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Original Research Article

# A Pharmacovigilance Study on Comparative Safety Assessments of Delamanid, Ofloxacin, Levofloxacin and Bedaquiline, in Tertiary Healthcare of Multi-Drug Resistant Tuberculosis

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**Abstract**

**Background:** Delamanid is bactericidal to *Mycobacterium tuberculosis* and *M. kansasii*. Ofloxacin is bactericidal to *M. tuberculosis*, MAC, *M. fortuitum*, and other atypical mycobacteria. Bedaquiline is consecutively bacteriostatic and bactericidal to *M. tuberculosis.*

**Objective:** A pharmacovigilance study on comparative safety assessments of delamanid, ofloxacin, levofloxacin and bedaquiline, in tertiary healthcare of multi-drug resistant tuberculosis.

**Materials and Methods:** Among 100 multi-drug resistant tuberculosis patients, Group A was prescribed delamanid 100 mg twice daily, Group B was prescribed ofloxacin 400 mg twice daily, Group C was prescribed levofloxacin 750 mg once daily, and Group D was prescribed bedaquiline 400 mg once daily followed by 200 mg thrice weekly, for 24 – 48 weeks. These anti-tubercular drugs' safety assessment was performed by monitoring the occurrence of any adverse drug reaction, like nausea, vomiting, headache, insomnia, dizziness, tinnitus, hypokalaemia, gastritis, decreased appetite, asthenia, diarrhoea, skin rash, arthralgia, constipation, ECG QT prolongation, myalgia, chest pain, or, haemoptysis, with Adverse Event Case Report Forms, on days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360 and on further follow-ups, which was statistically analysed.

**Results:** The safety assessments showed that among Group A patients, 1 patient had decreased appetite, among Group B patients, 1 patient had nausea, among Group C patients, no patients had any adverse drug reaction, and among Group D patients, 1 patient had myalgia. The occurrence of adverse drug reactions was statistically non-significant, among all 4 groups.

**Conclusion:** Delamanid, ofloxacin, levofloxacin and bedaquiline were safe and tolerable for treating multi drug-resistant tuberculosis tertiary healthcare patients.

**Keywords:** Pharmacovigilance, Safety assessment, Delamanid, Ofloxacin, Levofloxacin, Bedaquiline, Multi drug-resistant tuberculosis.

## Introduction

World Health Organisation (WHO) have estimated that 9% of over 5 lakhs cases of annual multidrug-resistant (MDR) tuberculosis, are affected by extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*. In 2020, 71% (2.1/3.0 million) of global patients, suffering from bacteriologically confirmed pulmonary TB, had undergone laboratory investigations for rifampicin resistance. The investigations had detected and confirmed that 132 222 cases had multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) and 25 681 cases had pre-extensively or extensively drug-resistant (DR) TB. Within the paediatric population, children of 0-14 years demonstrated 11% of the global tuberculosis burden, which is approximately 1 million cases every year, with more than 200,000 deaths. The causative factors behind MDR, to at least rifampicin and isoniazid, consisted mostly of (i) resistance acquired by alteration of the bacilli, or (ii) alteration of drug target through mutation, or (iii) bacilli titration of the drug through overproduction of target. Treatment success rates for MDR/RR-TB remain at 59%, wherein a considerable gap is observed between the estimated global incidence and people initiating treatment. This rational pharmacotherapeutic situation would improve with the availability and extensive utilisation of newer drug regimens containing bedaquiline and delamanid. Several clinical trials have shown that on the inclusion of bedaquiline or delamanid, in an optimized background regimen, an excellent response to treatment and a lower risk of death occur. The disadvantages of the MDR/XDR-TB pharmacotherapeutic regimens are that these are prolonged, expensive, produce further resistance, with an augmented occurrence of adverse drug reactions, and an unsatisfactory success rate, of almost < 20% cases with resistance patterns beyond XDR, on account of the insufficient number of active drugs during both intensive and continuation phases [1-6].

Delamanid, a nitro-dihydro-imidazo-oxazole, acts as an inhibitor of bactericidal cell wall methoxy-mycolic and keto-mycolic acids biosynthesis, in actively replicating, dormant, and intracellular tuberculosis, and among both drug-susceptible and drug-resistant strains of *M. tuberculosis* and *M. kansasii.* This facilitates better bacterial drug penetration, by decreasing the hydrophobicity. Delamanid promotes intracellular generation of microbiocidal nitrogen oxidative intermediaries, including nitric oxide, which is toxic even to the dormant *M. tuberculosis* [7].

Ofloxacin, the racemic mixture, and levofloxacin, the S-or levorotatory isomer of ofloxacin, are bactericidal to *M. tuberculosis*, *Mycobacterium avium* complex, *M. fortuitum*, and other atypical mycobacteria. They act with their inhibitory effect on DNA gyrase, DNA topoisomerase IV and pro-inflammatory cytokines interleukins, like, IL-1α, IL-6, IL-8 and tumour necrosis factor α, and with their superinducing effect on IL-2. Bedaquiline, a novel diarylquinoline, inhibits mycobacterial adenosine triphosphate synthase of *M. tuberculosis.* This causes disruption of mycobacterial energy metabolism and replication. Bedaquiline is unique in its mechanism of action, being initially bacteriostatic, and subsequently bactericidal, after 5-7 days [8-13].

According to the structure activity relationship studies of quinolones as antitubercular agents, the β-keto carboxylic acid moiety is required for hydrogen bonding interactions with DNA bases, and therefore it is essential for their anti-tubercular activity. Fluorine at C-6 is the best substituent, and it improves cell penetration and gyrase affinity. Substituents at the C-7 position are very essential and attribute to the physicochemical

properties, bioavailability, lipophilicity and safety [14].

Regimens containing bedaquiline and delamanid combination have shown good culture conversion, with no additive or synergistic QTc-prolongation after 6 months of treatment. The combination of bedaquiline with delamanid are efficacious among patients with MDR-TB who had previously been exposed to fluoroquinolones. These pharmacotherapeutic results are highly beneficial for restructuring better drug-resistant anti-tubercular regimens [5].

## Objective

This pharmacovigilance study was conducted for comparative safety assessments of delamanid, ofloxacin, levofloxacin, and bedaquiline, among multi-drug resistant tuberculosis patients, in global tertiary healthcare hospitals.

## Materials and Methods

### Ethical approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. Informed consent was obtained from each patient.

### Study design

This was a global, multi-centre, prospective, randomised, open-labelled study.

### Study population

The study population consisted of 100 treated multi drug-resistant tuberculosis patients.

### Selection criteria of the study population

**The inclusion criteria were as follows:** (i) patients of any gender, (ii) patients within 18 and 55 years, (iii) patients presenting with multi drug-resistant tuberculosis with a baseline drug susceptibility testing result confirming MDR-TB (sample collected either before starting MDR-TB treatment or ≤1 month after commencement), (iv) WHO definitions, criteria and categorisations for tuberculosis, (v) co-operative and conscious patients, (vi) patients willing to undergo all pre and post- treatment investigations and willing to complete the entire course of treatment, (vii) patients who have given consent and are willing to go for a follow-up, (viii) patients not taking any previous anti-tubercular drug, (ix) patients not taking any concomitant medication.

**The exclusion criteria were as follows:** (i) uncooperative or unconscious patients, (ii) patients below 18 and above 55 years, (iii) patients presenting with any category other than multi drug-resistant tuberculosis, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high risk diseases or co-morbidities, (vi) cardiac, renal or any other associated complications or co-morbidities, (vii) any chronic disease intervening with the study data, (viii) immunocompromised patients, (ix) patients suffering from gastrointestinal diseases like peptic ulcer, regional enteritis and ulcerative colitis, (x) pregnant or lactating women (women of child bearing potential are required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of study), (xi) children or very old patients, (xii) other associated medical illness or disorders having impact on study results, (xiii) female patients using hormonal contraceptives.

### Study period

The study period, comprising of the periods for the research study and the compilation of the study literature, was 1 year 5 months, from May, 2015 to September, 2015; and from January 2021 to September, 2022.

## Place of study

The research study and the compilation of the study literature was done in the Departments of Pharmacology, Clinical Pharmacology, Pharmacovigilance, Rational Pharmacotherapeutics, Pathology, Clinical Pathology, Internal Medicine, Respiratory Medicine, Tuberculosis and Chest Diseases, and Clinical Research in global multi-centre tertiary care hospitals, like, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Dr. Moumita Hazra's World Enterprises, J. J. M. Medical College and Hospital, Bapuji Hospital, Chigateri General Hospital, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College, and Mamata Hospitals.

## Study procedure

A global, multi-centre, prospective, randomised, and open-labelled study of 100 multi-drug resistant tuberculosis patients in tertiary care hospitals, was conducted. 100 patients were randomly allotted into Group A, who were prescribed oral delamanid 100 mg twice daily, Group B, who were prescribed oral ofloxacin 400 mg twice daily, Group C, who were prescribed oral levofloxacin 750 mg once daily, and Group D, who were prescribed oral bedaquiline 400 mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks, as part of MDR-TB treatment regimens, recommended by WHO, the American Thoracic Society, U.S.

Centers for Disease Control and Prevention, European Respiratory Society, Infectious Diseases Society of America and similar associations, ratified by Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, in accordance with the followed anti multi-drug resistant tuberculosis treatment regimens and the respective tuberculosis patient category, for 24 – 48 weeks [15,16]. For 100 multi drug-resistant tuberculosis patients, thorough patients' history with complete examination details and the prescription patterns were obtained with the study proforma, and the following data were observed, thoroughly analysed and recorded: the patients' participation assessment and adherence to treatment (including patients who completed the study thoroughly), patients who were dropout patients due to adverse effects, lost to follow-up patients, and patients who withdrew voluntarily; the demographic characteristics, including age, gender, race, body mass index, duration of symptoms of tuberculosis, severity of tuberculosis symptoms, present controller medications, the patients' present and past history, smoking history, respiratory history including respiratory infection and immunological history, chronic obstructive pulmonary disease, history of MDR-TB contacts, past TB treatment history, defined as new cases (≤1 month of antituberculosis treatment), previously treated cases (first and second line anti-tuberculosis drugs), presence of cavities on chest radiograph, sputum smear microscopy results (negative, low [scanty or 1+] and high bacillary load [2+ or 3+]), and drug susceptibility testing results, cardiac history, history of co-morbidities, family history, personal history, socio-economic history, reproductive history, concomitant medication history, surgical history, the symptomatic effect of treatment on tuberculosis.

Details of complete general physical examination, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory and cardio-pulmonary examinations, were recorded. The WHO definitions of treatment outcomes requiring at least five consecutive negative culture results during the final 12 months of treatment were to be classified as cured, and either 2 positive results among the five cultures recorded in the

final 12 months, one positive in any one of the final 3 cultures, or a clinical decision, was to be considered, to continue or discontinue treatment depending on the treatment success or failure respectively. Favourable outcome was defined as a combination of cured and treatment completed, and unfavourable outcome as a combination of death and failure. Multi drug-resistance was defined as resistance to at least rifampicin and isoniazid, that had been detected at baseline. The safety assessments of these anti-tubercular drugs were made by monitoring any adverse drug reaction occurrence, like nausea, vomiting, headache, insomnia, dizziness, tinnitus, hypokalaemia, gastritis, decreased appetite, asthenia, diarrhoea, skin rash, arthralgia, constipation, ECG QT prolongation, myalgia, chest pain, or, haemoptysis, that had occurred due to the drug therapy, witnessed by the patient or the doctor, during the treatment period or during the follow-up, with Adverse Event Case Report Forms, on days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and on further follow-ups.

The safety assessments for all 4 groups of patients were done by recording and thoroughly analysing the details of the suspected drug causing adverse effects, drug dose, route of administration, drug frequency, drug starting date, drug stopping date, expiry date of the drug, batch no. of the drug, generic name of the drug, indications for the usage of the suspected drug, any concomitant medicines, description of adverse reaction : clinical and pharmacological, supporting laboratory investigation results, treatment given for the adverse drug reaction, any specific antagonistic drug given to treat the adverse reactions, and clinical outcomes.

The adverse drug reactions listed by MedDRA System Organ Class and Preferred Term were taken into consideration, along with emphasis on the adverse reactions, within each System Organ Class, under frequency categories of very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

## Statistical Analysis

These pharmacovigilance patient findings were statistically analysed, with the test of significance by p value, and subsequent tabular illustrations.

## Results

The safety assessments conducted in this research study showed that among Group A patients, 1 patient had decreased appetite, among Group B patients, 1 patient had nausea, among Group C patients, no patients had any adverse drug reaction, and among Group D patients, 1 patient had myalgia, as depicted in Table 1. The occurrence of adverse drug reactions was statistically non-significant, among all 4 groups.

Adverse effects were negligible, and tolerability was good for all 4 groups.

**Table 1: The occurrence of adverse effects with delamanid, ofloxacin, levofloxacin and bedaquiline therapy**

| Adverse drug reactions | Number of patient occurrence of adverse drug reactions after delamanid therapy | Number of patient occurrence of adverse drug reactions after ofloxacin therapy | Number of patient occurrence of adverse drug reactions after levofloxacin therapy | Number of patient occurrence of adverse drug reactions after bedaquiline therapy | p value |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Nausea | 0 | 1 | 0 | 0 | Ns |
| Vomiting | 0 | 0 | 0 | 0 | Ns |
| Headache | 0 | 0 | 0 | 0 | Ns |
| Insomnia | 0 | 0 | 0 | 0 | Ns |
| Dizziness | 0 | 0 | 0 | 0 | Ns |
| Tinnitus | 0 | 0 | 0 | 0 | Ns |
| Hypokalaemia | 0 | 0 | 0 | 0 | Ns |
| Gastritis | 0 | 0 | 0 | 0 | Ns |
| Decreased appetite | 1 | 0 | 0 | 0 | Ns |
| Asthenia | 0 | 0 | 0 | 0 | Ns |
| Diarrhoea | 0 | 0 | 0 | 0 | Ns |
| Skin rash | 0 | 0 | 0 | 0 | Ns |
| Arthralgia | 0 | 0 | 0 | 0 | Ns |
| Constipation | 0 | 0 | 0 | 0 | Ns |
| ECG QT Prolongation | 0 | 0 | 0 | 0 | Ns |
| Myalgia | 0 | 0 | 0 | 1 | Ns |
| Chest pain | 0 | 0 | 0 | 0 | Ns |
| Haemoptysis | 0 | 0 | 0 | 0 | Ns |

ns = non-significant

## Discussion

In this research study, the safety assessments among Group A patients showed that, 1 patient had decreased appetite, among Group B patients, 1 patient had nausea, among Group C patients, no patients had any adverse drug reaction, and among Group D patients, 1 patient had myalgia. The occurrence of adverse drug reactions was statistically non-significant, among all 4 groups. Adverse effects were negligible, and tolerability was good for all 4 groups.

Delamanid, an “orphan drug”, is approved for the treatment of adult pulmonary MDR-TB, which is refractory to other anti-tubercular treatment modalities, due to its resistance or tolerability [17-19]. Delamanid can be administered with rifampicin as there are no drug-metabolising interactions. Thus, delamanid is advantageous over bedaquiline, which is metabolized by CYP [7]. Delamanid is largely metabolized by albumin in serum, and to a much less extent by cytochrome P450 enzymes. The natural resistance rate to delamanid is very low (1.3%). The inhibitory concentrations of delamanid (IC50) for methoxy and keto mycolic acid biosynthesis, 0.036 mcg/mL and 0.021 mcg/mL respectively, are very less [7]. Delamanid, rarely, might cause QTcF interval prolongation, which is associated with pre-existant hypoalbuminaemia.[20] Therefore, delamanid is contraindicated in patients with albumin level of 2.8 g/dL. QTc prolongation may also be produced due to co-administration with fluoroquinolones. Thus, frequent monitoring of electrocardiograms during treatment is recommended, if delamanid is required to be co-administered with these drug classes. The other adverse effects of delamanid are nausea, vomiting, dizziness, low serum potassium levels, paraesthesia, anxiety and tremor [21].

In several studies, on administering delamanid-containing regimens, favourable responses in the treatment of highly resistant TB patients, including extensively drug

resistant (XDR)-TB, have been found. Overall, delamanid appears to be a well-tolerated and safe anti-TB drug when compared to other MDR-anti-tubercular drugs [20]. Pre-clinical and clinical studies have shown that delamanid has advantages, like, high potency, least risk for drug-drug interactions and better tolerability, and also post-antibiotic effect against intracellular bacilli, which would be helpful in reducing the treatment time and risk of toxicity in MDR-TB [21].

A phase IIb randomised controlled trial in adults with pulmonary MDR-TB, showed improved rates of sputum culture conversion at 2 months when an OBR was augmented with delamanid, as compared to placebo. An open label extension of this trial found that patients who consumed delamanid for 2-6 months were cured or completed treatment, with lower mortality, than those who took delamanid for ≤ 2 months [22]. Researchers who are investigating the properties of the nitro-dihydro-imidazooxazoles, found that delamanid had superior activity against MTB than other similar anti-tubercular agents [7]. These new drugs would improvise MDR-tuberculosis treatment, with better outcomes and quality of life, for patients [23]. Delamanid is affordable and easily available for the patients [21]. Patients likely to benefit from delamanid treatment are XDR-TB, pre-XDR-TB and MDR-TB patients [20].

Fluoroquinolones, a family of 6-fluoro-7-piperazinyl-4-quinolones, are broad spectrum synthetic antimicrobial agents derived from quinolones with the addition of a fluorine atom attached to the central ring [24]. Substitution at C-7 or its N-4-piperazinyl moiety was found to affect potency, bioavailability, and physicochemical properties [14]. The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favourable safety and tolerability profiles [25].

The dual inhibitory activity of fluoroquinolones against the bacterial replication enzymes, DNA gyrase and topoisomerase IV, protects them from the development of resistance. A mutant prevention concentration (MPC) of an antibiotic for a particular organism can be defined, at which the selection of resistant mutants during treatment is suppressed. For MTB, the MPC90 (MPC for 90% of strains) for fluoroquinolones have been found to be ciprofloxacin > levofloxacin > gatifloxacin > moxifloxacin respectively. So, gatifloxacin and moxifloxacin are less likely to provoke the development of resistance. Several studies have recommended that levofloxacin is the first-choice fluoroquinolone for MDR-TB. Ofloxacin is also effective for MDR-TB, being the racemic mixture of the S-or levorotatory isomer of ofloxacin: levofloxacin [24]. Fluoroquinolones, like ofloxacin, levofloxacin, ciprofloxacin and moxifloxacin, are relatively new potent oral bactericidal drugs for TB, that have gained prominence as well tolerated alternatives to first line anti-tubercular drugs. They are active against *Mycobacterium avium* complex, *M. fortuitum* and some other atypical mycobacteria as well. Moxifloxacin is the most active fluoroquinolone against *M. tuberculosis*, while levofloxacin is more active than ofloxacin and ciprofloxacin. On the other hand, ciprofloxacin is more active than levofloxacin against atypical mycobacteria. Fluoroquinolones are a key component of all regimens for multi drug-resistant tuberculosis, except when the bacilli are found to be resistant to them.

The revised national tuberculosis control programme of India has included ofloxacin or levofloxacin in the standardized regimen for multi drug-resistant tuberculosis. If used as a monotherapy, mycobacterial resistance to ofloxacin, levofloxacin and ciprofloxacin develops rapidly by the mutation of DNA gyrase gene. Experimental data indicates that the resistance against moxifloxacin is slow to

develop [27]. Fluoroquinolones have early bactericidal activity (EBA), which is the decline in colony-forming units in sputum over the first two days of treatment, reflecting rapid killing of metabolically active organisms, an important factor in interrupting transmission, over days 2-7.

Experimental studies have demonstrated that levofloxacin exerts antioxidative and NO regulatory effects in an animal model of H1N1 influenza virus induced lung injury, and significantly improves survival. In particular, levofloxacin exhibited scavenging actions against neutrophil-derived hydroxyl radicals and suppressed NO production, leading to decreased markers of oxidative stress and NO metabolites in the lungs of H1N1 influenza virus infected animals [24].

Ofloxacin has more potent gram-positive activity; separation of the more active S-or levo rotatory isomer yields levofloxacin, which has even better anti-microbial activity. Bioavailability of both of these drugs is excellent, such that intravenous and oral doses are the same; levofloxacin is dosed once daily as opposed to twice daily dosing for ofloxacin [28].

In documented drug resistance, therapy should be based on the evidence of susceptibility, and should include: (1) At least three drugs to which the pathogen is susceptible, (2) with at least one of the injectable anti-TB agents, (3) In the case of MDR-TB, (4) Use of four to six medications for better outcome, (5) At least 18 months of therapy [28]. WHO recommendations state that the shorter regimen for MDR-TB would improve the adherence, and its relatively economical affordability would ensure sustainability; which are extremely important in developed as well as developing countries [29]. Till now, the use of bedaquiline and delamanid was WHO approved only among children aged ≥ 6 y and ≥ 3 y with MDR TB, respectively. However, WHO now recommends the use of bedaquiline even in children below 6 y, as part of the long all-oral and short all-oral regimes, and delamanid in children below 3 y as part of long all-oral regime for treatment of MDR TB. Although these are conditional recommendation, possessing very low certainty of evidence [6].

## Conclusion

In this research study, delamanid, ofloxacin, levofloxacin and bedaquiline were found to be safe and tolerable among multi-drug resistant tuberculosis patients in global tertiary care hospitals. This pharmacovigilance research study would delineate the development of newer anti-tubercular pharmacotherapeutics, for faster, better, safer, and more precise therapeutics, in the cure of patients suffering from drug-resistant tuberculosis, and, finally in improving their respiratory health, quality of life and life span, along the global pharmacoepidemiology.

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