Pharmacology and Clinical Pharmacy Research
Volume 9 No. 1 April 2024
ISSN:2527-7322 | e-ISSN: 2614-0020
doi: 10.15416/pcpr.v9i1.52762

Adverse Events of Bedaquiline Drug Use in the Treatment of Multidrug-Resistant Tuberculosis (MDR TB) Patients: A Review

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Abstract

Adverse Drug Reaction (ADR) is any unfavorable and unexpected drug response in patients dosed for prevention, diagnosis, or therapy. Tuberculosis is a contagious infectious disease caused by the bacterium Mycobacterium tuberculosis. Multi-drug resistance Tuberculosis (MDR TB) is caused by bacteria that are resistant to the two most powerful first-line anti-TB drugs - isoniazid and rifampicin; cases of resistance to both drugs result in worse treatment outcomes, longer treatment duration, high costs, and various other complications. All medications used to treat MDR TB patients have the potential to cause mild, moderate, and severe side effects, especially Bedaquiline. This article will explain information on drug side effects that occur in patients treated with MDR TB and Bedaquiline. The data was collected and discussed from primary journals through Google Scholar and PubMed online databases. Bedaquiline has the potential to cause side effects such as QT interval prolongation or irregular heart rhythm, cardiac arrhythmia, gastrointestinal disorders, joint and muscle pain, hearing loss, acne, and chest pain. Therefore, treatment of MDR TB with Bedaquiline requires monitoring to ensure patient compliance and early detection of possible side effects to ensure the safety and effectiveness of treatment.

Keywords: Adverse Drug Reaction, tuberculosis, MDR TB, bedaquiline

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Received: 22 January 2024. **Revised**: 10 July 2024. **Published:** 6 August 2024

Introduction

Tuberculosis (TB) is an infectious disease usually caused by Mycobacterium tuberculosis. TB typically affects the lungs (pulmonary TB) but can also affect other body parts such as the central nervous system, lymphatic system, circulatory system, genitourinary system, gastrointestinal system, and bones and joints. Standard treatment for patient TB is a 6-9 month regimen with four first-line drugs - isoniazid, rifampicin, ethambutol, and pyrazinamide. Many of the medications used to treat TB, especially second-line drugs, often have substantial toxicity profiles.[1] Backup many medicines are given together due to drug resistance, increasing overall toxicity through drug interactions.

Adverse Drug Reaction (ADR) can generally be classified into two types based on pharmacological effects and predictability. First, ADR type A is an undesirable reaction that can occur in everyone with a therapeutic dose, a pharmacological effect that can be predicted (predictable). The effect is dose-related and easy to overcome. Usually, this type of reaction has been recognized before the drug is released on the market. Secondly, type B ADR is unwanted reactions unrelated to the drug's pharmacological effects, so these reactions cannot be predicted and are not observed during the pharmacological and toxicological screening of the drug before the drug is marketed.[2,3]

Monitoring of adverse drug events is monitoring each patient's response to an undesirable drug, which occurs at the usual dose used in humans for prophylactic, diagnostic, and therapeutic purposes on drugs licensed to be marketed.[4] It is also used to detect or identify ADR as early as possible, especially those that are unrecognized, severe, and infrequent, as well as determine the frequency and incidence of known and newly discovered, prevent the recurrence of adverse drug reactions, and identify drugs or drug interactions that have a high potential to cause ADR.[5]

Based on the electronic platform of the Indonesian Food and Drug Authority data reported in 2021, there was a frequency of ADR in Indonesia with a total reporting of 8,691 cases, of which 4,842 came from reports from health workers and 3,847 from the pharmaceutical industry. Based on the reported data, ten pharmacological subgroups of drugs were suspected of causing ADR from the 2021 health worker report, the largest of which is the Drugs For Treatment Of TB group, followed by the Quinolone Antibacterial group. Of the ten active substances of the most reported ADR cases, there were three active substances reported, which were dominated by drugs for the treatment of TB, namely Bedaquiline (BDQ), Levofloxacin, and Clofazimine.[6]

Meanwhile, based on The Electronic Health Record (EHR) data reported in 2022, there was a frequency of adverse drug reactions in Indonesia with a total reporting of 10,749 cases, of which 6,852 were from health worker reports, and 3,897 were from pharmaceutical industry reports. Where the most reported cases of adverse drug events are suspected to be drugs used in the treatment of TB. From the reports recorded, there are ten active drug substances suspected of causing the most ADR reported in 2022, which are dominated by drugs for the treatment of TB, namely BDQ, Levofloxacin, Clofazimine, Cycloserine, Pyridoxine, Linezolid, and Ethambutol.[7]

Based on the EHR data reported, there is a drug that is thought to cause the most cases of adverse events, namely the drug BDQ,

which has the most reports, namely in 2021, as much as 17% or around 1477 out of 8,691 cases and 2022 as much as 1,353 out of 10,749 cases. Therefore, this journal will provide information on ADR in MDR TB treatment and using BDQ. The main objective of this literature review is to contribute to the scientific understanding of adverse events using BDQ in treating patients with MDR TB.

Methods

All primary data was collected and discussed in primary literature journals through online databases on Google Scholar and PubMed. The search was conducted by combining the keywords "BDQ," "TB-MDR," "Pharmacovigilance TB-MDR," and "Pharmacovigilance TB-MDR BDQ." The primary data sources used included research journals published in national and international journals.

The journals were screened with inclusion criteria of articles related to MDR TB treatment using BDQ and published in 2014-2024, as well as exclusion criteria of repository and review articles. Based on the keywords of this research, the results of searching journal libraries on Google Scholar and PubMed, journal libraries numbering 3,050; 1,273; 1,660; 5,559; 115, and 24 articles for each keyword were obtained.

Results and Discussion

TB is a contagious infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) infection. This *M. tuberculosis* bacteria is a rod-shaped bacteria with acid-resistant properties, also often called Acid Resistant Bacilli. TB is an infectious disease that is the leading cause of death worldwide.[17]

Based on information related to drug side effects that occur in patients with MDR TB patients in the form of depression, nausea, vomiting, dyspepsia, arthralgia, hepatotoxicity, ototoxicity, peripheral neuropathy, electrolyte depletion, renal impairment, hepatic impairment, erythrocytosis, myelosuppression, QT prolongation or irregular heart rhythm, psychiatric/psychiatric disorders, neurology, insomnia, depression, confusion, hearing impairment, digestive disorders, and visual impairment.[8–10]. Information related to drug side effect studies in MDR TB regimens can be seen in Table 1.1.

The goal of TB treatment is one of the most efficient efforts to prevent further spread of *M. tuberculosis* bacteria. The treatment regimen for TB disease is divided into 2 stages, namely the initial/intensive stage, which is treatment given every day for 2 months and aims to reduce the number of germs in the body.

Drugs such as Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E); then proceed to the advanced stage of treatment, which is treatment given every day for 4 months which aims to kill the remaining germs still in the body with drugs such as Isoniazid and Rifampicin.[18]

TB patients are classified based on the results of sensitivity testing to antibiotics used in anti-TB drug therapy regimens. The categories include monoresistant, which refers to resistance to one type of first-line anti-TB drug, and poliresistant, which means resistance to more than one type of first-line anti-TB drug, excluding isoniazid (H) and rifampicin (R) simultaneously, such as resistance to isoniazid and ethambutol. Multidrug-resistant TB (MDR TB) is characterized by resistance to at least both isoniazid (H) and rifampicin (R) simultaneously.

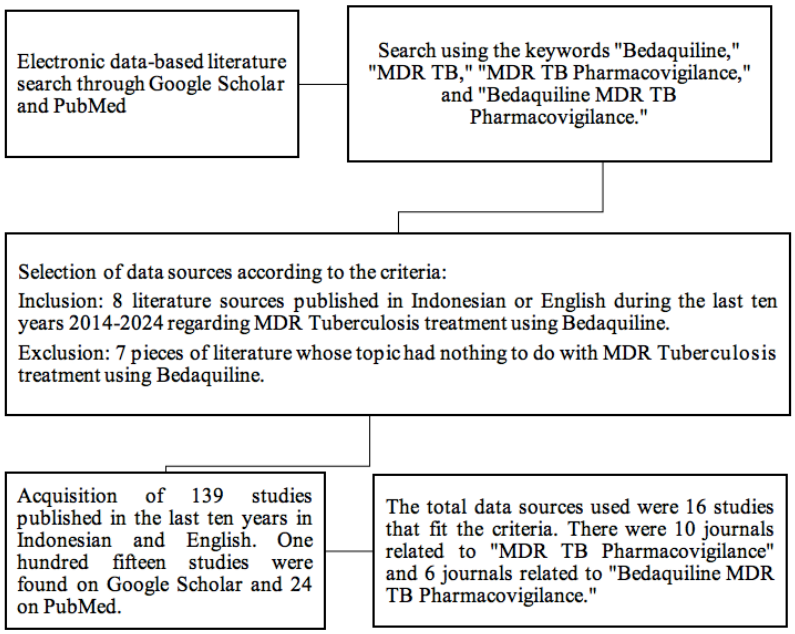

Figure 1. Methods

Extensively drug-resistant TB (XDR TB) refers to MDR TB that is also resistant to one of the fluoroquinolones and one of the second-line injectable drugs (kanamycin, capreomycin, and amikacin). Rifampicin-resistant TB (RR TB) is defined as resistance to rifampicin, confirmed by either genotyping (rapid test) or phenotyping (conventional) methods, with or without resistance to other anti-TB drugs. TB patients with rifampicin resistance have the possibility of developing resistance to other drugs, such as MR TB, PR TB, MDR TB, and XDR TB, that are proven to be resistant to rifampicin.[18]
Intensive Phase : 2 months H - R - Z - E
Advanced Phase : 4 months H - R

Multidrug-Resistant Tuberculosis (MDR TB)
MDR TB is a condition in which a patient has TB disease but has developed resistance to the drugs isoniazid and rifampicin simultaneously with or without resistance to other first-line drugs, both of which are the most effective drugs in TB treatment. There are two regimens for the treatment of MDR TB, namely long-term and short-term therapy regimens.[19]

Patients with cases of resistance to both drugs will have worse treatment outcomes, higher mortality rates, longer treatment duration (about two years), high costs, and various other complications, so the treatment of MDR TB is more complicated than drug-sensitive TB. Therefore, monitoring is needed to ensure that patients undertake treatment well.[17]

MDR TB treatment is started with at least five TB drugs that effective and at least three medications for the remainder of therapy after BDQ is discontinued.[20] Treatment for MDR TB patients generally involves short-term treatment using a combination of 7 drugs given daily for 4-6 months: Bedaquiline (Bdq), Levofloxacin (Lfx), Clofazimine (Cfz), high-dose Isoniazid (H), Pyrazinamide (Z), Ethambutol (E), and Ethionamide (Eto); or a 4-drug combination given daily for 5 months of Levofloxacin (Lfx), Clofazimine (Cfz), Pyrazinamide (Z), and Ethambutol (E); then given long-term treatment with a combination of 5 drugs given daily for 6 months using Bedaquiline (Bdq), Levofloxacin (Lfx), Clofazimine (Cfz) or Cicloserine (Cs), Pyrazinamide (Z);

or can also use a combination of 4 drugs given daily for 14 months, namely Levofloxacin (Lfx), Clofazimine (Cfz) or Cicloserine (Cs), Pyrazinamide (Z).[20]

Intensive Phase
4-6 months Bdq - Lfx - Cfz - H - Z - E - Eto / 5 months Lfx - Cfz - Z - E
Advanced Phase
6 months Bdq - Lfx - Lzd - Cfz or Cs - Z / 14 months Lfx - Lzd - Cfz or Cs - Z

ADRs during MDR TB treatment are more common in male. In addition, there is a high incidence of ADRs in patients with HIV co-infection and those receiving injectable drugs as part of their treatment regimen due to long-term treatment, which can decrease patient adherence.[21] Monitoring the occurrence of drug side effects is very important during MDR TB treatment. All anti-TB drugs used for MDR TB patients can cause mild to severe side effects. Health workers should continuously monitor and immediately act if side effects are found.

Some of the side effects of drugs that are also found in patients treated with MDR TB are strong joint and muscle pain.[22] Studies show that side effects are managed with pharmacological and non-pharmacological interventions. Side effects also do not always lead to temporary or permanent discontinuation of MDR TB treatment, nor do they negatively affect treatment outcomes. This highlights the importance of continuous monitoring and prompt action in the event of adverse events so that treatment can be continued.[23]

MDR TB patients often have comorbidities or additional medical conditions. Some common comorbidities include diabetes, kidney disease, liver disease, HIV/AIDS, and immune disorders. These extra conditions can complicate the treatment of MDR TB and increase the risk of side effects. Therefore, more careful management and personalized therapy is required.[23]

Bedaquiline
Bedaquiline (BDQ) is used in the treatment of MDR TB and is the first new anti-TB drug to be introduced to the market in nearly 50 years. It belongs to the diarylquinoline category and has a novel mechanism of action against *M. tuberculosis*. In Indonesia, BDQ was only registered with the Food and Drug Administration in 2018, and there are limited studies systematically investigating the use of BDQ in MDR TB therapy.[19]

This review reflects some of the prospects and challenges faced using BDQ for TB therapy. One major obstacle is the high cost of the drug, which may limit its accessibility in low- and middle-income countries. In addition, further research is needed to refine the dose and duration of BDQ treatment and identify biomarkers that can predict response to treatment and potential side effects.

On the other hand, BDQ's prospects show promising potential. It is highly effective in treating MDR TB, and there is a possibility of utilizing it in combination with other drugs to improve treatment effectiveness. In addition, ongoing studies are also exploring the potential use of BDQ in addressing other mycobacterium infections, including non-tuberculous mycobacterium lung diseases. These analyses imply that BDQ could have a significant role in global initiatives to fight drug-resistant TB 24. From the search results for reference journals, information on the drug BDQ can be seen in Table 1.2.

BDQ is a diarylquinoline that works by a novel mechanism inhibiting adenosine triphosphate synthesis in bacterial microenvironments, disrupting bacterial energy metabolism. The

use of BDQ occurs as part of a short-term treatment regimen for patients with MDR TB. Such patients receive a combination of seven drugs administered daily over 4-6 months.[25] The application of BDQ in the clinical management of MDR TB has brought encouraging results. Studies have shown that BDQ-containing therapeutic regimens produce positive results in most patients, while its tolerability over prolonged treatment periods is generally satisfactory.[24]

BDQ Therapy Regimen / Interval

Treatment for MDR TB involves the use of more potent drug combinations and a longer duration of treatment compared to standard TB therapy. Typically, MDR TB therapy involves administering drugs such as fluoroquinolones, aminoglycosides, and cycloserine, as well as other drugs such as linezolid, clofazimine, and BDQ. The duration of MDR TB treatment is generally longer, ranging from 18 to 24 months, and can be adjusted depending on the patient's response to treatment. Close supervision and regular monitoring are required in MDR TB therapy to ensure patient adherence to treatment and detect possible adverse effects.[26]

The use of BDQ to treat MDR TB provides good synergy when combined with other anti-TB antibiotics. Some combinations that have been tested for efficacy include:

1. BDQ and delamanid (Dlm): shown promising results for MDR/XDR TB patients, but be aware of the possibility of higher cardiac toxicity.
2. BDQ and pyrazinamide: shown to suppress bioenergy and deplete the energy reserves of TB cells, thereby reducing the burden of infection.
3. BDQ and cephalosporins enhanced BDQ's bactericidal activity against *M. tuberculosis*.
4. BDQ and pretomanid have a strong synergistic effect on MDR TB.
5. The combination of BDQ, pretomanid, and linezolid showed high culture conversion rates and low relapse rates for extensively resistant TB.[24]

Pharmacodynamics / Mechanism of Action of Bedaquiline

BDQ is the latest drug the World Health Organization (WHO) recommended for treating MDR TB in 2013. BDQ works as an ATP synthase inhibitor that affects microbial membranes and became the first drug to receive the Food and Drug Administration's (FDA) approval for TB treatment after more than 40 years. BDQ is integrated into combination therapy for MDR TB patients who do not respond to standard treatment.[26]

BDQ is an anti-TB drug that operates by inhibiting ATP synthase, an enzyme crucial in microbial energy metabolism. In this way, BDQ interferes with the energy production process required by TB bacteria for survival. Because of this, BDQ is an efficient drug in treating TB that is unresponsive to standard treatment. Moreover, BDQ also has lipophilic properties that allow it to penetrate the cell membrane of TB bacteria more efficiently. Combining these two mechanisms of action makes BDQ the first choice in treating MDR TB.[36]

BDQ utilizes its antimicrobial activity by inhibiting the synthesis of ATP in *M. tuberculosis*. The drug targets the central region of the enzyme's c subunit, disrupting the energy production process and arresting the micro-development of the bacteria, ultimately leading to death. This unique mechanism of action makes BBQ a promising addition to the existing arsenal of anti-TB agents, especially in regions where MDR TB is standard.[25]

Pharmacokinetics of Bedaquiline

BDQ was administered orally and underwent rapid absorption, reaching a peak time to maximum plasma concentration (Tmax) within 4 hours. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased with the BDQ dose, showing a linear pharmacokinetic profile up to 700 mg. BDQ has a high plasma protein level (>99%) and is metabolized primarily in the liver via the enzyme CYP3A4. The major metabolite of BDQ, M2, also has activity against *M. tuberculosis*. BDQ and its metabolites are eliminated mainly through feces, with small amounts excreted through urine. The pharmacokinetics of BDQ are not influenced by factors such as age, gender, or race.[25]

BDQ is metabolized via cytochrome P450 enzyme isoenzyme 3A4, which catalyzes N-demethylation to form metabolite M2, whose activity is approximately three to six times that of BDQ. Although M2 circulates at concentrations 10 times lower than BDQ, the potential risk of toxicity makes it a cause for concern. Preclinical trials have shown that M2 has a more substantial phospholipidosis-inducing effect and is more cytotoxic than BDQ. M2 concentrations were also associated with QT interval prolongation then undergoes an N-demethylation process, most likely executed by the same enzyme.

Although excretion of BDQ through the kidneys is considered less significant, excretion through the feces does occur. BDQ and M2 have high protein binding rates, exceeding 99.9% and 99.7%, respectively. The safety of BDQ use involves several aspects, including its ability to cause moderate QT interval prolongation and an unexplained increase in mortality observed in one randomized phase II trial. The approved BDQ use regimen includes a 2-week loading phase at a dose of 400 mg daily, followed by a dose of 200 mg three times a week until week 24.[27]

Information related to BDQ's ADME profile can be described as follows:

- Absorption: oral ingestion, increases when taken with food, aiming to optimize efficiency and absorption. The time to reach the peak concentration in plasma is about 4-6 hours.
- Distribution: high degree of distribution into tissues and bind to blood transport proteins. The distribution of BDQ within the body allows exploitation of its bactericidal activity against *M. tuberculosis*.
- Metabolism: processes in the liver, mainly through cytochrome P450 enzymes, resulting in the formation of metabolites.
- Excretion: excreted via feces. The drug is eliminated slowly from the body, with a final elimination half-life of about 5.5 months.[24]

Side effects of Bedaquiline

BDQ has potentially severe side effects, such as QT interval prolongation and cardiac arrhythmias. The QT interval measures the time for blood to be pumped by the heart, and its prolongation can lead to dangerous heart rhythm disturbances. In addition, BDQ may also cause nausea, vomiting, headache, as well as elevated liver enzymes. Due to these risks, BDQ requires close monitoring and regular examination of patients to detect symptoms of side effects.[26]

Based on data from the Indonesian Ministry of Health, BDQ has the potential to cause several side effects, such as joint pain and muscle pain, joint and muscle inflammation, liver function disorders, gastrointestinal complaints, and cardiac disorders such as QT interval prolongation, irregular and dangerous

heartbeats (ventricular arrhythmias).[20]

BDQ can also cause liver function-related side effects; it also has dangerous drug interactions with CYP3A4 inductors and inhibitors, as well as other QT interval-prolonging drugs. In clinical trials, the most common side effects associated with BDQ were nausea, limb pain, bilateral hearing loss, acne, and chest pain.[25]

The use of BDQ with other drugs needs to be done with caution due to potential interactions and side effects. Besides the risk of side effects and drug interactions related to BDQ, there are other essential considerations in its use:

1. BDQ should only be used in combination, as monotherapy can lead to bacterial resistance.
2. Patients with a history of heart disease or who are taking QT-prolonging drugs need to be cautious.
3. Hepatitis patients need extra monitoring because BDQ runs on the liver.
4. There is limited data on the safety and benefits of BDQ for HIV patients.
5. Pregnant and breastfeeding women need special consideration as safety data is limited.
6. A minimum of 6 months and more of BDQ therapy is needed for optimal results, with regular monitoring of liver function, electrolytes, and ECG.

Fatal serious adverse events are reported through SITB by the pharmacy or clinical pharmacy staff or ADR officer-in-charge as soon as possible within 24 hours of the occurrence, while non-fatal serious adverse events are reported no later than 15 days after the occurrence. SITB will inform directly to all interested parties who have access. Meanwhile, non-serious ADRs can be reported through SITB or the EHR page as soon as possible since they are known to have occurred.[18]

Providing information on the occurrence of ADR is the duty of pharmacists, as well as preventing and reducing the incidence of ADR, especially in TB and MDR TB patients who require high compliance by providing information on the correct use of drugs, namely:

1. Take medicine according to the schedule and doctor's recommendations.
2. Avoid drinking alcohol and smoking while taking MDR TB drugs.
3. Get enough rest and avoid overexertion.
4. Eat a balanced and nutritious diet.
5. Drink plenty of water.
6. Manage your intake of salt, sugar, and fat.
7. Control vital signs regularly. Low blood pressure can aggravate nausea and vomiting.
8. Additional vitamins are recommended to treat anemia.
9. Avoid excessive stress, as it can worsen the body's condition.
10. Communicate with your doctor is essential to address side effects and maximize treatment. Compliance is key.

The use of BDQ in the treatment of MDR TB has good potential to improve treatment success rates, but it is essential to be aware of the possibility of drug interactions and side effects in patients. Therefore, it is necessary to monitor and report any adverse drug events, whether mild, moderate, or severe. Through close monitoring, it is hoped that treatment can run safely and effectively according to the goals of MDR TB treatment.

Pharmacists have a role in detecting ADR in patients, recording and exploring data related to ADR, conducting tertiary literature studies, matching ADR data with suspected drug data, searching for information on other reports,

analyzing causality using the Naranjo scale, formulating recommendations to clinicians, making reports, and reporting ADR to the ADR reporting system. This shows that ADR reporting by pharmacists is an essential part of the spontaneous reporting system.[28]

ADR can usually be identified when pharmacists visit patients or provide drug information to counseling patients and others. Each reported ADR will then be observed or collected related to information on drug use history, disease history, possible drugs that cause ADR, and Naranjo scale assessment. ADR reporting by healthcare professionals is done as soon as possible spontaneously when an adverse event occurs.

The minimum types of information that must be submitted in ADR reports are patient-related information in the form of patient initials, age and date and year of birth, gender, and weight; ADR information in the form of ADR description, date of ADR occurrence, date of ADR reported, laboratory test results or other appropriate tests if available, other relevant patient information/history, adverse event outcome; information related to the suspected drug in the form of drug name (active substance and trade name), dose, frequency, and route of drug administration, date of drug start, an indication of drug use.[29]

Information on whether the ADR improved after the drug was stopped or the dose was reduced, batch number, information on whether the ADR occurred when the drug was re-administered, drugs taken with the suspected drug and the date of starting to take the drug; and reporter information in the form of name, address, telephone number, and occupation/profession.[29]

ADR reporting allows for causality assessment of adverse drug events. The causality assessment is the result of evaluating the complaints or clinical manifestations experienced by patients related to drug use using the Naranjo scale. The Naranjo scale is a scale developed to assist in the standardization of causality assessment for adverse drug events.
Probability is given through a particular score, may occur, is not specific to happen, or is doubtful. This naranjo scale can only be filled out by health professionals 30. Drug side effect categories based on the Naranjo scale can be divided into Highly probable categories with scale values ≥ 9, Probable is 5-8, Possible categories is 1-4, and Doubtful is 0.[31]

It is recommended that suspected ADR be reported to determine the incidence, so that there is no need to worry that ADR are minor or unimportant. At the same time, the current management and extraction of information related to side effects that occur in patients is still incomplete. There is a need for SOPs related to receiving adverse event reports from patients. Serious adverse drug events are those that can cause death, are life-threatening, result in extended or unexpected hospitalization, cause congenital abnormalities, lead to disability, and require medical or surgical intervention to prevent a worse condition.

The results of this article review are expected to provide information on the side effects of BDQ in MDR TB patients, as well as provide recommendations for monitoring patients undergoing treatment with the drug to help improve the quality of MDR TB treatment and reduce the risk of side effects caused by the use of BDQ. In addition, with a better understanding, pharmacists can play a more active role in monitoring patients undergoing treatment with the drug. They can also provide recommendations to clinicians regarding the

monitoring and management of side effects that may occur. In addition, pharmacists can also use the information obtained from this journal to report adverse drug events to the FDA reporting system, thus helping improve patient safety in using BDQ.

Conclusion

BDQ is used as part of combination therapy for MDR TB patients unresponsive to standard treatment. BDQ works by inhibiting ATP synthase on the microbial membrane. BDQ can cause various side effects, such as QT interval prolongation, cardiac arrhythmias, gastrointestinal disorders, joint and muscle pain, hearing loss, acne, and chest pain. Therefore, treatment of MDR TB with BDQ requires close monitoring and supervision. This aims to ensure patient compliance and early detection of side effects that may occur to ensure treatment safety and effectiveness.

Funding

Nil

Conflict of Interest

None declare

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Volume 9 No. 1 April 2024
ISSN:2527-7322 | e-ISSN: 2614-0020

Table 1. Studies of Drug Side Effects in MDR TB Regimens

Author	Sample	Method	Result	MDR TB Therapy
(Farrukh, et.al., 2023) [11]	This multicenter prospective cohort study included patients with MDR TB who started treatment with new and reused drugs in routine care from April 2015 to September 2018 in 17 countries. Between April 1, 2015, and March 1, 2023, 1057 women of childbearing age (15-49 years) received treatment with BDQ and demand, and 48 pregnancies in 43 women were reported to the study. For both cohorts, all MDR/RR-TB patients who reported pregnancy during treatment or follow-up were included in the study.	A multicenter prospective cohort study	Among 43 pregnant women who received MDR/RR TB treatment with BDQ and Dlm, 98% had good treatment outcomes. Of the 31 pregnancies that continued, 81% delivered live babies without malformations, and 68% of neonates had average weight. Effective treatment of MDR/RR TB during pregnancy can improve pregnancy outcomes without jeopardizing the newborn. These data can be confirmed by comparison of other groups and identification of factors contributing to low birth weight in infants of mothers with MDR/RR TB.	Treated pregnant women received MDR/RR TB treatment with Linezolid, BDQ, Clofazimine, Dlm, Amikacin, Capreomycin, and Kanamycin.
(Hurgea, et.al., 2022) [12]	A prospective, multicenter observational study in 14 countries examined MDR TB/RR patients who received concomitant Bdq-Dlm between April 1, 2015, and September 30, 2018. All severe and adverse events that led to changes or were judged significant by clinicians were monitored and documented.	A multi-centric, prospective observational cohort study	472 patients received concurrent Bdq and Dlm. Most also received linezolid (89.6%) and clofazimine (84.5%). Almost all (90.3%) had severe disease, and most (74.2%) were fluoroquinolones resistant. The most common AESIs were peripheral neuropathy (28.4%) and electrolyte depletion (19.9%). Acute kidney injury and myelosuppression were seen in 8.5% and 5.1% of patients, respectively. QT prolongation occurred in 1.5% of patients. 78.0% had a successful outcome, 8.9% died, and 7.2% failed. Concurrent use of Bdq, Dlm, linezolid and clofazimine is safe and effective for severe MDR TB. It is an excellent therapeutic option for multidrug-resistant patients.	Of the 2731 patients in the final TB cohort, some received BDQ and Dlm concurrently at the initiation of MDR/RR TB treatment. Most patients also received linezolid and clofazimine in addition to BDQ and Dlm. Injectable drugs such as aminoglycosides or polypeptides were also given concurrently with BDQ and Dlm at treatment initiation, as were patients who later received a combination of these drugs.

Pharmacology and Clinical Pharmacy Research
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ISSN:2527-7322 | e-ISSN: 2614-0020

Table 1. Studies of Drug Side Effects in MDR TB Regimens (cont..)

Author	Sample	Method	Result	MDR TB Therapy
(Gao, et.al., 2021) [9]	This study data was prospectively collected with demographic, bacteriologic, radiologic, and clinical data from 54 sites across China at enrollment and during treatment between February 2018 - December 2019. This interim analysis included patients still in and having completed treatment. Descriptive analysis was performed on patients evaluated in the Cohort.	A multicenter prospective cohort study	As of December 31, 2019, 1162 patients received anti-TB treatment containing BDQ. A total of 1563 AEs were reported, 66.9% minor (Grade 1-2) and 33.1% serious (Grade 3-5). The mean duration of BDQ was 167.0 [interquartile range (IQR): 75-169] days. 86 patients (7.4%) received treatment for 36 weeks with BDQ. The incidence of AEs and serious AEs were 47.1% and 7.8%, respectively. The most commonly reported AEs were QT prolongation (24.7%) and hepatotoxicity (16.4%). There were 14 (1.2%) AEs that caused death. Based on Fridericia's formula-based corrected QT interval (QTcF) data, 3.1% (32/1044) had a post-baseline QTcF≥500 ms, and 15.7% (132/839) at least one QTcF change≥60 ms from baseline. 49 patients (4.2%) experienced QT prolongation AEs that led to BDQ discontinuation. Nineteen patients reported 361 AEs with second-order hepatotoxicity. Thirty-four patients reported 43 AEs of liver injury attributable to BDQ, much lower than prothionamide, pyrazinamide, and para-aminosalicylic acid individually.	The therapeutic regimen consists of a combination of various formulations of anti-TB drugs, such as BDQ, moxifloxacin, Levofloxacin, linezolid, clofazimine, amikacin, capreomycin, prothionamide, cycloserine, pyrazinamide, ethambutol, para-aminosalicylic acid, high-dose isoniazid, meropenem, and amoxicillin/clavulanate.
(Khan, et.al., 2019) [13]	The endTB observational study protocol enroll 2600 patients (April 2015 to September 2018) in 17 countries. Patients: essential subgroups (XDR and pre-XDR-TB patients, children, pregnant women, extra-pulmonary TB patients, and with comorbidities). The patients were on BDQ or Dlm active ingredient regimen treatment in routine care. Data collection: a customized open-source electronic medical record (EMR) system developed in 17 countries.	A multicenter prospective observational cohort study	The late TB observational study protocol and discussion should have presented specific results. However, the study aimed to generate evidence on the safety and efficacy of BDQ and demand-based regimens in a large, highly diverse cohort of MDR TB patients from 17 epidemiologically diverse countries. The study collected repeated effectiveness and safety data and analyzed the data to improve the quality of evidence available to inform MDR TB treatment and policy decisions.	This treatment refers to the national TB and MDR TB treatment guidelines, which reflect the guidelines for BDQ or Dlm regimens.

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Table 1. Studies of Drug Side Effects in MDR TB Regimens (cont..)

Author	Sample	Method	Result	MDR TB Therapy
(Lachenal, et.al., 2020) [14]	Launched with full support from UNITAID in April 2015, the endTB (Expanding Access to New Drugs for Tuberculosis Disease) initiative facilitated the treatment of 2600 patients with BDQ and Dlm in 17 countries. It contributed to the establishment of a universal patient safety database.	Narrative Review	Between April 1, 2015, and March 31, 2019, PVU received and assessed 626 cases of severe adverse events (ESBs) experienced by 417 patients on BDQ treatment. It reviewed unexpected ESBs that may be drug-related to detect safety signals. Experts discussed high-risk patient groups, especially polypharmacy, and the use of non-prescription drugs, which encouraged a patient-centered care approach. Setting up advanced PV in routine care is feasible but resource-intensive. It makes more sense for local/national programs to focus more on clinical management, reporting to the DSM system only for critical data such as ESB.	The study included MDR TB patients who received a BDQ-containing regimen. During treatment, patients were also given other drugs such as linezolid, clofazimine, levofloxacin/moxifloxacin, or Dlm.
(Koirala, et.al., 021) [15]	A 28-year-old man from Egypt, with previous history of TB treatment. Status: diabetes, HIV, or alcohol abuse are negative. Current diagnosis: MDR/RR pulmonary TB with cavitary lesions. A 45-year-old woman from Mexico, no previous TB treatment. Status: managed diabetes without complications and free from HIV or alcohol. Current diagnosis: pulmonary MDR/RR TB with cavitary lesions. A 20-year-old man from Vietnam, no history of TB. Status: diabetes and alcohol are negative, HIV positive. Current diagnosis: pulmonary MDR/RR TB without cavitary lesions. This illustrates the global impact of MDR TB across different demographics and health backgrounds.	A large global cohort	Geographical variations in success rates explained the diverse treatment outcomes. The study also highlighted the severity of drug resistance patterns, with a proportion experiencing multi-drug resistant TB. Finally, the duration of anti-TB treatment, BDQ, and Dlm was explained for patients with an outcome. The results of this study highlight the efficacy of regimens containing BDQ and Dlm in managing multidrug-resistant TB.	All patients treated with BDQ and Dlm (including children/adolescents) are first registered and managed according to WHO and national guidelines respectively.

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Table 1. Studies of Drug Side Effects in MDR TB Regimens (cont..)

Author	Sample	Method	Result	MDR TB Therapy
(van der Walt, et.al., 2020) [16]	This study investigated treatment, as well as pregnancy and infant birth outcomes, in a cohort of pregnant women with drug-resistant tuberculosis (DR-TB) from three MDR TB hospitals from 2010 to 2018.	Retrospective record review	The mean age was 29 years (standard deviation ± 5.1), ranging from 21 to 40 years. Eleven individuals (42.3%) had previously undergone treatment using first-line TB drugs, another eleven (42.3%) had not previously undergone treatment, and four individuals (15.4%) had been treated for drug-resistant tuberculosis (DR-TB). Of the total 26 women, 15 (57.7%) experienced at least one Adverse Drug Effect (ADE), but the majority experienced more than one ADE. 17 were successfully treated, and 22 live births were recorded. There was a significant association between live birth outcomes and the trimester in which DR-TB treatment was initiated (p = 0.036). The proportion of live births for the trimester of pregnancy at the start of DR-TB treatment was 60.0%, 90.9%, and 100.0% for the first, second, and third trimesters, respectively.	The drugs used in the treatment of MDR TB are P-aminosalicylic acid, Linezolid, Clofazimine, Levofloxacin, Ofloxacin, BDQ, Isoniazid, Kanamycin, Capreomycin, Ethambutol, Pyrazinamide, Terizidone, Moxifloxacin, and Ethionamide. Most pregnancy status was ascertained before the start of MDR TB treatment, during the intensive phase of treatment, and after the intensive phase.
(Hewison, et.al., 2022) [8]	This prospective, multicenter observational study (conducted in 16 countries) describes the incidence and frequency of adverse events of clinical relevance and concern (AEs) in patients undergoing treatment for drug-resistant tuberculosis (MDR TB). MDR TB/RT treatment includes the use of BDQ and Dlm. Serious adverse events (AESIs) were previously defined as significant events caused by the use of BDQ, Dlm, linezolid, injectable drugs, and other commonly used drugs. These AESIs were also reported when exposed to the causative agent.	A multicenter, prospective, observational cohort study	Of the 2,296 patients, the most clinically common adverse events were peripheral neuropathy (26.4%), electrolyte depletion (26.0%), and hearing loss (13.2%). The incidence per 1000 persons per month of treatment for the three adverse events was 21.5 (95% confidence interval [CI]: 19.8-23.2), 20.7 (95% CI: 19.1-22.4), and 9.7 (95% CI: 8.6-10.8) respectively. The increase in QT interval occurred in 2.7% or 1.8 (95% CI: 1.4-2.3)/1000 person-months of treatment. Patients who received injections (N=925) and linezolid (N=1826) had the highest risk of experiencing adverse events during exposure. Hearing loss, acute renal failure, or electrolyte depletion occurred at a rate of 36.8% or 72.8 (95% CI: 66.0-80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis, and myelosuppression occurred at a rate of 27.8% or 22.8 (95% CI: 20.9-24.8) times/1000 patient months of linezolid exposure.	The drugs included in the baseline treatment regimen of the study were BDQ, Dlm, BDQ and Dlm, Linezolid, Clofazimine, Cycloserine, Moxifloxacin or Levofloxacin, Prothionamide/Ethionamide, Kanamycin, capreomycin, or amikacin, P-aminosalicylic acid, Imipenem/Cilastatin or meropenem, pyrazinamide.

Table 2. Bedaquiline Drug Information

	Drug Information	References
Goals	Diarylquinoline	(Chahine, et al., 2014) [25]
Indications	TB - MDR	(Indonesian Ministry of Health, 2020) [20]
Dosage	BDQ was administered at the recommended dose of 400 mg once daily for 14 days, followed by 200 mg thrice weekly for the remaining 22 weeks.	(Gao, et.al., 2021) [9]
Pharmacodynamics / Mechanism of Action	An adenosine triphosphate (ATP) synthase inhibitor that acts on the microbial membrane, disrupting the bacteria's energy metabolism.	(Guglielmetti, et.al., 2017) [26]
Pharmacokinetics	**Absorption**: BDQ is administered orally and absorbed rapidly, Tmax 4 hours. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) increase proportionally with increasing doses of BDQ, which displays a linear pharmacokinetic profile up to a dose of 700 mg. **Distribution**: BDQ is widely distributed in tissues and can be bound to plasma proteins (>99%). **Metabolism**: BDQ is metabolized via cytochrome P450 (CYP) isoenzyme 3A4, which catalyzes N-demethylation to form metabolite M2. BDQ and M2 have high protein binding, >99.9% and >99.7%, respectively. **Excretion**: BDQ and its metabolites are excreted mainly through feces, with a small amount excreted through urine.	(Chahine, et.al., 2014; Svensson, et.al., 2016) [25,27]
Side effects	QT interval prolongation, cardiac arrhythmias, nausea, vomiting, headache, elevated liver enzyme levels, joint pain and muscle pain, joint and muscle inflammation, impaired liver function, gastrointestinal disorders, bilateral hearing loss, acne, and chest pain.	(Kemenkes RI, 2020; Chahine, et.al., 2014; Guglielmetti, et.al., 2017) [20,25,26]