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ADVERSE DRUG REACTIONS IN BEDAQUILINE-BASED REGIMENS FOR DRUG-RESISTANT TB UNDER NTEP: A PROSPECTIVE STUDY FROM WESTERN INDIA

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ABSTRACT

Introduction: Drug-resistant tuberculosis (DR-TB) remains a major public health challenge. Although Bedaquiline-based all-oral regimens have improved treatment outcomes, adverse drug reactions (ADRs) may affect adherence and treatment success. This study was conducted to describe the incidence, type, severity, and management of ADRs in DR-TB patients on BDQ-based all-oral longer regimens under NTEP at a tertiary care hospital in Western India.

Methodology: A prospective observational study was conducted among 50 microbiologically confirmed DR-TB patients receiving Bedaquiline-based all-oral regimens at a tertiary care hospital in Western India. Patients were monitored through clinical assessment, ECG, hematological, hepatic, renal, and neurological evaluations. ADRs were assessed using active drug safety monitoring and management protocols.

Results: At least one ADR occurred in 26 (52%) patients. Peripheral neuropathy (18%), QTc prolongation (16%), and anemia (12%) were the most common ADRs. QTc >500 ms occurred in 2 (4%) patients and was managed with temporary Bedaquiline interruption. Treatment modification was required in 7 (14%) patients, while no ADR-related deaths were reported.

Conclusion: Bedaquiline-based all-oral regimens demonstrated an acceptable safety profile in DR-TB patients. Most ADRs were mild to moderate and manageable, highlighting the importance of active pharmacovigilance for safe programmatic implementation.

KEYWORDS: Adverse Drug Reactions, Bedaquiline, Drug-resistant tuberculosis, Drug Safety Monitoring, Linezolid/adverse effects, QT Prolongation.

INTRODUCTION

Tuberculosis (TB), a serious global health issue, has been prominently affecting low- and middle-income countries. Despite several decades of control efforts, drug-resistant tuberculosis (DR-TB), is resistant to the primary drugs and has a more complex regimen, is still looming in the background to undermine the effectiveness of control efforts in tuberculosis elimination[1]. According to the World Health Organization, in 2022, an estimated 10.6 million people in the world contracted tuberculosis, and around half a million patients were reported to have either multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), with India contributing a quarter of the total estimated patients to the world's tally[2].

Historically, DR-TB therapy consisted of injectable regimens, which had been plagued by poor compliance, high toxicity, and a considerable number of lost patients in the roll-out of the treatment regimen[3]. The advent of new anti-tubercular agents, especially the use of Bedaquiline (BDQ), has thus brought about a paradigm shift in DR-TB therapy, as this drug currently makes fully oral DR-TB regimens a reality[4]. The drug, which belongs to the diarylquinoline class and acts on the ATP-synthesizing enzyme of Mycobacterium tuberculosis, has been found to have high potency in the treatment of both actively replicating and dormant M. tuberculosis strains[5].

In light of accumulating evidence, WHO (World Health Organization) has recommended all-oral longer regimens and shorter regimens combining Bedaquiline, Linezolid, Clofazimine, and other Group A & B agents as the standard of care for MDR/RR-TB6. Although all of these regimens have improved administration, success rate and acceptability to a significant level, still there is no complete absence of adverse drug reactions (ADRs). Cardiac intolerance such as QT interval prolongation, Linezolid-induced hematologic inhibition, hepatotoxicity, and neuropsychiatric symptoms persist as major ADR concerns[6-9]. In public health settings, such kind of ADR can negatively impact treatment adherence, pose challenges to health system resources, and jeopardize achievements against TB control programs[7,8].

Realizing the challenges, WHO and the TB programs in the country, have promoted the incorporation of Active Drug Safety Monitoring and Management (aDSM) in DR-TB treatment[9]. In the Indian setting, the National Tuberculosis

Elimination Program (NTEP) has made it necessary for there to be clinical, laboratory, and electrocardiographic monitoring for patients on a Bedaquiline-based treatment regimen, in addition to the assessment of causality of adverse effects for reporting purposes[10]. Successful aDSM implementation is very important not only for individual patient well-being but also for the healthcare quality assurance, including TB treatment[9].
There is limited evidence regarding the safety performance of extended combination regimens containing Bedaquiline in India. Data are largely collected from clinical trials and selected patient populations, which often fail to realistically capture situations encountered in public health facilities[10,11]. Incidence, pattern, intensity, and also treatment response regarding ADRs, therefore, warrant understanding under practical settings.

Objectives
In this background, it was necessary for this study to be conducted in a tertiary care institute in Western India to scientifically assess ADRs among patients undergoing all-oral extended regimen treatment of DR-TB as a part of NTEP. Through this study, it is attempted to provide program-oriented evidence to enhance pharmacovigilance practices to ensure safe implementation of DR-TB treatment and achieve TB elimination.

METHODOLOGY

Study Design and Setting
A prospective observational study was conducted in the Department of Pulmonary Medicine, P.D.U. Government Medical College and Civil Hospital, Rajkot, Gujarat, India, a tertiary care referral center for drug-resistant tuberculosis (DR-TB). The study was carried out from April 2023 to September 2024 to evaluate adverse drug reactions (ADRs) among patients receiving Bedaquiline-based all-oral regimens under the National Tuberculosis Elimination Program (NTEP).

Study Participants
Adult patients (≥18 years) with microbiologically confirmed multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB), who were initiated on a Bedaquiline-containing all-oral longer regimen according to NTEP guidelines were eligible for inclusion. Patients who had received Bedaquiline or Linezolid for more than one month before enrolment, had baseline QTc interval >500 ms, uncontrolled cardiac arrhythmias, or were pregnant or lactating were excluded. Patients with pre-existing peripheral neuropathy were not excluded; however, baseline neurological assessment was performed before treatment initiation and only treatment-emergent or worsening neuropathic symptoms during follow-up were considered ADRs attributable to therapy.

Sample Size and Sampling Technique
The study employed a consecutive enrolment approach. All eligible patients initiated on Bedaquiline-based regimens during the study period were included. As the study was conducted under routine programmatic conditions and aimed to describe the pattern, frequency, severity, and management of ADRs, a formal sample size calculation was not performed. A total of 50 eligible patients were available and enrolled during the study period.

Ethical Considerations
Ethical approval was obtained from the Institutional Ethics Committee of P.D.U. Government Medical College, Rajkot (PDUMCR/IEC/46/2023 dated 06/04/2023). Written informed consent was obtained from all participants prior to enrolment.

Data Collection and Follow-up
Baseline information was recorded using a structured case record form and included demographic characteristics, clinical history, comorbidities, laboratory investigations, radiological findings, and treatment details. Baseline investigations included complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), serum electrolytes, blood glucose, thyroid-stimulating hormone (TSH), chest radiography, and electrocardiography (ECG).

Patients were followed according to NTEP recommendations. ECG monitoring was performed weekly during the first month of Bedaquiline therapy and monthly thereafter. Laboratory investigations were repeated periodically or whenever clinically indicated.

Assessment of Adverse Drug Reactions
Adverse drug reactions were monitored using the Active Drug Safety Monitoring and Management (aDSM) framework recommended by the World Health Organization (WHO)[12]. All adverse events occurring from treatment initiation until completion of follow-up were documented systematically. For each suspected ADR, information regarding onset, clinical presentation, suspected drug, management, and outcome was recorded in a predefined documentation format.
Causality assessment was performed using the WHO–Uppsala Monitoring Centre (WHO-UMC) causality assessment system[13]. Severity of ADRs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 developed by the National Cancer Institute[14]. Particular attention was given to cardiac toxicity (QTc prolongation), hematological abnormalities, hepatotoxicity, nephrotoxicity, and neurological adverse events.

Statistical Analysis
Data were entered into Microsoft Excel and analysed using appropriate statistical software. Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), whereas categorical variables were presented as frequencies and percentages.

RESULTS
A total of 50 patients with culture-positive drug-resistant tuberculosis on Bedaquiline-based all oral therapy were recruited into this study. Most patients were male (64.0%), and most of them were within the age group of 30-49 years. Most patients had a poor socioeconomic status. Patients suffering from diabetes mellitus, hypertension, and HIV/AIDS constituted 12.0%, 8.0%, and 4.0%, respectively (Table 1).
The electrocardiogram analysis showed that the QTcF interval was maintained within the normal limit (< 450ms) in 84.0% of the patients during follow-up period. 12.0% of the patients had a QTcF interval of 451 - 500ms while 4.0% had QTcF interval > 500ms. Electrolyte correction and discontinuation of the drug were used to handle this complication. No clinical arrhythmia or cardiac deaths were recorded (Table 2).
Liver, renal and electrolyte abnormalities were found in some of the individuals. Elevation of liver enzyme levels was the most common biochemical abnormality detected, followed by mild elevation of serum creatinine and blood urea nitrogen levels. Electrolyte abnormalities were rare but could be corrected by appropriate interventions. None of the participants experienced severe hepatotoxicity or nephrotoxicity necessitating cessation of treatment (Table 3).
In total, 26 (52.0%) patients had adverse drug reactions (ADRs) during treatment. Since some patients had several ADRs, the frequency of particular ADRs was higher than the total number of patients who had the ADRs. Peripheral neuropathy (18.0%) was the most common ADR, followed by QTcF prolongation (16.0%) and anemia (12.0%). There were no frequent reports of GI symptoms, skin hyperpigmentation, headache, altered mood, sleep disorder or seizures. ADRs were predominantly categorized as CTCAE = Common Terminology Criteria for Adverse Events Grades 1 or 2 and were managed conservatively. Seven (14.0%) patients needed modifications of treatment; most cases of change in therapy were caused by QTc prolongation, hematological ADRs, and neurotoxicity. One case of seizure linked with Cycloserine led to cessation of treatment. No mortality was linked with ADRs during this trial (Table 4).
Comparison of hematologic parameters prior to initiating therapy and following completion of therapy revealed that hemoglobin levels and platelet counts decreased during therapy. At baseline, 64.0% of patients had “normal” quantities of hemoglobin; at follow-up, this percentage decreased to 50.0%. A greater number of patients experienced mild-to-moderate anemia than previously. Thrombocytopenia increased in prevalence during treatment; most of these cases were mild and clinically manageable. There were few instances of severe hematologic toxicity, all of which were resolved with drug dose reduction or the withdrawal of the suspected agent (Table 5).

Tables:

Table 1. Demographic and Baseline Characteristics of Study Participants (n=50)

Characteristic	Category	n (%)
Age (years)	18–29	10 (20.0)
	30–39	15 (30.0)
	40–49	12 (24.0)
	50–59	8 (16.0)
	≥60	5 (10.0)
Gender	Male	32 (64.0)
	Female	18 (36.0)
Socioeconomic Status	Lower	28 (56.0)
	Lower-middle	18 (36.0)
	Middle and above	4 (8.0)
Baseline Hemoglobin	Normal	32 (64.0)
	Mild anemia	14 (28.0)
	Moderate-severe anemia	4 (8.0)
Comorbidities	Diabetes Mellitus	6 (12.0)
	Hypertension	4 (8.0)
	HIV infection	2 (4.0)
	None	38 (76.0)

Table 2. QTcF Interval Distribution Among Study Participants (n=50)

QTcF Category	n (%)	Clinical Action
≤450 ms	42 (84.0)	No intervention
451–500 ms	6 (12.0)	ECG monitoring and electrolyte correction
>500 ms	2 (4.0)	Temporary Bedaquiline interruption and cardiology consultation
Total	50 (100.0)	—

Table 3. Organ System Laboratory Profile During Treatment (n=50)

Parameter	Patients with Abnormal Values n (%)	Maximum Recorded Value (Mean ± SD)	Clinical Management
Alanine Aminotransferase Elevation (ALT)	6 (12.0)	78.4 ± 15.2 U/L	Supportive treatment
Aspartate Aminotransferase (AST) elevation	5 (10.0)	70.6 ± 18.9 U/L	Monitoring
Hyperbilirubinemia	2 (4.0)	2.4 ± 0.6 mg/dL	Conservative management
Alkaline Phosphatase Elevation (ALP) elevation	3 (6.0)	145 ± 21.4 U/L	No intervention
Elevated serum creatinine	3 (6.0)	1.8 ± 0.3 mg/dL	Monitoring
Elevated Blood Urea Nitrogen (BUN)	2 (4.0)	34.2 ± 5.1 mg/dL	Hydration
Hyponatremia	1 (2.0)	128 mEq/L	IV fluid correction
Hypokalaemia	2 (4.0)	2.9 ± 0.4 mEq/L	Potassium supplementation
Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m²	1 (2.0)	52 mL/min/1.73m²	Follow-up
Any laboratory abnormality	13 (26.0)	—	Managed as required

Table 4. Adverse Drug Reactions, Severity, Time of Onset and Management (n=50)

Adverse drug reactions	n (%)†	Suspected Drug(s)	Mean Time to Onset (days)	CTCAE Grade	Management
Peripheral neuropathy	9 (18.0)	Linezolid, Cycloserine	55	1–2	VitaminB6, Gabapentin/Amitriptyline
QTc prolongation	8 (16.0)	Bedaquiline, Clofazimine	42	1–2	ECG monitoring, electrolyte correction
Anemia	6 (12.0)	Linezolid	68	2–3	Dose reduction
Elevated liver enzymes	6 (12.0)	Bedaquiline, Pyrazinamide	40	1–2	Observation
Gastrointestinal symptoms	5 (10.0)	Ethionamide, para amino salisylic acid(PAS)	18	1	Symptomatic treatment
Skin hyperpigmentation	4 (8.0)	Clofazimine	60	1	Counselling
Headache/Dizziness	3 (6.0)	Cycloserine	20	1	Supportive treatment
Depression/Mood changes	2 (4.0)	Cycloserine, Ethionamide	45	2	Psychiatric referral
Sleep disturbance	2 (4.0)	Cycloserine	30	1	Symptomatic treatment
Seizure	1 (2.0)	Cycloserine	75	3	Drug withdrawal
Any ADR*	26 (52.0)	—	—	—	Individualized management

†Percentages calculated using total study population (n=50).*Patients may have experienced more than one ADR.

Table 5. Hematological Parameters Before and After Treatment (n=50)

Category	Baseline n (%)	Follow-up n (%)
Heamoglobin status		
Normal (≥12 g/dL)	32 (64.0)	25 (50.0)
Mild anemia (10–11.9 g/dL)	10 (20.0)	15 (30.0)
Moderate anemia (8–9.9 g/dL)	6 (12.0)	7 (14.0)
Severe anemia (<8 g/dL)	2 (4.0)	3 (6.0)
Platelets count status		
Normal (>150,000/mm³)	44 (88.0)	38 (76.0)
Mild thrombocytopenia (100,000–150,000/mm³)	4 (8.0)	8 (16.0)
Moderate thrombocytopenia (50,000–99,999/mm³)	2 (4.0)	3 (6.0)
Severe thrombocytopenia (<50,000/mm³)	0 (0.0)	1 (2.0)

DISCUSSION

This is a prospective observational study on 52% of patients using a Bedaquiline (BDQ) defined as "all oral" were reported to have developed at least one Adverse Drug Reaction (ADR). The types of ADRs that became most frequently reported were peripheral neuropathy (18%), QTc prolongation (16%), anemia (12%) and elevated liver enzymes (12%). Most of

the ADRs were comparatively mild-moderate in severity and were resolved through supportive care, dose reduction or temporary interruption of treatment. No patient died directly due to an ADR during this prospective observational study, supporting an acceptable Bedaquiline (BDQ) risk profile when Active Drug Safety Monitoring and Management (aDSM) is appropriately utilized in a programmatic setting[11,15].

The overall rate of adverse drug reactions (ADRs) reported in this study would appear to be in line with rates documented in other programmatic studies in India. Findings from Dutta Gupta et al. indicated that ADRs are frequent among patients with drug-resistant TB (DR-TB), but most ADRs are manageable, so there was relatively little need to permanently discontinue treatment[10]. Vaman et al. similarly documented a high burden of ADRs among patients receiving DR-TB therapy in the Kerala program, including frequent reports of neurological, hematologic, and gastrointestinal ADRs[11]. The variation in reported rates of ADRs between studies could be due to differences in patient legibility, regimen formulations, duration of treatment, intensity of monitoring, and criteria used to report ADRs. In addition, because aDSM systematically tracks use of DR-TB medicines in all patients, regularly conducting these types of routine monitoring can result in a higher percentage of patients experiencing mild ADRs than would likely be identified if studied in an experimental sample of DR-TB patients.

Peripheral neuropathy emerged as the most prevalent ADR in our study cohort. This observation conforms to the well-known side effect profile of Linezolid, which has remained an important part of modern DR-TB regimens. Several studies have shown that long-term administration of Linezolid leads to accumulation of mitochondrial toxicity and causes neuropathy both peripherally and optically[8,16]. In a multicentre Indian study, Mishra et al. have observed peripheral neuropathy as one of the most prevalent ADRs caused by Linezolid-based regimens16. Peripheral neuropathy has also been seen as a frequent ADR in systematic reviews assessing the safety of Linezolid for treating DR-TB[8]. The prevalence of neuropathy in our study could be attributed to prolonged use of medication and close monitoring of adverse reactions. Most patients were managed by pyridoxine and other treatments and continued with their therapy.

QTc interval prolongation continues to be the most relevant issue in terms of safety related to treatment protocols with BDQ due to the possibility of developing dangerous cardiac arrhythmias. In our case series, we found that QTc interval prolongation was diagnosed in 16.0% of patients, whereas in just 4.0% of cases, QTc exceeded 500 ms. None of the cases had serious clinical arrhythmia or death of a cardiac nature. Our results are corroborated by a trend in literature, which shows that despite QTc interval prolongation being relatively common, its complications are rare[17,18]. According to Okello-Obol et al., in the course of their systematic review and meta-analysis, they showed that clinically significant QT prolongation was rare among the patient population and was usually not followed by any life-threatening issues18. In addition, Fekadu et al. have shown that BDQ-containing protocols are safe due to a favourable benefit-risk ratio, despite ECG abnormalities being observed[15]. In conclusion, these results must be seen as further confirmation of the drug's safety in Western India.

In our study, Anemia was found as important ADR among patients. It was characterized by reduced hemoglobin levels in patients treated with Linezolid and an increased incidence of mild to moderate anemia. This result appears logical, considering the known side effect of myelosuppression in case of long-term treatment with Linezolid. Other researchers have found similar associations between Linezolid use and anemia and thrombocytopenia in patients undergoing anti-TB therapy[8,16]. Most of the hematological adverse effects were not serious and were manageable through dose reductions. The low incidence of severe anemia can be associated with close monitoring of blood parameters within NTEP programs.

Liver enzyme elevation was detected in 12.0% of all patients but did not require stopping drug therapy in any of them. Mild liver damage has been noted in other studies in Indian and international settings using BDQ in drug-resistant TB treatment[10,11.] Due to the complex regimen used for treating patients with drug-resistant tuberculosis, it is often complicated to link hepatotoxicity to individual drugs. Nonetheless, based on our results, hepatotoxic events are most likely mild and detectable early and manageable through careful monitoring.

Moreover, this study illustrates the significance of aDSM implementation for the effective working of NTEP. The early recognition of the risk factors like QTc prolongation, neuropathy, anemia, and liver problems helped to intervene on time and avoid further adverse effects. The usefulness of such measures in terms of pharmacovigilance systems has been observed in various studies done in multicenter settings and assessing DR-TB treatment outcomes[9]. Since most of the ADRs related to Linezolid, Cycloserine, Clofazimine, and BDQ are cumulative in nature and develop after weeks or months of treatment, such interventions might prove helpful for the safe continuation of the regimen.

The current study offers real-life data regarding the safety of BDQ regimen in the context of Western India where there is not enough evidence available regarding BDQ-associated safety issues. While the results obtained are consistent with the existing literature, this study provides significant information regarding ADR profile among patients receiving BDQ-containing regimens under regular NTEP care. Further multicenter studies with larger sample size and more prolonged follow-up periods are recommended.

Strengths of the study:

This was carried out under the normal program conditions of NTEP so the findings were more applicable to real life conditions. Prospectiveness with efficient active drug safety monitoring and management (aDSM) led to early identification, rational assessment and proper treatment of the ADR. Use of standard tools for causality (WHO-UMC causality assessment tool) and for the severity assessment (CTCAE 5.0) increases the validity and consistency of ADR assessment. The study looked into the varied types of ADR including cardiac, hemato-toxicities, hepatic, renal and neurological toxicities of the Bedaquiline based all oral regimens.

Study Limitations

The limitations of this study include: being a single-center, tertiary referral, and small study population with limited generalizability to all DR-TB settings. The lack of a control or comparative arm made it impossible to calculate relative risk from specific drugs in the multi-drug combination. Patients were treated and followed prospectively but the length of follow-up might have been too short to diagnose late-onset toxicities including optic neuropathy and chronic neurotoxicity which can develop during prolonged therapy. There was no access to drug-level monitoring or pharmacogenetics in this study so individual differences in patient drug exposure and risk for specific toxicities could not be measured. The selection bias for a more advanced or clinically ill group can occur in a tertiary referral center setting. In spite of the enhanced Active Drug Safety Monitoring system some of the relatively benign or self-resolving side effects might have gone unreported.

CONCLUSION

All-oral all-oral Bedaquiline-based regimens showed acceptable safety profile in patients of multidrug resistant tuberculosis managed under standard conditions of NTEP. More than half of patients suffered from one or more ADRs; common among which are peripheral neuropathy, prolongation of QTc, anemia and increase in liver enzyme levels. But majority of the ADRs were mild to moderate in intensity and could be successfully managed by the intervention in time and resulted in no ADR related mortality. Thus we can still consider continuing the BDQ regimens with regular monitoring of ECG, hematological and biochemical parameters as indicated in aDSM guidelines. Multicentre studies with larger number of subjects are need to know long term safety and predictors of serious toxicity.

Recommendations

1. With 16% of patients showing prolongation of QTc and 4% patients having QTc > 500ms, ECG monitoring has to be maintained throughout the treatment especially in the initial months of treatment with BDQ.
2. Peripheral neuropathy in 18% of cases warrants neurological evaluation at follow-up visit in the Linezolid-treated population.
3. Regular CBC counts should be carried out in order to pick up hematological toxicity during the treatment because anemia and thrombocytopenia were seen in considerable number of patients.
4. Liver function should be carried out regularly due to the increase in liver enzymes seen in 12% of the patients.
5. The aDSM program needs programmatic strengthening for the prompt detection and management of neuro, cardio and hematological ADRs which were most frequent causes of ADRs in the current study population.

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Approval of Institutional Ethical Review Board

From IRB committee, PDU Medical College, Rajkot
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Authors' Contributions

1.Dr.Ruchita Sakaria : Design, data collection, Paper writing
2.Dr.Bina Modi: Study design, Results writing, overall monitoring-corresponding author
3.Dr. Sai Aditya Nayudu : Study design, Results writing, overall monitoring
4.Dr.Prajes Kumar Chattopadhyay: Design, data collection, Paper writing
5.Dr.Rubia Singh: Design, data collection, Paper writing
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