Scientific Research Publishing

Journal of Tuberculosis Research, 2022, 10, 61-74
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Interim Outcomes and Adverse Events among Drug-Resistant Tuberculosis Patients Treated with Bedaquiline in the Philippines

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How to cite this paper: Lofranco, V.S., Torres-Cervas, M.R.A., Asence, K.A., Del Mundo, K.M.A., Balanag, V.M., Santiago, M.R.T., Garfin, A.M.C.G. (2022) Interim Outcomes and Adverse Events among Drug-Resistant Tuberculosis Patients Treated with Bedaquiline in the Philippines. *Journal of Tuberculosis Research*, **10**, 61-74.
https://doi.org/10.4236/jtr.2022.102005

Received: March 3, 2022
Accepted: April 21, 2022
Published: April 24, 2022

Abstract

Objectives: This study aimed to assess the interim outcomes for drug-resistant tuberculosis (DR-TB) patients treated with bedaquiline regimen under the operational research conditions compared to DR-TB patients treated without bedaquiline in their regimen, and to describe the adverse events that occurred among patients treated with bedaquiline in the Philippines. **Design:** Patients who were treated with a bedaquiline-containing regimen from June 2016 to May 2017 were included in this study as the intervention group, while patients who were treated without bedaquiline regimen from January 2013 to May 2016 were included as the comparison group. The interim treatment outcomes were compared using Chi-square test. The analysis of time to culture conversion within 6 months of treatment was conducted. A Cox proportional hazard model was constructed to identify the variables associated with a favorable interim treatment outcome. The R program was used for statistical analysis. **Results:** On the 6th month of treatment, the culture conversion for patients treated with a bedaquiline-containing regimen was significantly higher than with the comparison group [63/75 (84.0%) vs 84/117 (71.8%), p = 0.012)]. Nearly 15% of the patients treated with bedaquiline were lost to follow-up. Frequent adverse events included vomiting, dizziness, nausea, joint pain, and abdominal pain. **Conclusion:** The patients who were treated with bedaquiline-containing regimen have better interim treatment outcomes than those treated without bedaquiline, but the proportion of patients who were lost to follow-up remains substantial.

Keywords

Operational Research, New Anti-TB Drug Regimen Drug, Interim Outcomes, Adverse Events

1. Introduction

The Philippines is one of the 30 high tuberculosis (TB) and drug-resistant TB (DR-TB) burden countries. The 2016 National Tuberculosis Prevalence Survey reported that the estimated prevalence of pulmonary TB (PTB) was 983 per 100,000 based on Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) test and was 587 per 100,000 based on Mycobacterium tuberculosis (MTB) culture test [1]. The estimated number of incident multidrug-resistant TB (MDR-TB) cases was 20,000 in 2017 [2]. The 2012 National Tuberculosis Drug Resistance Survey (DRS) found MDR-TB in 2% of new cases and 22% of retreatment cases [3]. Treatment success rate for the 2016 MDR-TB patient cohort was 57% and the loss of follow-up was a major challenge in the Philippines accounting for the 31% of patients in the 2016 cohort [4].

A conventional treatment regimen (CTR) was used for the treatment of DR-TB until 2016. The regimen included pyrazinamide (Z), kanamycin (Km), levofloxacin (Lfx), prothionamide (Pto), and cycloserine (Cs). The duration of the intensive phase was 6 months, while the continuation phase lasted for 12 months. In June 2013, the World Health Organization (WHO) published the interim policy guidelines on the use of bedaquiline (Bdq) for the treatment of MDR-TB [5].

The bedaquiline is the first new anti-TB drug introduced to the market after 45 years [6]. The drug belongs to a new class called diarylquinoline and has a novel mechanism of action against *Mycobacterium tuberculosis* [6] [7]. It received conditional approval both from the United States Food and Drug Administration in 2012 and European Medicines Association in 2014 after it showed improved efficacy compared with the standard therapy for DR-TB [7]. The use of bedaquiline when combined with other active drugs has the potential to achieve high culture conversion rates in complicated MDR-TB and XDR-TB cases, with a reassuring safety profile after 6 months of treatment [8].

In the Philippines, the bedaquiline was initially introduced under operational research conditions in 2016 for patients who met the specific criteria for the treatment regimen. All of the included patients were treated according to good clinical practice, and were informed about the expected benefits and potential side effects of bedaquiline and other anti-TB drugs. In this study, we compared the interim outcomes among patients with DR-TB treated with a bedaquiline-containing regimen to those who were treated without bedaquiline. We also assessed the types and frequency of adverse events among patients treated with a bedaquiline regimen.

2. Materials and Methods

2.1. Study Design

This is a comparative cohort study using the data collected from the prospective study of bedaquiline-containing regimen implemented under the operational research conditions from June 2016 to May 2017 (intervention group) and the retrospective data routinely collected from the matched DR-TB cohort of patients who were treated without bedaquiline under program conditions between January 2013 to May 2016 (comparison group).

2.2. Study Population and Setting

The study population included all of the DR-TB patients treated with a bedaquiline-containing regimen from nine programmatic management of drug-resistant tuberculosis (PMDT) study sites from June 1, 2016 to May 31, 2017.

The inclusion criteria of patients to be enrolled for the treatment with bedaquiline-containing regimen were: age 18 - 64 years; with pulmonary tuberculosis with documented resistance to fluoroquinolones (FQs) or second-line injectable drugs (SLIs), or both as extensively drug-resistant tuberculosis (XDR-TB) by line probe assay (LPA) or conventional drug-susceptibility test (DST) in addition to MDR-TB, and patients in whom a WHO-recommended regimen with 4 effective drugs could not be constructed due to resistance or intolerance of medications. Patients had to provide written consent and must be willing to completely receive directly observed treatment (DOT).

Meanwhile, the exclusion criteria for patients who were not eligible for the bedaquiline-containing regimen were females who were pregnant or breastfeeding, with refusal in any of the required laboratory tests, with severe intractable extrapulmonary TB (unless pulmonary TB was also present), had known allergy to bedaquiline, could not take oral medications, with concomitant medications contraindicated with bedaquiline, any condition (social or medical) that would make study participation unsafe based on investigator's opinion, inability to attend or comply to treatment or the follow-up schedule, had a heart rate-corrected QT (QTc) interval of >450 msec based on electrocardiogram (ECG) result upon screening, with history of Torsade de pointes or cardiac ventricular arrhythmia or severe coronary artery disease, or elevated level of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of >5 times than the upper limit of normal value. Prior to starting the treatment with a bedaquiline-containing regimen, the clinical information of patients was presented to the TB Medical Advisory Committee (TB MAC), a committee of experienced MDR-TB clinicians that provides guidance on management of difficult TB cases. The bedaquiline was given for six months to qualified patients as per WHO guidelines [7]. The DR-TB patients from the same facilities and with matched FQ and/or second-line injectable (SLI) resistance pattern, but who were not treated with bedaquiline during the period of January 1, 2013 to May 31, 2016 were selected as a comparison group.

2.3. Sample Size

To determine the number of cases needed for the comparison group, we assumed that 50% of patients in this group would have a favorable interim outcome compared to 75% of patients treated with a bedaquiline-containing regimen. The power to detect the difference between the two groups was set at 80% with a type 1 error of 5%. Based on these assumptions, the sample size needed was 50 patients for the intervention group and 100 patients for the comparison group. We included all of the 75 patients treated with a bedaquiline regimen under the operational research conditions in the study and aimed to identify 150 patients for the comparison group.

2.4. Data Management

The data were collected using a standardized tool and were entered into a database in EpiData Manager version 4.4.0 (EpiData Association, Odense, Denmark). Dual data entries were done and data were checked for accuracy, consistency, and completeness. For all of the patients, the data on age, sex, occupation, body mass index (BMI), monthly sputum smear microscopy and culture results, and history of diabetes mellitus, TB disease, HIV, and substance abuse were collected. Data on the interim treatment outcomes in the 6th month were collected. A favorable interim treatment outcome was defined as two consecutive negative cultures taken at least 30 days apart at the end of six (6) months of treatment. Patients who had positive culture in the 6th month of treatment, lost to follow-up, or died were categorized as having unfavorable outcomes.

The adverse event data were collected for patients treated with a bedaquiline-containing regimen under operational research conditions. The data on documented symptoms and laboratory tests were collected at baseline evaluation and monthly thereafter. Electrocardiograms were done at baseline, 2 hours after the initial dose, and at least after 2, 12, 24, 36 and 48 weeks of treatment, and repeated during the treatment of patients manifested any sign or symptom related to heart rhythm and conduction disturbances. All adverse event data were recorded. If the same adverse event was reported more than once in a given month, information on the most severe event was recorded.

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to define the severity of adverse events of special interest (AESI) [9] including grade 3 or higher hepatotoxicity which is defined as serum glutamic pyruvic transaminase (SGPT) or serum glutamic oxaloacetic transaminase (SGOT) level five times higher than the upper limit of normal value, and QT interval prolongation which is defined as a corrected QTcF ≥ 451 msec using the Fridericia formula. Renal insufficiency was defined as a creatinine level with >3 higher times than the upper limit of normal. Ototoxicity was defined as a decrease in hearing to profound bilateral loss with an absolute threshold of more than 80 decibels at 2 kilohertz and above [9]. A serious adverse event (SAE) was defined as an event or any undesirable experience associated with the use of

medical product in patient resulting in death, life threatening situation, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, a requirement of intervention to prevent permanent impairment or damage, or other medically important events that are not within the conditions already included [10].

2.5. Data Analysis

The Chi-square test was used for the categorical variables to test for a difference between the 2 groups. A p-value < 0.05 was statistically significant. The analysis of time to culture conversion within 6 months of treatment among baseline culture positive patients was conducted using the Kaplan-Meier method and log-rank test. Cox proportional hazard regression analysis was conducted to identify the variables associated with a favorable interim treatment outcome. Statistical analyses were performed using the R software (version 3.5.1).

Among patients treated with bedaquiline, the types and frequency of adverse events were assessed. The frequency of adverse events of special interest (hearing loss, hepatotoxicity, QTcF prolongation, and renal insufficiency) and serious adverse events were reported.

2.6. Ethics Approval

The study protocol was approved by the Lung Center of the Philippines Institutional Ethics Review Board.

3. Results

In the demographics and clinical characteristics of 75 patients in the intervention group, 50 (66.7%) were male and most patients were aged 18 - 54 years (88%). A total of 117 patients who were treated without bedaquiline were included in the comparison group in whom 72 (61.5%) were male and most patients were aged 18 - 54 years (86%). Among the patients treated with bedaquiline regimen, there were only 8 (10.7%) who were classified as new for TB treatment, while 67 (89.3%) of them were retreatment cases.

The groups were similar in terms of most characteristics. However, patients in the comparison group were more likely to have a positive culture at baseline and differed in terms of smoking, alcohol use, and substance use (see **Table 1**).

3.1. Interim Outcomes at the End of the 6th Month

The interim outcomes at the end of 6 months are presented in **Table 2**. It shows that among the patients treated with bedaquiline regimen, 63 (84.0%) of them had negative culture at 6 months. The proportion of patients with a negative culture is higher among those who were treated with the bedaquiline regimen as compared to those treated without bedaquiline (p = 0.012). Loss to follow-up was substantial among bedaquiline patients 11 (14.7%). Only 1 (1.3%) patient died at the end of 6 months.

Table 1. Demographics and clinical characteristics of patients with MDR-TB by treatment regimen.

Characteristics	Total		With bedaquiline		Without bedaquiline		p-value
	No.	%	No.	%	No.	%	
All cases	192	100	75	100	117	100	
Age group							0.71
17 - 34	80	41.7	34	45.3	46	39.3	
25 - 54	87	45.3	32	42.7	55	47.0	
55 - 65	25	13.0	9	12.0	16	13.7	
Employment history							0.02
Employed	33	17.2	10	13.3	23	19.7	
Unemployed	146	76.0	64	85.3	82	70.1	
Unknown	13	6.8	1	1.3	12	10.3	
Sex							0.57
Male	122	63.5	50	66.7	72	61.5	
Female	70	36.5	25	33.3	45	38.5	
History of TB treatment							0.65
New	17	8.9	8	10.7	9	7.7	
Retreatment	175	91.1	67	89.3	108	92.3	
Social history[b]							
Smoking							0.03
Yes	89	46.4	31	41.3	58	49.6	
No	96	50.0	44	58.7	52	44.4	
Unknown	7	3.6	0	0	7	6.0	
Alcohol use							<0.001
Yes	82	42.7	9	12.0	73	62.4	
No	103	53.6	66	88.0	37	31.6	
Unknown	7	3.6	0	0	7	6.0	
Substance Use							<0.001
Yes	21	10.9	4	5.3	17	14.5	
No	147	76.6	71	94.7	76	65.0	
Unknown	24	12.5	0	0	24	20.5	
With comorbidities[a,b]							1
Yes	157	81.8	61	81.3	96	82.1	
No	35	18.2	14	18.7	21	17.9	
Body mass index (abnormal)[b]							0.94
No	121	63.0	48	64.0	73	62.4	
Yes	71	37.0	27	36.0	44	37.6	

Continued

Baseline sputum test results							
Smear							0.35
Negative	52	27.1	25	33.3	27	23.1	
Positive	135	70.3	46	61.3	89	76.1	
Unknown	5	2.6	4	5.3	1	0.9	
Culture							<0.0001
Negative	36	18.8	24	32.0	12	10.3	
Positive	142	74.0	42	56.0	100	85.5	
Unknown	14	7.3	9	12.0	5	4.3	

[a]Comorbidities: diabetes mellitus, renal insufficiency, liver disease, HIV and cancer; [b]Social history and comorbidities were based on patients' self-report; [c]Abnormal BMI = underweight (<18.5 kg) and obese (≥18.5 kg).

Table 2. Interim treatment outcome of patients at the end of 6th month of treatment.

Interim Outcome	With bedaquiline		Without bedaquiline		Total		p-value
	No.	%	No.	%	No.	%	
With negative TB culture result	63	84.0	84	71.8	147	76.6	0.012
With positive TB culture result	0	0	6	5.1	6	3.1	
Lost to follow up	11	14.7	15	12.8	26	13.5	
Died	1	1.3	12	10.3	13	6.8	

3.2. Factors Associated with Culture Conversion

Among the 42 patients in the intervention group with a positive culture at baseline, there were 38 (90.5%) who had a negative culture after 6 months. Among the 100 patients with a positive culture result at baseline in the comparison group, 72 (72.0%) of them had a negative culture result in the sixth month of treatment. The factors associated with culture conversion within 6 months are shown in Table 3. The intervention group was more likely to have culture conversion within 6 months of treatment than patients in the comparison group (adjusted hazard ratio 2.2, 95% confidence interval 1.3 - 3.1).

3.3. Time to Initial Culture Conversion within 6 Months among Culture-Positive Positive of Patients at Baseline

The time to culture conversion among patients with a positive culture at baseline was compared between the two groups. The intervention group achieved culture conversion earlier than those with comparison group ($p < 0.001$) (see Figure 1). In the intervention group, 39 (90%) achieved culture conversion at the end of two months of treatment and all patients achieved culture conversion at the end of three months. Among the comparison group, 84 (55%) and 13 (85%) had culture converted by the end of two and four months of treatment, respectively (see Figure 1).

Table 3. Factors associated with culture conversion at 6th month among patients who are culture-posiitve at baseline.

Factors	Total no. of patients	With culture conversion		Univariate		Multivariate		
		No.	%	Hazard ratio	95%	Hazard ratio	95%	p-value
TB treatment								
With bedaquiline	42	38	41.7	34	45.3	2.2	(13 - 3.1)	<0.001
Without bedaquiline	100	72	72.0	Reference group				
Age								
18 - 34	56	43	76.8	Reference group				
35 - 54	66	49	74.2	1.1	(0.7 - 1.7)			
55 - 64	20	18	90.0	1.6	(0.9 - 2.8)			
Sex								
Male	88	67	76.1	Reference group				
Female	54	43	79.6	1.1	(08 - 1.7)			
Employment status								
Employed	103	79	76.7	0.8	(0.5 - 1.3)			
Unemployed	27	22	81.5	Reference group				
Unknown	12	9	75.0	0.7	(0.3 - 1.3)			
Social history								
Smoking								
No	63	50	79.4	1.6	(1.1 - 2.3)	1.4	(1.0 - 2.1)	0.07
Yes	79	60	76.0	Reference group				
Alcohol use								
No	71	55	77.5	1.5	(1.1 - 2.3)			
Yes	71	55	77.3	Reference group				
Substance use								
No	104	88	84.6	1.8	(1.1 - 2.9)	1.4	(0.9 - 2.3)	0.17
Yes	38	22	52.6	Reference group				
History of TB treatment								
New	12	11	91.7	1.7	(0.9 - 2.3)			
Retreatment	130	99	76.2	Reference group				
Comorbidities (diabetes mellitus, renal insufficiency, liver disease, HV, and cancer)								
No	115	81	81.0	1.0	(0.6 - 1.6)			
Yes	27	19	62.5	Reference group				
Body mass index (BMI): Underweight								
No	95	64	75.8	1.0	(0.7 - 1.5)			
Yes	47	36	83.3	Reference group				
Baseline smear result								
Negative								
Positive								

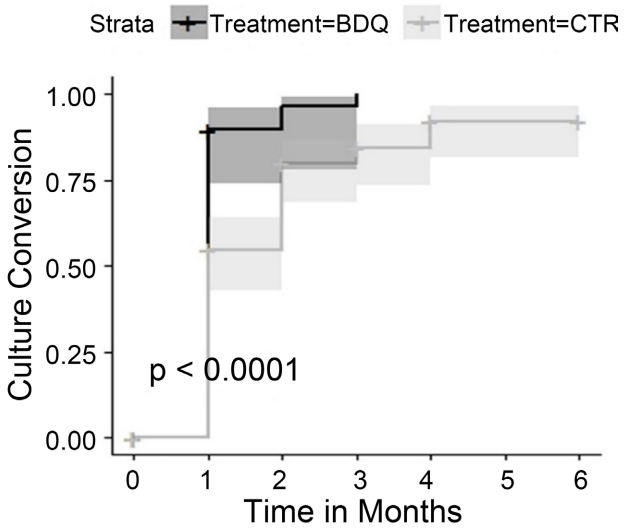

Figure 1. Time to initial conversion within 6 months of treatment.

3.4. Common Adverse Events and Adverse Events of Special Interest among Patients in the Intervention Group

The five most common adverse events (see **Figure 2**) during the intensive phase of treatment were vomiting, dizziness, cough, nausea, and increased creatinine. More adverse events of special interest were observed during the intensive phase compared to the continuation phase (see **Table 4**).

3.5. Serious Adverse Events

Among the 75 patients in the intervention group, 53 (70.7%) experienced a total of 86 episodes of SAEs (see **Figure 3**). Five (5.8%) of these resulted in death due to asphyxia secondary to hemoptysis, multi-organ failure, cardiac arrhythmia, and acute respiratory failure; the cause of death for one patient was unknown. There were 63 (73.3%) episodes of SAEs linked to other medically important events including hypokalemia in 11 (17.5%) patients, hypermagnesemia in four (4.8%) patients, hyperglycemia in four (4.8%) patients, hyperuricemia in nine (14.3%) patients, and QTcF > 450 msec in 28 (44.4%) patients. Three (4%) out of 70 patients had QTcF of ≥501 msec.

4. Discussion

The primary objective of this study was to compare interim treatment outcomes among patients with DR-TB treated with bedaquiline compared to patients treated without bedaquiline. Patients treated with bedaquiline-containing regimen together with the background regimen led to faster culture conversion and higher rates of culture conversion after six months of treatment than in the background regimen plus the placebo arm [11]. In our study, the culture conversion rate was 84% after six months of bedaquiline.

Results from one study in Armenia and Georgia showed culture conversion in 54 (84.4%) patients in the sixth month, but 10 (18.5%) reverted back to positive

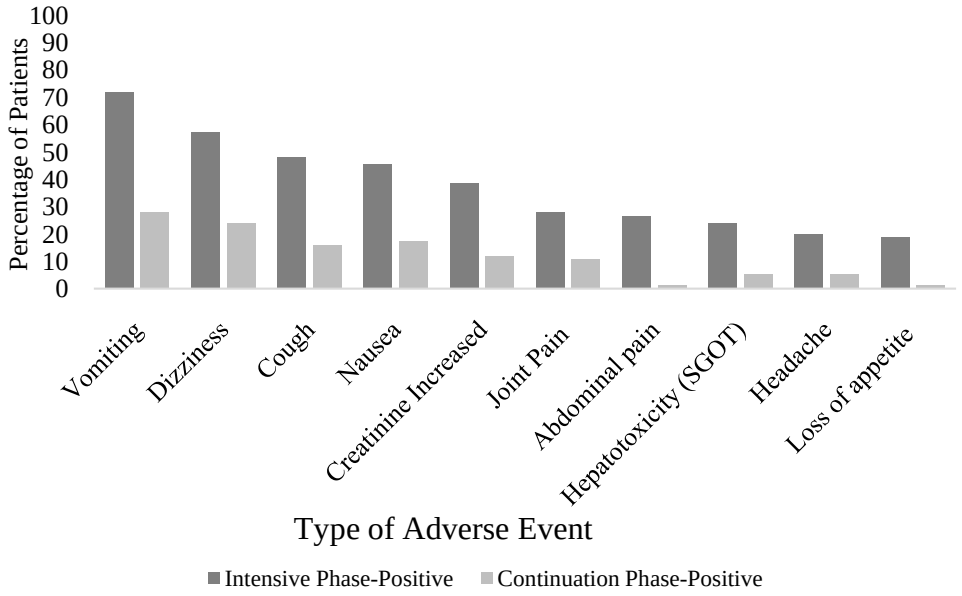

Figure 2. Common adverse events identified among patients with bedaquiline in the regimen (intensive phase vs. continuation phase).

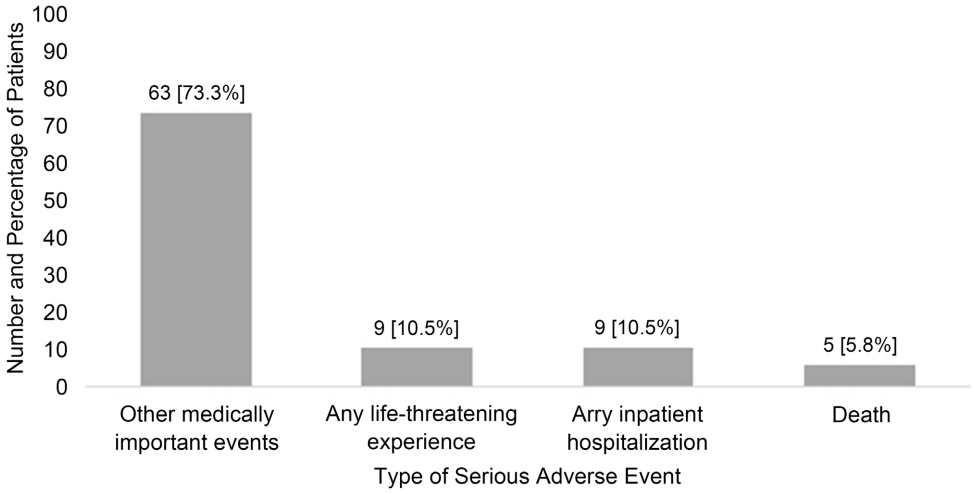

Figure 3. Serious adverse events.

Table 4. Adverse events of special interest.

AESI	*n*	Intensive phase		Continuation phase		Overall	
		No.	%	No.	%	No.	%
Hepatotoxicity[a]							
Elevated SGPT level	74	2	(2.7)	0	0	2	2.7
Elevated SGPT level	74	3	(4.1)	0	0	3	4.1
Renal insufficiency[b]							
Elevated creatinine clearance level	75	1	(1.3)	0	0	1	1.3

Continued

Hearing impairment[c]							
Left ear	46	2	(4.3)	0	0	2	4.3
Right ear	49	3	(6.1)	0	0	3	6.1
QTcF prolongation[d]	70	18	(25.7)	2	2.7	18	(25.7)

AESI definitions: [a]Hepatotoxicity is defined as SGPT or SGOT level five times higher than the upper limit of normal value. [b]AESI definition: Renal insufficiency is the creatinine level five times higher than the upper limit of normal value. [c]AESI definition: Hearing impairment is the decrease in hearing to profound bilateral loss with absolute threshold of more than 80 dB at 2 kHz and above. [d]AESI definition: QT prolongation is the corrected QTcF ≥ 450 msec using the Fridericia formula.

and the median time to reversion was 4.2 months (IQR 2.3 - 10.5) [12]. In our study, bedaquiline was given for 24 weeks and no reversion was noted at the end of six months. It would be important to assess reversions in our study group to see if the reversion rate was comparable to other studies. A multicenter study conducted in different countries showed that the bedaquiline reduced the median time to culture conversion, as compared with placebo, from 125 days to 83 days ($p < 0.001$) and increased the rate of culture conversion in 24 weeks (79% vs. 58%, $p = 0.008$) [12] and in 120 weeks (62% vs. 44%, $p = 0.04$) [13]. The bedaquiline-containing regimens achieved a culture conversion rate of >90% at the end of treatment [14]. In our study, 1 (1.3%) patient died during the sixth month of treatment, which is similar to the study by Diacon, *et al.* [11]. However, we only assessed outcomes up to 6 months, thus our results may not be directly comparable to the data reported by Diacon, *et al.* after 24 weeks of treatment.

In this study, adverse event data were only assessed among patients treated with bedaquiline. Prolongation of QTc interval with >501 msec was seen only in three patients. Several anti-TB drugs could prolong the QT interval, including moxifloxacin, clofazimine, and bedaquiline. Among the patients with a QTc interval of >450 msec, the majority of them (28, 44%) were asymptomatic. In a retrospective study by Guglielmetti, *et al.*, a QT prolongation of >500 msec was found in 11% of patients with MDR-TB who received bedaquiline, but none experienced clinically significant adverse cardiac events [15]. The benefits and risks of adding bedaquiline, which could prolong the QT interval, should be considered in the DR-TB regimen composition and regular monitoring of QT interval by ECG should be practiced [16]. Other drugs, including moxifloxacin and clofazimine, may prolong the QT interval and may amplify the risk of arrhythmias when used in combination with bedaquiline [17].

The loss to follow-up was still a major issue among both groups. The National TB Control Program has been implementing several strategies since 2014 to reduce the proportion of patients who were lost to follow-up, [18] including decentralization of services, community-based treatment, patient enablers including transportation reimbursement, patient support groups, and the use of new

anti-TB drugs and novel regimens. However, additional strategies to reduce the proportion of patients who were lost to follow-up need to be identified and be implemented to improve the treatment outcomes for DR-TB.

There were several limitations to our study. Only patients with pulmonary DR-TB were included, as were adults with ≥18 years of age so the findings may not be generalizable to patients with extra-pulmonary TB or children. Second, we only compared interim outcomes in the sixth month and did not compare the final treatment outcomes between the two groups. Additionally, this study was implemented in only nine selected PMDT facilities that had more experience in treating and managing DR-TB. Patients in the bedaquiline study underwent more thorough supervision and monitoring visits from the health workers thus the results may not be generalizable to patients treated under program conditions in other PMDT facilities. There were insufficient data on adverse events for patients treated without bedaquiline, thus, we were unable to compare the types and frequency of adverse events between the two groups. Another limitation was the small sample of patients treated with bedaquiline under operational conditions. However, the study still contributes important evidence on the use of bedaquiline for the treatment of DR-TB.

5. Conclusion

The proportion of patients with culture conversion among patients with a positive culture at baseline is higher among patients who were treated with bedaquiline compared to those who were treated without bedaquiline. Additionally, the time to culture conversion is faster among those treated with a bedaquiline-containing regimen. However, loss to follow-up remains substantial. The rational use of bedaquiline and close monitoring is important to improve the patient's adherence to treatment.

Data Availability

The datasets supporting the conclusions of this article are included within the article.

Authors' Contributions

All authors contributed to the manuscript conceptualization, design, literature review, analysis, and writing of the paper. They approved the final submitted paper.

The authors declared that they have agreed to publish in this journal.

Funding Statement

All operating expenses during the research team's collection of data at all implementing facilities were shouldered by The Global Fund assistance through Philippine Business for Social Progress (PBSP) as the principal recipient allowing the existing rules and regulation of the project assistance.

Acknowledgements

This study was made possible by the generous support of the American people through the United States Agency for International Development (USAID) through the TREAT TB Cooperative Agreement No. GHN-A-00-08-00004-00. The contents are the responsibility of the authors and do not necessarily reflect the views of USAID or the United States government Additional support was provided by the Philippine Department of Health-National Tuberculosis Control Program of the Disease Prevention and Control Bureau, National Center for Pulmonary Research-Lung Center of the Philippines, and Philippine Business for Social Progress-ACCESS TB Project of The Global Fund.

The authors would like to extend the gratitude to all PMDT staff (doctors, nurses, support staff) in the study sites headed by following physicians in the selected study sites: Dr. Joan Samoy-Tuy, Lung Center of the Philippines National Center for Pulmonary Research; Dr. Chiqui Villegas-Torres, Dr. Jose N Rodriguez Memorial Hospital; Dr. Nancy Rose Labarete, Sorsogon Medical Mission Group Hospital and Health Services Cooperative; Dr. Chester Directo, Ilocos Regional Training and Research Medical Center; Dr. Sheryll Magayanes, Jose B Lingad Memorial and General Hospital; Dr. Alimar Nassaie, Eversley Childs Sanitarium and General Hospital; Dr. Leonnie Fortin, Western Visayas Medical Center; Dr. Leslie Christine Magsayo-Salon, Xavier University-Community Health Care Center; and Dr. Marcelino Medina, Zamboanga City Medical Center.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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