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The Introduction of Bedaquiline Regimen for Drug-Resistant Tuberculosis in the Philippines: An Operational Study

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Abstract

Objectives: Bedaquiline (BDQ) is the first new anti-tuberculosis (TB) drug introduced to the market after 45 years. Recent studies have shown the potential benefits of adding bedaquiline to regimens for drug-resistant TB (DR-TB). In search of more effective regimens for DR-TB, bedaquiline was introduced in the TB program in the Philippines under operational research to assess its effectiveness, safety, and tolerability when given with background regimens among patients with multi-or extensively DR-TB (MDR/XDR-TB). **Design:** A prospective cohort study of patients with MDR/XDR-TB was given with a bedaquiline-containing regimen from June 2016 to May 2017. Demographic data, presence of comorbidities, and microbiologic profile on entry were recorded. Bedaquiline was administered at the recommended dose of 400 mg once daily for 14 days, then 200 mg three times a week for 22 weeks together with World Health Organization (WHO)-compliant background regimen. The time to culture conversion, interim outcomes at the 6th month of treatment, end-of-treatment outcomes, and post-treatment follow-up outcomes after one year was determined. The frequency and severity of adverse events (SAE) were recorded as part of pharmacovigilance. **Results:** Seventy-five patients were given with bedaquiline-containing regimen during the study period. Forty-two (56.0%) had second-line injectable resistance, 23 (30.7%) had fluoroquinolone-resistance, 6 (8.0%) had MDR-TB, and 4 (5.3%) had XDR-TB. In the 6th month of post-enrolment, 79% were culture-negative. The treatment success rate was 65.3% (37 were cured and 12 completed treatment), 7 (9.3%) died, 17 (22.7%) lost to follow-up, and 2 (2.7%) were

withdrawn from treatment. Adverse events included vomiting (80%), dizziness (69%), nausea (52%), cough (44%), and headache (36%). The post-treatment follow-up of 49 patients in the 12th month showed 92% were culture-negative while 8% of TBC were not done. **Conclusion**: Bedaquiline-containing regimens for patients with MDR/XDR-TB were highly effective with an acceptable safety profile and favorable treatment outcomes, but the proportion of patients who lost to follow-up remains substantial.

Keywords

Bedaquiline, Drug-Resistant TB, XDR-TB

1. Introduction

The Philippines is considered by the World Health Organization (WHO) as one of the 30 countries with a high burden of tuberculosis (TB) [1]. 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 and 587 per 100,000 based on *Mycobacterium tuberculosis* (M. tuberculosis) culture [2]. In 2017, the estimated number of incident multidrug-resistant TB (MDR-TB) cases was 20,000 [3].

The treatment for drug-resistant TB is long and expensive with several adverse events. The conventional treatment regimen (CTR) used for the treatment of DR-TB under the National TB Control Program (NTP) included pyrazinamide (Z), kanamycin (Km), levofloxacin (Lfx), prothionamide (Pto), and cycloserine (Cs). The intensive phase was 6 months, and the continuation phase was for at least 12 months. The treatment success rate for the 2016 MDR-TB patient cohort was 57%, and loss to follow-up was a major challenge accounting for 31% of patients [4]. One of the major reasons for withdrawal of treatment for multidrug-resistant TB (MDR-TB) is the presence or fear of adverse drug effects [5].

In June 2013, the WHO published interim policy guidelines on the use of bedaquiline (BDQ) for the treatment of MDR-TB [6]. Bedaquiline is the first new anti-TB drug introduced to the market after 45 years [7]. The drug belongs to a new class called diarylquinoline and has a novel mechanism of action against *Mycobacterium tuberculosis* [7] [8]. The introduction of bedaquiline in regimens for DR-TB has the potential to improve clinical outcomes and can have a major impact on the control of tuberculosis. This is operational research to determine the effectiveness, safety, and tolerability of bedaquiline when given with WHO-compliant background regimens for MDR/XDR (extensively drug-resistant)-TB.

2. Materials and Methods

2.1. Study Design

This is a prospective cohort study of bedaquiline-containing regimens imple-

mented under operational research conditions from June 2016 to May 2017.

2.2. Study Population and Setting

The study population consisted of DR-TB patients recruited for treatment with a bedaquiline-containing regimen from nine (9) Programmatic Managements of Drug-resistant Tuberculosis (PMDT) sites from June 1, 2016 to May 31, 2017.

The inclusion criteria for a bedaquiline-containing regimen were: 1) age 18 - 64 years; 2) pulmonary tuberculosis with resistance to fluoroquinolones (FQs) or second-line injectable drugs, or both (XDR-TB), by line probe assay (LPA) or conventional drug-susceptibility test (DST) in addition to MDR-TB, and 3) patients to whom a WHO-recommended regimen with four effective drugs could not be constructed due to resistance or intolerance of medications. Patients must provide written consent and willingness to receive directly observed treatment (DOT) regularly.

Exclusion criteria were: 1) pregnancy or breastfeeding; refusal to undergo any required laboratory tests; 2) severe intractable extrapulmonary TB (EPTB), unless pulmonary TB was also present; 3) known allergy to bedaquiline; 4) cannot take oral medications; concomitant medications contraindicated with bedaquiline; 5) any condition (social or medical) that would make study participation unsafe based on investigator's opinion; 6) inability to attend or comply treatment or the follow-up schedule; 7) a heart rate-corrected QT (QTC) interval of >450 msec on ECG at screening; 8) history of Torsade de Pointes or cardiac ventricular arrhythmia or severe coronary artery disease; 9) or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal.

Before starting treatment with a bedaquiline-containing regimen, clinical information of the patient was presented to the TB Medical Advisory Committee (TB MAC), a committee of experienced MDR-TB clinicians that guides the management of difficult cases. Bedaquiline was given for 6 months to qualified patients as per WHO guidelines [9].

2.3. Procedure

For all patients, baseline demographic data on age, sex, occupation, body mass index (BMI), and presence of co-morbidities like diabetes mellitus, human immunodeficiency virus (HIV), and substance abuse were collected. Initial microbiologic profile [including AFB (acid-fast bacilli) smear, LPA, and M. tuberculosis culture results] on enrolment was obtained and recorded.

Bedaquiline was administered at the recommended dose of 400 mg once a day for 14 days, then 200 mg three times a week for 22 weeks. It was prescribed together with a regimen that may include pyrazinamide, an FQ (usually levofloxacin), an injectable like kanamycin or capreomycin (Cm), prothionamide (Pto), and cycloserine (Cs) given for up to 12 months under programmatic conditions. Clinical assessment was done monthly and or as the need arose and recorded on the patient progress report form. Laboratory tests and microbiological assess-

ments were done monthly for 6 months on AFB sputum examination, sputum culture, serum creatinine, serum potassium, calcium, magnesium, and liver function tests.

A self-administered, close-ended questionnaire was administered to study sites to gather perception/insights from health staff involved in the study and patients treated with a bedaquiline-containing regimen.

Monitoring visits to study sites were scheduled monthly for the first 6 months and quarterly thereafter.

2.4. Interim Outcome at 6th Month and End of Treatment

Data on interim treatment outcomes at 6th month and the end of treatment were collected. A favorable treatment outcome was defined as three or more consecutive negative cultures taken at least 30 days apart after the intensive phase without evidence of failure. Post-treatment follow-up was after the 6th and 12th months. For this operational research, an additional outcome category was included-withdrawn was defined as a patient who was taken off the bedaquiline regimen for any reason other than treatment failure and provided with routine care.

Adverse event data were collected from patients treated with a bedaquiline-containing regimen under operational research conditions. Data on documented symptoms and laboratory tests were collected at baseline and monthly thereafter. Electrocardiograms (ECG) were done at baseline, 2 hours after the initial dose, and at least at 2, 12, 24, 36, and 48 weeks of treatment, and repeated during the treatment if the patients manifested any sign or symptom related to heart rhythm and conduction disturbances. All adverse events regardless of severity and seriousness were 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].

2.5. Sample Size

In the 2012 cohort, there were 80 pre-XDR-TB and XDR-TB patients who started on a second-line regimen recorded in the proposed study sites. Hence, for this operational research study and account for the possible exclusions, a total of 75 patients will be enrolled.

2.6. Data Management and Analysis

Data from the 9 study sites were collected using a standardized tool and double entry data for verification into the database in EpiData Manager version 4.4.0 (EpiData Association, Odense, Denmark). All data were checked for accuracy, consistency, and completeness. Descriptive data analyses including frequencies and percentages were used to describe basic demographic and clinical variables. A quantitative analysis of data collected from a closed-ended questionnaire was done. Analysis of time to culture conversion within 6 months of treatment and

the end of treatment was done including the proportion of successful treatment outcomes and post-treatment outcomes after one year. The types and frequency of adverse events and serious adverse events were assessed.

2.7. Ethics Approval

The study protocol was approved by the Lung Center of the Philippines Institutional Ethics Review Board. Permission from the Regional Health Offices and ethics clearance of the 9 PMDT facilities were obtained respectively.

3. Results

A total of 75 drug-resistant patients were treated with the bedaquiline regimen from June 1, 2016 to May 31, 2017 in 9 study sites. The baseline demographics and clinical characteristics of the 75 patients were 50 (66.7%) male and most patients were 18-34 years (45.3%). The majority of patients, which is 67 (89.3%), had a previous history of tuberculosis treatment, 14 (18.7%) had co-morbidities. Before the start of treatment, 46 (61.3%) were smear positive, and 42 (56.0%) had positive culture result (Table 1).

As to initial microbiologic profile, 42 (56.0%) had resistance to SLI, 23 (30.7%) resistance to FQ, 6 (8.0%) had MDR-TB, and 4 (5.3%) had XDR-TB (Figure 1).

3.1. Interim Outcomes at the End of 2nd, 4th, and 6th Months of Treatment

Sputum culture conversion at the end of 2nd month showed 65 (86.8%) as culture negative, 9 (12.0%) with culture not done, and 1 (1.3%) still with positive M. tuberculosis culture. At the end of the 4th month, 62 (82.7%) were culture negative, and 13 (17.3%) culture not done. At the end of the 6th month, 59 (78.6%) showed culture negative, and 16 (21.3%) of culture were not done (Figure 2).

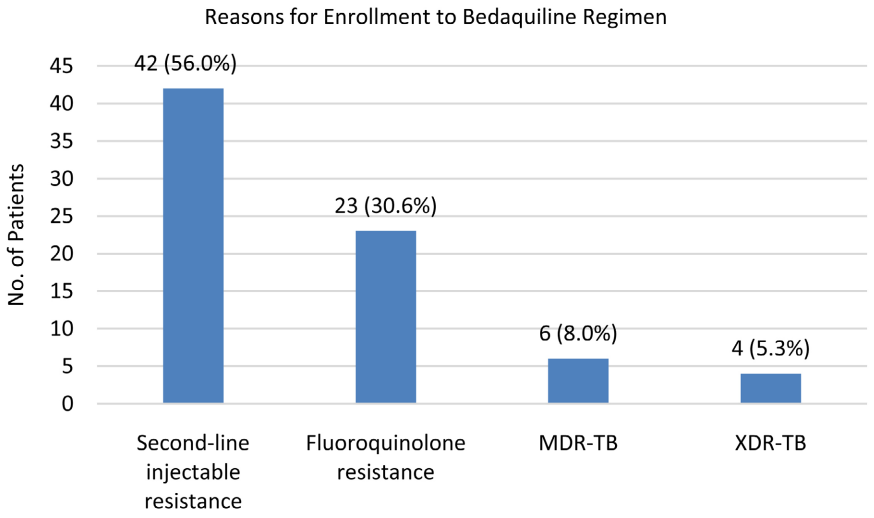

Figure 1. Reasons for treating patients with bedaquiline regimen.

Table 1. Demographics and clinical characteristics of patients with bedaquiline regimen.

Characteristics	Number (N = 75)	Percentage
Age		
18 - 34	34	45.3
35 - 54	32	42.7
55 - 76	9	12.0
Sex		
Male	50	66.7
Female	25	33.3
History of previous TB treatment		
New	8	10.7
Retreatment	67	89.3
Social History[b]		
Smoking		
Yes	31	41.3
No	44	58.7
Unknown	0	0
Alcohol Use		
Yes	9	12.0
No	66	88.0
Unknown	0	0
Substance Use		
Yes	4	5.3
No	71	94.7
Unknown	0	0
Co-morbidities[a]		
Yes	14	18.7
No	61	81.3
Abnormal body mass index (BMI)[b,c]		
Yes	27	36.0
No	48	64.0
Baseline Smear result		
Negative	25	33.3
Positive	46	61.3
Unknown	4	5.3

Continued

Baseline culture result		
Negative	24	32.0
Positive	42	56.0
Unknown	9	12.0

a. Co-morbidities: diabetes mellitus, renal insufficiency, liver disease, HIV, and cancer; b. Based on patients' self-report; c. Abnormal BMI: Underweight (<18.5) and obese (≥18.5).

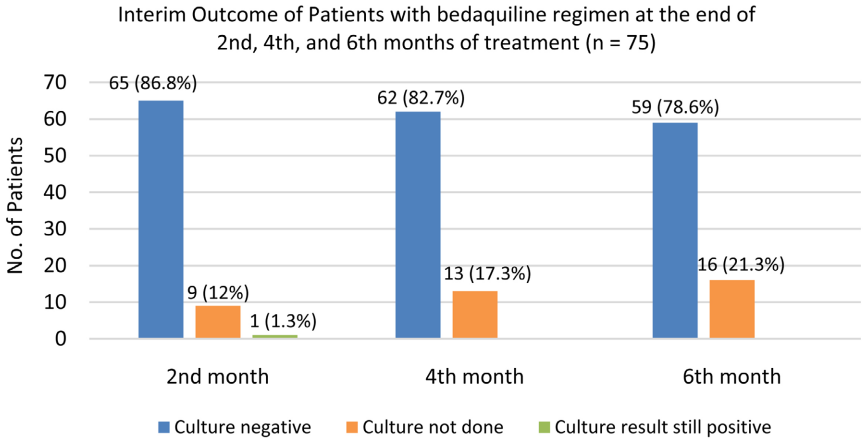

Figure 2. Interim treatment outcome of patients with bedaquiline regimen at the end of 2nd, 4th, and 6th months of treatment.

3.2. Treatment Outcome

Out of 75 patients treated with bedaquiline regimen, treatment success was 49 (65.3%), with 37 (49.3%) cured, 12 (16.0%) treatment completed, 7 (9.3%) died, 17 (22.6%) loss to follow-up, and 2 (2.7%) withdrawn from treatment. (**Table 2**)

There were seven (7) deaths that were reported within 24 hours to the Global Drug Facility and the National TB Control Program of the Department of Health. The causes of death included 4 (57.1%) respiratory failure, 1 (14.3%) multi-organ failure, 1 (14.3) asphyxia secondary to massive hemoptysis, and 1 (14.3%) for an unknown reason.

Post-treatment follow-up of the 49 patients showed 41 (83.7%) were culture negative at 6 months, and 8 (16.3%) culture not done; and at the end of 12 months, 45 (91.8%)were culture negative and 4 (8.2%) culture not done (**Table 3**).

3.3. Adverse Events

Based on system organ classification the top five most frequent adverse events among patients with the bedaquiline regimen were gastrointestinal (518), metabolism/nutrition (430), hepatic (355), ototoxicity/vestibular (233), and respiratory (219) (**Figure 3**).

The most common adverse events during the treatment of bedaquiline at 6 months were: vomiting 60 (80.0%), dizziness 52 (69.3%), nausea 39 (52.0%),

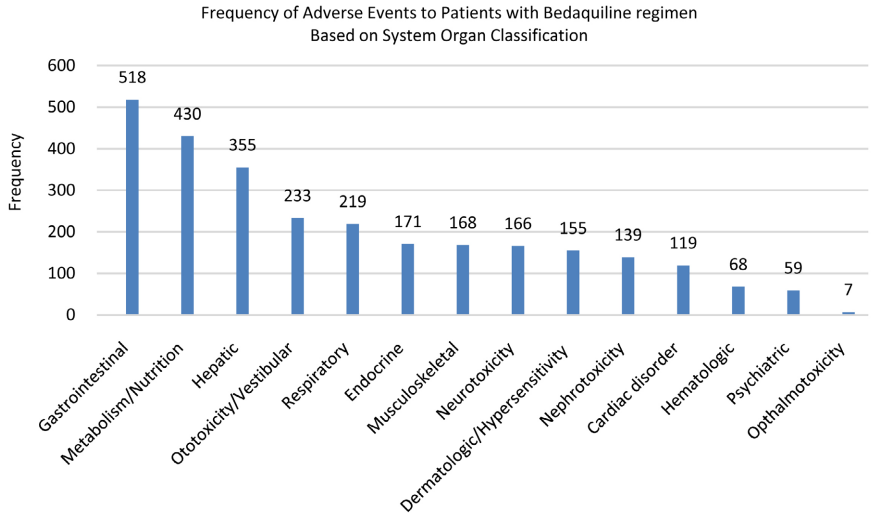

Figure 3. Frequency of adverse events based on system organ classification.

Table 2. Treatment outcome of patienrs treated with bedaquiline regimen.

Variables	Number	Percentage
(a) Favorable outcome		
Cured	37	49.3%
Treatment completed	12	16.0%
(b) Unfavorable outcome		
Died	7	9.3%
Lost to follow up	17	22.7%
Withdrawn[a]	2	2.7%

a. Withdrawn: Refused to participate in the study and returned back to the conventional treatment.

Table 3. Culture done during post-treatment follow-up.

Month	No. of culture done	Percentage	No. of culture not done	Percentage
6th month	41	83.7%	8	16.3%
12th month	45	91.8%	4	8.2%

cough 33 (44.0%), headache 27 (36.0%), abdominal pain 26 (34.7%), increase creatinine 21 (28.0%), hepatotoxicity 18 (24.0%), loss of appetite 10 (13.3%), and joint pains 4 (5.3%) (Figure 4).

3.4. Serious Adverse Events

Among the 75 patients, there were 7 (9.3%) patients who died due to the following: asphyxia secondary to hemoptysis, multi-organ failure, cardiac arrhythmia, and acute respiratory failure. The cause of death for one patient was unknown.

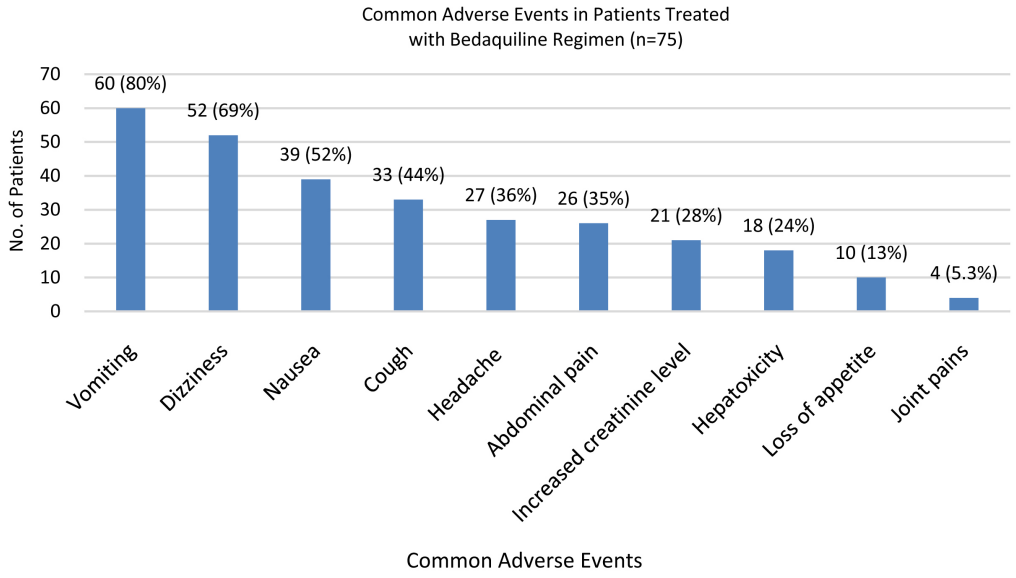

Figure 4. Common adverse events in patients treated with bedaquiline regimen.

A total of 88 episodes of serious adverse events (SAEs) were recorded. There were 63 (71.6%) episodes of SAEs linked to other medically important events. This includes hypokalemia in 11 (17.5%) patients, hypermagnesemia in 7 (11.11%) patients, hyperglycemia in 8 (12.7%) patients, hyperuricemia in 9 (14.3%) patients, and QTcF > 450 msec in 28 (44.4%) patients (**Table 4**). Only 3 (4.0%) of the 75 patients had QTcF of ≥501 msec.

3.5. Perception of Healthcare Staff in Implementing the Bedaquiline Regimen

A total of 17 (94.4%) healthcare staff in the study sites answered the self-administered questionnaire. Six (35.3%) said that the bedaquiline regimen had fewer side effects for patients, 5 (29.4%) said it was easy to administer, 3 (17.6%) said that bedaquiline regimen was effective, 2 (11.8%) control infection of patients, 1 (5.9%) injection less was better and accepted by patients (**Figure 5**).

3.6. Perception of Patients with Bedaquiline-Containing Regimen

A total of 32 (42.6%) random patients were given a self-administered questionnaire. The following are the perceptions of the patients: 31 (97%) said that bedaquiline regimen are beneficial to the patient's body and 30 (94%) encouraged its use in other MDR-TB patients (**Table 5**).

4. Discussion

The treatment of MDR- and XDR-TB is long, complex, expensive, poorly tolerated, and with poor outcomes, generally requiring the use of 4 or more medications for a duration of 18 - 20 months [10] [11] [12] [13]. The aim of this operational research is to assess the effectiveness, safety, and tolerability of bedaquiline with background regimens among patients with MDR-TB and XDR-TB.

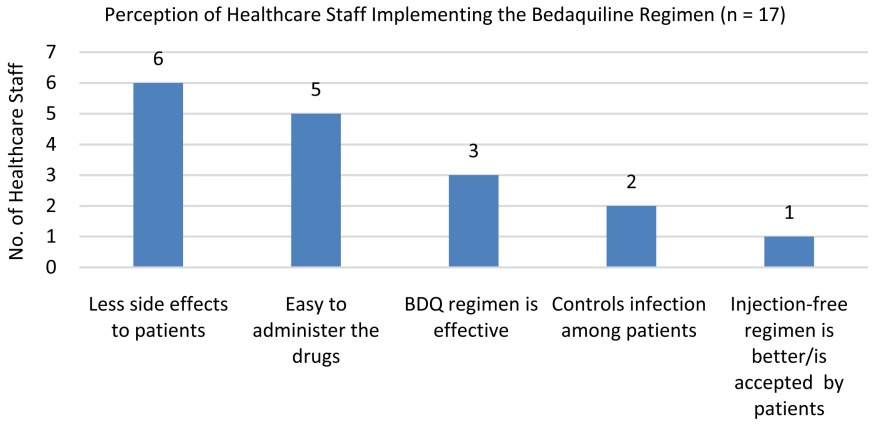

Figure 5. Perception of healthcare staff in implementing the bedaquiline regimen.

Table 4. Serious adverse events.

Serious Adverse Events	Number	Percentage
Other medically important events	63	71.6%
Any life-threatening experience	9	10.2%
Any in-patient hospitalization	9	10.2%
Death	7	9.3%

Table 5. Perception of patients treated.

Serious Adverse Events	Yes	No
Bedaquiline regimen had beneficial effects to the patient's body.	31 (96.8%)	1. (3.1%)
Patients did experience adverse effects.	28 (87.5%)	4 (12.5%)
Patients were thinking that the inclusion of the bedaquiline regimen had beneficial effect for MDR-TB patients.	32 (100%)	0 (0%)
Will encourage other patients with drug-resistance TB to take bedaquiline regimen.	30 (93.8%)	2 (6.3%)

The inclusion of bedaquiline for 6 months in the treatment regimen was associated with good clinical outcomes in our cohort, with 78.6% culture conversion at the end of 6 months and 65.8% treatment success rate, and a death rate of 9.3%. These findings indicate a favorable efficacy and safety, and beneficial effect of the addition of bedaquiline to background MDR/XDR-TB regimens.

In the pre-bedaquiline era, the success rate of MDR-TB was only 54% to 58% and with death rates of 13.8% - 15% [14] [15]. In the study, the treatment success rate of bedaquiline-containing regimen showed an improvement but the result was slightly lower than the findings in the Borisov study (71.3%) [11], Ndjeka study in Africa (73%) [16] and Guglielmetti study (80%) [17].

In the study, almost all patients treated with bedaquiline-containing regimen

experienced at least one adverse event (100%), and episodes of serious adverse were noted in 75 patients. The QT prolongation which is a major concern for bedaquiline was uncommon, seen in only 4% who had QTcF of ≥501 msec. The observed death rate was only 9.3%. In the study of Mbuagbaw L., et al, the death rate was 11.7%, 91.1% (95% CI 82.2% - 95.8%) of the patients who experienced more than 1 adverse event, and 11.2% (95% CI 5.0% - 23.2%) experienced a serious adverse event [18].

The most common adverse events noted during the treatment with bedaquiline were: vomiting in 60 (80.0%), 52 (69.3%) with dizziness, 39 (52.0%) with nausea, 33 (44.0%) with cough, and 27 (36.0%) with headache. These adverse events in the study were similar in nature but higher in numbers compared to the study of Diacon, *et al.* [19], wherein in the 8 weeks of treatment with bedaquiline [20] [21] most of the observed adverse events were those commonly seen in DRTB patients receiving second-line treatment drugs for multidrug-resistant tuberculosis [22] [23]. Most frequent adverse events based on system organ classification are gastrointestinal, metabolism/nutrition, hepatic, ototoxicity/vestibular, and respiratory. As patients received second line anti TB drugs, it can be difficult to pinpoint the precise drugs responsible for the hepatotoxic effects [24] In the study, second-line drugs such as fluoroquinolones and clofazimine were given to patients and these might result in cardiologic or any other adverse events [10] [25] [26] QTcF of ≥450 msec was seen in 28 patients (44%) who were asymptomatic, while only 3 (4%) had >501 msec.

The following strengths of the study were the regular recording and reporting of adverse events using the Pharmacovigilance Monitoring Systems (PVIMS). PVIMS is an open-source web-based application developed by USAID that has the capability to receive, store, and analyze adverse events reported by patients. It can also analyze System Organ Classification (SOC) and has the capacity to conduct an initial causality assessment which ensures the appropriate and promptly addresses the reported adverse events. Secondly, the patients with ongoing treatment of the bedaquiline regimen in the study sites had better supervision and more frequent clinic visits and were monitored by the clinic staff and other supervisors in selected facilities with expertise and experience in treating MDR/XDR-TB. Loss to follow-up was a challenge but the clinic staff exerted extra effort to minimize this by providing timely counseling, additional food support, and free ancillary drugs to all patients who experienced adverse events.

There were limitations in the study. First, the sample size of patients treated with bedaquiline regimen under operational research conditions in 9 selected PMDT facilities was small. This was based on the number of patients on previous data on pre-XDR and XDR-TB. Second, the findings are limited to adults of 18 years of age and above with pulmonary DR-TB, so the findings do not apply to patients with extra-pulmonary TB and children [17]. Another limitation was the lack of comparability in the frequency of adverse events to measure safety since there was no systematic gathering of information during the pre-bedaquiline regimen.

5. Conclusion

The results showed promising outcomes of the bedaquiline-containing regimen in a cohort including XDR-TB patients and reassuring safety profile and favorable treatment outcomes. The inclusion of bedaquiline-containing regimen to other second line anti TB drugs among difficult-to-treat cases is highly recommended following the World Health Organization (WHO) guidelines. Likewise, the WHO Active TB Drug Safety Monitoring and Management (aDSM) was introduced and showed that it is feasible. Thus, this activity should be supported and encouraged, provide on-going monitoring, to be able to address drug toxicity promptly and improve patient's treatment adherence. However, loss to follow-up remains a challenge to be addressed.

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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.

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Conflicts of Interest

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

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