms at baseline or had a history of a prolonged QTc interval; (b) renal dysfunction (creatinine clearance <30 ml/min or creatinine serum >3× the upper normal limit); and (c) liver impairment (serum glutamic-oxaloacetic transaminase [SGOT] or serum glutamic-pyruvic transaminase [SGPT]) >3 × the upper normal limit or total bilirubin >2 × the upper normal limit.

Treatment regimens

ITR consists of all oral with at least five effective drugs. All drugs in ITR were administered once daily for every day, meanwhile, bedaquiline was given every day for initial 2 weeks and thrice weekly for the remaining 22 weeks, and delamanid was given at a dose of 100 mg daily for a total of 24 weeks.

Effectiveness assessment

The initial treatment outcome was sputum culture at the end of 6 months. Sputum samples were collected monthly for culture as part of routine examination until 6 months was done. We restricted patients in our study who had a positive baseline sputum culture to further analysis. Culture conversion was defined as culture positive to negative within 6 months in two consecutive, negative culture collected at least 28 days apart in Lowenstein–Jensen medium.

Safety assessment

To assess safety, QTc interval and laboratory data including hemoglobin level, liver function test (SGOT, SGPT, and total bilirubin), renal function test (creatinine serum, blood urea nitrogen [BUN]), albumin, and potassium), albumin, and potassium level were measured at baseline and at each visit. Since bedaquiline and delamanid were administered for 6 months, we evaluated the safety every 3 months until 6 months of treatment. We used the Fredericia formula to calculate the QTc interval.

Statistical analysis

Categorical variables were reported as number or percentage, meanwhile, continuous data were expressed as median and interquartile ranges. Rate of sputum culture conversion was reported as percentage. Since sputum culture was categorical data, we used Chi-square to analyze the differences between the two groups. To analyze the differences for each group among continuous data including QTc interval, hemoglobin level, renal and liver function, potassium, and albumin level during 6 months of treatment, we used Wilcoxon signed rank test. We used Mann–Whitney to analyze the differences between the two groups for continuous data. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). P <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The demographic and clinical characteristics and the flowchart of the included patients were shown in Table 1

Table 1: Demographic and clinical characteristics of drug-resistant tuberculosis patients receiving individualized treatment regimen

Variable	BDQ (*n*=41), *n* (%)	BDQ + DLM (*n*=10), *n* (%)
Sex		
Male	21 (51.2)	6 (60.0)
Female	20 (48.8)	4 (40.0)
Age (years), median (IQR)	43.0 (20.0-62.0)	44.5 (19-69)
BMI (kg/m^2), median (IQR)	20.1 (13.8-28.0)	20.9 (14.8-24.0)
Prior anti-TB treatment		
Newly	24 (58.5)	7 (70.0)
Relapse/failed	17 (41.5)	3 (30.0)
Complications		
DM	12 (29.2)	2 (20.0)
HIV	1 (2.4)	0
Cavitary	16 (39.0)	2 (20.0)
Resistance TB		
MDR-TB	34 (82.9)	8 (80.0)
Pre-XDR-TB	7 (17.0)	1 (10.0)
XDR-TB	0	1 (10.0)
Culture positive at baseline	35 (85.3)	8 (80.0)
Smear positive at baseline	32 (78.0)	6 (60.0)
1+	9 (28.2)	2 (33.3)
2+	7 (21.8)	2 (33.3)
3+	16 (50.0)	2 (33.3)
Companion drugs		
BDQ	41 (100.0)	10 (100.0)
Clofazimine	41 (100.0)	9 (90.0)
Cycloserine	29 (70.7)	7 (70.0)
Levofloxacin	29 (70.7)	5 (50.0)
Linezolid	29 (70.7)	3 (30.0)
Ethambutol	10 (24.3)	2 (20.0)
DLM	0	10 (100.0)
Pirazinamide	8 (19.5)	3 (30.0)
Moxifloxacin	1 (2.4)	1 (10.0)

BDQ=Bedaquiline, DLM=Delamanid, IQR=Interquartile range, TB=Tuberculosis, DM=Diabetes mellitus, MDR=Multidrug-resistant, XDR=Extensively drug-resistant, BMI=Body mass index

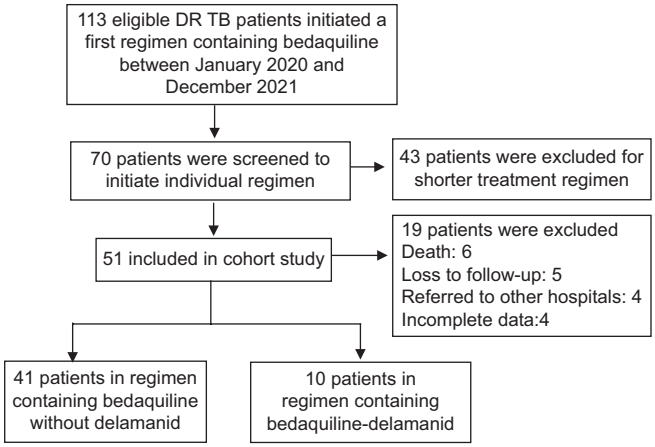

Figure 1: Overview of the study cohort

and Figure 1, respectively. All of the included patients had resistance to rifampicin and isoniazid.

A total of 51 DR-TB patients who met the inclusion criteria received ITR between January 2020 and December 2021. Of these, 41 patients were included in a regimen containing bedaquiline, and 10 were included in bedaquiline with delamanid. Thirty-eight of 51 patients (74.5%), the initial sputum smears were positive, and 43 of 51 (84.3%) had positive sputum cultures. All patients received bedaquiline with a backbone regimen between the two groups.

Treatment effectiveness

Cumulative sputum culture conversion during treatment is shown in Table 2. At 2 months after treatment, 31/35 (88.5%) and 6/8 (75.0%) patients had culture conversion in the bedaquiline and bedaquiline-delamanid groups, respectively. Sputum culture conversion at 6 months (24 weeks) was 97.1% and 100%, in the bedaquiline and bedaquiline-delamanid groups, respectively, with no significant difference ($P \geq 0.05$).

Safety

Safety of both groups at baseline, 3 and 6 months including QTc interval, hemoglobin level, SGOT, SGPT, total bilirubin, BUN, creatinine, and potassium are shown in Table 3. For QTc interval, there was no difference for each group and between the two groups during the study period ($P > 0.05$). For hemoglobin level, we found no difference for each group and between the two groups ($P > 0.05$).

DISCUSSION

This is the first study of DR-TB patients in Indonesia who have been treated with ITR containing bedaquiline and delamanid under programmatic conditions. Among 51 patients, 20 of them (39.2%) had a history of TB treatment. Prior exposure to antituberculosis drugs may increase six times more likely to develop MDR-TB.[9] One-fifth of the patients in our study had diabetes mellitus (DM); however, the overall sputum culture conversion at week 24 was satisfactory. A study by Shi *et al*. reported that MDR/XDR-TB patients with diabetes who received a regimen containing bedaquiline, sputum conversion at week 24 were 90%.[10] According to acid-fast bacilli, the positive smears were observed in 38/51 (74.5%) patients. High smear grading was significantly associated with MDR-TB.[11]

The 6 months of sputum culture conversion was 97.1% versus 100%, in the bedaquiline and bedaquiline-delamanid groups, respectively. These are the highest rates of culture conversion ever reported in DR-TB patients. Observational studies reported a 6 months sputum culture conversion ranging from 74.0%–94.7%.[12,13] For patients in the BDQ-DLM group, sputum conversion at the 3rd month was below 80%, but at the 6th month, all patients achieved

Table 2: Sputum culture of drug-resistant tuberculosis patients between two groups

Period (months)	BDQ (*n*=35)		Percentage conversion	BDQ + DLM (*n*=8)		Percentage conversion	*P*
	Positive	Negative		Positive	Negative		
Baseline	35	0	0	8	0	0	
1	11	24	68.5	3	5	62.5	0.741
2	4	31	88.5	2	6	75.0	0.318
3	3	32	91.4	2	6	75.0	0.191
4	2	33	91.4	1	7	87.5	0.497
5	2	33	91.4	0	8	100.0	0.498
6	1	34	97.1	0	8	100.0	0.629

BDQ=Bedaquiline, DLM=Delamanid

Table 3: Safety of bedaquiline and delamanid between two groups

Variable/months	Group, median (IQR)		*P*
	BDQ (*n*=41)	BDQ + DLM (*n*=10)	
Baseline			
QTc interval (ms)	430 (325-493)	448 (325-493)	0.575
Hemoglobin (g/dL)	12.20 (6.70-16.60)	11.4 (7.80-15.00)	0.767
SGOT (U/L)	24.00 (12.00-165.00)	30.0 (16.0-92.0)	0.028‡
SGPT (U/L)	22.50 (8.00-227.00)	29.0 (13.0-79.0)	0.059
Total bilirubin (mg/dL)	0.54 (0.09-6.20)	0.5 (0.20-0.60)	0.508
BUN (mg/dL)	8.00 (4.00-43.00)*	8.50 (4.00-15.00)	0.157
Creatinine serum (mg/dL)	0.80 (0.40-2.10)	0.85 (0.60-2.80)	0.325
Potassium (mEq/L)	4.20 (2.80-5.40)	4.00 (3.00-4.40)	0.035‡
Albumin (g/dL)	3.50 (2.50-4.30)	3.60 (2.66-4.45)	0.475
3 months			
QTc interval (ms)	431 (323-492)	431 (323-492)	0.333
Hemoglobin (g/dL)	11.90 (7.40-15.30)	11.25 (8.30-14.30)	0.799
SGOT (U/L)	27.50 (11.30-130.00)	25.00 (14.00-149.00)	0.594
SGPT (U/L)	20.00 (5.00-151.00)	34.0 (13.0-110.0)	0.069
Total bilirubin (mg/dL)	0.56 (0.20-1.15)	0.53 (0.24-0.87)	0.241
BUN (mg/dL)	10.00 (4.00-27.00)**	11.00 (6.00-14.00)	0.799
Creatinine serum (mg/dL)	0.80 (0.47-1.80)	0.84 (0.55-5.55)	0.240
Potassium	4.30 (3.20-5.20)	4.10 (3.40-4.70)	0.678
Albumin (g/dL)	3.70 (2.84-4.40)**	3.70 (0.73-4.15)	0.799
6 months			
QTc interval (ms)	429 (343-481)	445 (396-484)	0.678
Hemoglobin (mg/dL)	12.15 (8.60-15.50)	11.10 (7.20-13.40)	0.332
SGOT (U/L)	29.00 (14.50-71.00)	27.5 (12.0-76.0)	0.594
SGPT (U/L)	21.50 (9.00-64.00)	21.5 (11.0-62.0)	0.779
Total bilirubin (mg/dL)	0.51 (0.22-1.24)	0.48 (0.33-0.60)	0.799
BUN (mg/dL)	10.00 (3.00-30.00)***	10.00 (9.00-14.00)	0.514
Creatinine serum (mg/dL)	0.90 (0.50-1.51)***	1.01 (0.70-1.41)	0.005‡
Potassium (mEq/L)	4.30 (3.20-5.70)	3.95 (2.90-5.00)	0.838
Albumin (g/dL)	3.90 (3.20-5.70)***	3.86 (3.41-4.80)	0.093

*Significant between baseline and 3 months, **Significant between 3 and 6 months at level, ***Significant between baseline and 6 months at level, ‡Significant between two groups. BDQ=Bedaquiline, DLM=Delamanid, IQR=Interquartile range, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase, BUN=Blood urea nitrogen

sputum conversion. A high rate of sputum conversion at the 6th month can be used to predict treatment success at the end of the 24th month after the administration of bedaquiline. A lower culture conversion rate at 24 weeks (69%) in patients receiving bedaquiline-delamanid than our findings has been reported by Das *et al*.[7] However, almost all patients were pre-XDR and XDR-TB. Those with pre-XDR and XDR-TB are reported to have poor culture conversion.[14]

We found no patients with a more than 500 ms QTc interval in both groups during the study period. We did not find any significant increase in the QT interval from baseline to 6 months for each group. This finding is similar to the study by Das *et al*., who also reported no QTc longer than 500 ms in patients who received a regimen containing bedaquiline-delamanid.[7] The absence of QTc prolongation in our study could not be separated from potassium levels within the normal limit during the study period. Hypokalemia is a risk factor for QTc prolongation. DR-TB patients who received the regimen containing bedaquiline and with QTc prolongation, baseline potassium levels were lower compared to those without QTc prolongation.[4] Therefore, periodic monitoring of potassium levels is highly recommended for early detection of QTc prolongation.

7/51 patients (13.7%) had Hb <10.5 g/dl at baseline in our study. Hemoglobin level at baseline <10.5 g/dl was a risk factor for anemia related to linezolid. Compared to a study by Dayyab *et al*. reported that 30.77% of patients had anemia (Hb <8 g/dl) related to linezolid at a median 9.9 weeks after treatment initiation.[15] Level of hemoglobin when decrease more than 10% after administration of linezolid for 4 weeks confers sensitivity and specificity, 82% and 84%, respectively, to predict severe anemia.[16]

For liver function test, we found no patients had symptoms of hepatotoxicity such as jaundice and malaise during the study period. A study in Indonesia by Azis *et al*. demonstrated that MDR-TB patients who received a shorter treatment regimen, the incidence of hepatoxicity was 41/129 (31.78%), with the majority of onset >14 days.[17] For renal function test, we found a significantly higher serum creatinine in the bedaquiline-delamanid group at 6 months, however, its level was within normal limit. An increase level of creatinine was associated with concomitant use of levofloxacin and or moxifloxacin. Although our study indicates a good safety profile in the concurrent use of bedaquiline with delamanid, active pharmacovigilance is required for reporting any possible adverse effects to strengthen the safety of drug use.[18]

This study had several limitations. In the beginning, since it was retrospective, only some clinical complaints of patients can be found in the medical record, and thus, we did not classify the severity of adverse effects due to limited information. In addition, due to limited laboratory data, we only reported for baseline, 3, and 6 months after initiation of bedaquiline and delamanid. A further prospective study is urgently needed by increasing the number of patients to obtain more comprehensive data regarding the safety and effectiveness of ITR containing bedaquiline and delamanid in DR-TB patients.

CONCLUSION

ITR with five oral drugs containing bedaquiline-delamanid achieved a high proportion of sputum culture conversion at 6 months and with a good safety profile to manage DR-TB patients.

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Conflicts of interest
There are no conflicts of interest.

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