CASE REPORT

# Extensively Drug Resistance Tuberculosis with Bedaquiline Toxicity: A 2-year Case Report

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## Abstract

Tuberculosis (TB) is a contagious disease that usually attacks the lungs and spreads to others organs also. In the twentieth century, TB was a leading cause of death in the USA. Tuberculosis mostly affects adults in their most productive years. However, all age-groups are at risk. Over 95% of cases and deaths are in developing countries. In 2020, 86% of new TB cases occurred in the 30 high TB burden countries. The following eight countries accounted for two-thirds of the new TB cases: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. A latent or active TB infection can also be drug resistant. In some cases, more severe drug resistance can develop. Multidrug-resistant tuberculosis (MDR-TB) remains a public health crisis and a health security threat. Only about one in three people with drug-resistant TB accessed treatment in 2020. Without good support, treatment adherence is more difficult in tuberculosis.

**Keywords:** Bedaquiline, Bedaquiline toxicity, Extensively drug resistance tuberculosis, *Mycobacterium tuberculosis*, Multidrug-resistant tuberculosis.

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## Background

Tuberculosis has existed for millennia and remains a major global health problem. The Global TB report 2017 estimated that India has the world's highest share, that is, 27% of people are affected with TB.[1] The estimated incidence of all forms of TB in India was 188/100,000 population (129–257 per 100,000 population) for the year 2020, the total number of TB patients (relapse and new) notified was 19,33,381 which was 19% higher than that of 2020 (16,28,161).[2]

It is noted that worldwide, approximately 4.1% of new TB patients and 19% of previously treated TB patients have MDR-TB, that is, TB resistant to at least two of the first-line drugs—isoniazid and rifampicin.[3] The Centers for Diseases Control and Prevention (CDC) and World Health Organization (WHO) concluded that 20% of the 17,690 strains analyzed worldwide from 2000 to 2004 were Multidrug-resistant (MDR).[4] When the TB patients have non-compliance with TB medications, it can be one of the reasons for MDR-TB.

The MDR-TB treatment is difficult because the second-line TB drugs are mostly weak and toxic.[5] Bedaquiline (BDQ) is the most promising drug for MDR-TB[4] conditionally approved by the United States Food and Drug Administration (FDA) for the treatment of MDR-TB.[5] It is a diarylquinoline anti-mycobacterial used as part of combination therapy in adults with pulmonary MDR-TB.[6] Bedaquiline is registered for a treatment duration of 24 weeks. During the first 2 weeks, the recommended dose is 4 pills of 100 mg every day, then 2 pills of 100 mg 3 times per week.[7] It has been shown to improve cure rates of smear-positive MDR-TB, though with some concern for increased adverse effects and rates of death.[8]

Extensively drug resistance tuberculosis is a rare type of MDR-TB which is a global threat and has great importance for public health and TB control. Extensively drug resistance tuberculosis caused by *Mycobacterium tuberculosis* strains that fulfill the definition of MDR/RR-TB and also resistant to any fluoroquinolone (FQ) and at least one additional group A drug – the drugs that are the second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise moxifloxacin, BDQ, levofloxacin, and linezolid.[9]

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## Case Description

A 21-year-old woman, a mother of two children who was apparently healthy till May 2019 had developed fever and cough as initial symptoms and was diagnosed with microbiologically confirmed tuberculosis by June 2019. Cartridge-based nucleic acid amplification test (CBNAAT) reported TB positive and rifampicin (sensitive). She was started with antituberculosis therapy–intensive phase (ATT–IP) of four fixed dose combinations of H: isoniazid, 75 mg; R: rifampicin, 150 mg; Z: pyrazinamide, 400 mg; E: ethambutol hydrochloride, 275 mg isoniazid, rifampicin, pyrazinamide, ethambutol (HRZE) were given followed by # fixed dose combination (FDC) of continuation phase (CP). Her 6-months course of anti-TB treatment was completed with a sputum test negative on December 2019. During this course of treatment, she was found to be irregular with treatment.

**Table 1:** Inclusion criteria to start BDQ drug

| *Guidelines of (NTEP)* | *Patient profile* |
|---|---|
| • Age above 18 | • Patient's age: 21 years |
| • Patient should neither be pregnant nor be using effective non-hormone-based birth control methods | • Her urine pregnant test (UPT) was negative. She was neither pregnant nor having any hormonal pills for birth control measures |
| • Patients with controlled stable arrhythmias can be considered after cardiac consultation | • Cardiac opinion received. She did not have any abnormal rhythms |
| • Patients with marked/prolongation of QT/QTc, family history of long QT and other cardiac issues such as heart failure, hypokalemia need to be excluded for the BDQ therapy | • Her ECG were normal, and no family history of long QT |
| • Patients with anemia [hemoglobin (Hb) <6.5 gm/dL] | • Her Hb was 9.3 gm% |
| • Normal values of LFT, RFT, CBC | • Patient's laboratory test values were within normal range |

BDQ, bedaquiline; CBC, complete blood count; ECG, electrocardiogram; LFT, liver function test; NTEP, national tuberculosis eradication program; QT, QT interval; RFT, renal function test

**Table 2:** Laboratory report

| *Complete blood count* | | *Liver function test* | | *Electrolytes* | |
|---|---|---|---|---|---|
| Hemoglobin | 9.3 gm% | Total bilirubin (mg/dL) | 0.8 mg% | Sodium | 139 mEq/L |
| RBC | 3.74 | Direct bilirubin (mg/dL) | 0.3 mg% | Potassium | 3.6 mEq/L |
| HCT | 30.6% | Indirect bilirubin (mg/dL) | 0.5 mg%, | Chloride | 98 mEq/L |
| WBC: Neutrophils | 7.9% | Total protein (gm/dL) | 7.2 gm/dL | Bicarbonate | 27 mEq/L |
| Lymphocytes | 1.47% | Albumin (gm/dL) | 4.2 gm/dL | | |
| Monocytes | 0.60% | Albumin, globulin ratio | 1.25 | | |
| Eosinophils | 0.10% | AST (SGOT) (U/L) | 16 IU/L | | |
| Basophils | 0.07% | ALT (SGPT) (U/L) | 24 IU/L | | |
| Platelets | 270,000/mL | | | | |
| Chest X-ray: Consolidation B/L upper lobes | | | | | |
| CT: B/L Pulmonary Koch's sequel with the cavity formation and traction of bronchiectasis changes, collapse consolidation changes seen in the RLL | | | | | |
| Bronchial wash<br>Endometrial tissue-detected MTB | | | | | |
| Sputum smears, CBNAAT culture<br>TB positive resistant to drug rifampicin, INH | | | | | |

B/L, bilateral; CT, computerized tomography; RLL, right lower lobe; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase;

Within 3 months, she once again approached the hospital with complaints of cough, fever, fatigue, and weight loss. She had a relapse after a full course of treatment with a first-line regimen. The CBNAAT result detected *Mycobacterium tuberculosis* rifampicin resistant – I line-resistant to rifampicin and isoniazid (INH); II line sensitive to second-line injectable drugs (SLID); and FQ. She was treated with a shorter MDR-TB; capsule clofazimine, 100 mg; tablet ethambutol, 800 mg; tablet moxifloxacin, 400 mg; tablet pyrazinamide, 1,250 mg; tablet pyridoxine, 100 mg, injection kanamycin, 1 gm intra muscular (IM); isoniazid, 600 mg; and ethinamide 500 mg. She had non-compliance with the treatment regimen. By May 2021, the culture report showed positive, smear acid fast bacillus (AFB) (positive) resistant to rifampicin, FQ, and became sensitive to INH, SLID.

After 2 months, she had worsened symptoms of breathlessness, fever, cough, and chest pain. She was brought to the hospital in the semiconscious stage to the emergency department. She was initiated with symptomatic management of oxygen, bronchodilator, dexamethasone, antibiotics, and antihistamines. She was diagnosed as pre-relapse extensively drug-resistant TB (XDR-TB). She was started with tablet BDQ on 2 July 2021 after the expert committee's discussion with the inclusion criteria described in Table 1. Pretreatment evaluation including all risk assessments [laboratory tests to check for adverse events, audiometry, visual acuity, and electrocardiogram (ECG)] was done. Treatment adherence history and tolerance to drugs were also collected.

## Result of Physical Examination and Laboratory Results during Hospitalization

Our patient was semiconscious and emaciated on the day of admission. Her vitals were as follows: Temperature: 102°F; pulse: 92 beats/minute; blood pressure (BP): 90/60 mm Hg; respiration: 48 breaths/minute; $SpO_2$: 82% (room air); and $O_2$: 94% with 6 L. The body mass index (BMI) was 13.3 kg/m$^2$ (severe thinness). Baseline details and investigations (Table 2) were done.

Then tablet bedaquiline (400 mg) was initiated along with ATT in the intensive phase. Special attention was paid to monitoring the adverse events in particular hepatic and cardiac events in patients. Hence, daily monitoring of vital signs, ECG, and blood investigations were done (Table 3). After a few days, she was found to have changes in the QT interval (QT)-prolongation had arrhythmias and derange of liver function test (LFT). Hence, BDQ was withheld for 3 days till she was stabilized. Later, she

**Table 3:** The BDQ toxicity assessment

| | *Treatment* | *QTcF (<450 msec)* | *AST (<40 U/L)* | *ALT (<56 U/L)* |
|---|---|---|---|---|
| Day 1 | Patient got admitted | | | |
| Day 2 | Regimen commenced | 396 msec | 32 U/L | 40 U/L |
| Day 3 | | 387 msec | – | – |
| Day 4 | | – | 36 U/L | 25 U/L |
| Day 5 | BDQ toxicity developed | 487 msec | 31 U/L | 21 U/L |
| Day 6 | | 474 msec | – | – |
| Day 7 | | 448 msec | 33 U/L | 39 U/L |
| Day 9 | | 420 msec | 31 U/L | 23 U/L |
| Day 10 | | 415 msec | 20.4 U/L | 16.5 U/L |
| Day 11 | | 411 msec | 18.5 U/L | 26 U/L |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BDQ, bedaquiline; QTcF, Fridericia's (cube root) correction

was continued the treatment with observation and continuous monitoring. However, she was transferred to a higher institution for continuous care as she had poor improvement.

## Care Focused on Our Patient

- Consent: Obtained informed consent before starting the BDQ drug; explained the benefits and risk involved.
- Patient counseling and education: It was an important area to discuss with her. Explained to the patient and family members about MDR-TB and its management, the importance of adherence, and regular follow-up.
  - Breathing management: Proper body alignment for maximum breathing pattern was maintained. Educated the patient or significant others on proper breathing, coughing, and splitting methods.
  - Dietary management: Reinforced the intake of protein foods including animal origin (milk, eggs, fish, and meat), vegetable origin (cereals and pulses), and good sources of all micronutrients in the form of vegetables and fruits.
  - Management of nausea and vomiting: Instructed her to eat small frequent meals and avoid foods with a strong odor.
- Treatment was closely monitored for effectiveness and safety. The adverse effects on the hepatic and cardiac (QT interval prolongation) system were assessed and managed using the sound treatment and management protocols.
  - Monitoring for hepatotoxicity: Patients' aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase were tested at baseline, monthly, and whenever symptomatic.
  - Monitoring of adverse effects: Follow-up ECG was monitored after treatment was started.
  - Monitoring for renal toxicity: The serum drug level was assessed to assess the renal impairment.
  - Monitoring for additional side effects: The patient was observed for side effects such as nausea, headache, hemoptysis, chest pain, arthralgia, and rash.

## Conclusion

Multidrug resistance tuberculosis is a life-threatening illness that leads to major physical and mental suffering for patients. This suffering always does not end with a good prognosis and the disease leaves major complications. The non-compliance was one of the major causes for our patient to get into major complications and poor prognosis during coronavirus disease-2019.

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