Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

A Quantitative Comparative Pharmacovigilance Scoring of Causality Assessment Grading and Staging of Delamanid and Ofloxacin, Among Global Multidrug-Resistant Tuberculosis Patients, and a Molecular Pharmacological Analysis of Delamanid, as an Antitubercular Drug

Moumita Hazra[1,2,3,4,5,6,7]

[1]Medical Director, Consultant Multi-Specialist Clinical Pharmacological Physician, Consultant Clinical Pathologist, Consultant Rational Pharmacotherapeutic Physician, Pharmaco-Haemo-Materio-Vigilance Specialist, Head Hospital Operations Management, Chief Executive Officer, Medical Superintendent, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, Howrah, West Bengal, India, [2]Associate Professor, Head of Department in Charge, Department of Pharmacology, Pharmaco-Haemo-Materio-Vigilance Specialist, Pharmacovigilance Committee, Mamata Medical College and Hospitals, Khammam, Telangana, India; Former Associate Professor, Head of Department in Charge, Department of Pharmacology, Rama Medical College Hospital and Research Centre, Rama University, Hardaspur, Uttar Pradesh, India, [3]Former Resident and Tutor, Departments of Pharmacology and Pathology, J. J. M. Medical College and Hospitals, Davanagere, Karnataka, India, [4]Former Academic and Research Scholar, Department of Business Administration, Sikkim Manipal University (DE); Department of Clinical Research, Symbiosis International University (DE); Departments of Zoology, Physiology and Chemistry, Presidency College, West Bengal; Former Senior Research Fellow, Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, India, [5]Former Assistant Director, Medical Editor, GIOSTAR Institute of Regenerative Medicine, Institutes, Hospitals and Laboratories, New Delhi, Ahmedabad, India, United States of America, World, [6]Former Assistant Professor, Head of Department, Department of Pharmacology, Hi-Tech Medical College and Hospital, Rourkela, Odisha, India, [7]Consultant Pathologist, Former Laboratory Director, Indus Nursing Home and Diagnostic Center, Indus Diagnostic Center and Polyclinic, Mahuya Diagnostic Centre and Doctors' Chamber, General Patho Clinic, Medilab Pathology Laboratory, India

Abstract

Introduction: Delamanid, a nitro-dihydro-imidazoxazole, is a bactericidal cell wall methoxy-mycolic and keto-mycolic acids biosynthesis inhibitor in actively replicating, dormant, and intracellular *Mycobacterium tuberculosis*, and both drug-susceptible and drug-resistant strains of *M. tuberculosis* and *Mycobacterium kansasii*, decreasing hydrophobicity, and facilitating better bacterial drug penetration. Delamanid promotes intracellular generation of microbiocidal nitrogen oxidative intermediaries including nitric oxide, toxic even to dormant *M. tuberculosis*. Ofloxacin, the racemic mixture, is bactericidal to *M. tuberculosis*, *Mycobacterium avium* complex, *Mycobacterium fortuitum*, and other atypical mycobacteria, with inhibitory effect on DNA gyrase, DNA topoisomerase IV, and IL-1α, IL-6, and IL-8.

Objectives: A quantitative comparative pharmacovigilance scoring of causality assessment grading and staging of delamanid and ofloxacin, among global multidrug-resistant (MDR) tuberculosis patients, and a molecular pharmacological analysis of delamanid, as an antitubercular drug.

Methods: A multicenter, prospective, comparative, randomized, and single-blinded study of 100 MDR tuberculosis patients and a molecular pharmacological analytical study were performed. For 24–48 weeks, Group A patients were prescribed oral delamanid 100 mg twice daily, and Group B patients were prescribed oral ofloxacin 400 mg twice daily, in accordance with the followed anti-MDR tubercular treatment regimens and the respective tuberculosis patient category. The comparative antitubercular pharmacotherapeutic occurrence of adverse effects, due to oral delamanid therapy and oral ofloxacin therapy, was thoroughly analyzed, by performing the causality assessment score estimation, deduced from the grading and staging of the adverse drug reactions, sequentially. The pharmacovigilance safety assessment was done by the monitoring of adverse drug reactions, such as nausea, vomiting, headache, insomnia, dizziness, tinnitus, hypokalemia, gastritis, decreased appetite, and asthenia,

Access this article online

www.ijss-sn.com

Month of Submission : 10-2021
Month of Peer Review : 11-2021
Month of Acceptance : 11-2021
Month of Publishing : 12-2021

Corresponding Author: Dr. Moumita Hazra, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, Jagadishpur Road, P.O. Domjur, Howrah - 711 405, West Bengal, India.

among Group A patients (delamanid therapy), and monitoring of adverse drug reactions, such as nausea, vomiting, diarrhea, pruritis, insomnia, headache, vaginitis, and dizziness, among Group B patients (ofloxacin therapy), with Adverse Event Case Report Forms, on days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 and on further follow-ups. Evaluation of the patient compliance and molecular pharmacological analysis of delamanid were also performed. The quantitative data recordings were statistically analyzed.

Results: The safety assessment showed that both in Group A and Group B patients, the occurrence of adverse effects was statistically non-significant. For both delamanid and ofloxacin, the causality grading was "No" = –1, with causality staging of "None," for all the causality assessment attributes, as there were no occurrence of any adverse effect, with delamanid or ofloxacin. The causality assessment scoring for delamanid: –12, none on average = unlikely causality of adverse drug reaction, and the causality assessment scoring for ofloxacin: –12, none on average = unlikely causality of adverse drug reaction. All the patients completed the treatment thoroughly, with no dropout patients due to adverse effects, no lost to follow-up patients, and no voluntarily withdrawn patients. The molecular pharmacological analysis of delamanid depicted its molecular efficiency in MDR antitubercular pharmacotherapeutic applications.

Conclusions: Both delamanid and ofloxacin were safe and tolerable among MDR tuberculosis patients; with nil causality association of adverse drug reactions. The patients' adherence to antitubercular treatment was very high. The molecular pharmacological analysis of delamanid depicted its molecular efficiency in MDR antitubercular pharmacotherapeutic applications.

Key words: Causality assessment grading and staging score, Delamanid, Fluoroquinolones, Molecular pharmacotherapeutics, Multidrug-resistant tuberculosis, Nitroimidazoles, Ofloxacin, Pharmacovigilance.

INTRODUCTION

The World Health Organization (WHO) estimated that over 480,000 cases of multidrug-resistant (MDR) tuberculosis occur every year globally, 9% of them being affected by extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*. MDR, to at least rifampicin and isoniazid, is mainly acquired by alteration of the bacilli or by alteration of drug target through mutation or bacilli titration of the drug through overproduction of target. The treatment of MDR/XDR TB is unfortunately long, expensive, producing further resistance, with increased occurrence of adverse events, and the success rate largely unsatisfactory (<20% among cases with resistance patterns beyond XDR), mostly due to the insufficient number of active drugs during both intensive and continuation phases.[1-4] Delamanid, a nitro-dihydro-imidazoxazole, is a bactericidal cell wall methoxy-mycolic and keto-mycolic acids biosynthesis inhibitor in actively replicating, dormant, and intracellular *M. tuberculosis*, and both drug-susceptible and drug-resistant strains of *M. tuberculosis* and *Mycobacterium kansasii*, decreasing hydrophobicity, and facilitating better bacterial drug penetration. Delamanid promotes intracellular generation of microbiocidal nitrogen oxidative intermediaries including nitric oxide, toxic even to dormant *M. tuberculosis*.[5] Ofloxacin, the racemic mixture, is bactericidal to *M. tuberculosis*, *Mycobacterium avium* complex, *Mycobacterium fortuitum*, and other atypical mycobacteria, with their inhibitory effect on DNA gyrase, DNA topoisomerase IV, and pro-inflammatory cytokines interleukins: IL-1α, IL-6, IL-8, and tumor necrosis factor α, along with their superinducing effect on IL-2.[5-11]

Objective

The objective of this quantitative comparative study was the pharmacovigilance scoring of causality assessment grading and staging of delamanid and ofloxacin, among global MDR tuberculosis patients, and a molecular pharmacological analysis of delamanid, as an antitubercular drug.

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 the 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 in compliance with the global regulatory requirements. The patients who were included in the study were assured confidentiality, and an informed consent was obtained from each patient.

Study Design

It was a global, multicenter, prospective, comparative, randomized, and single-blinded study and a molecular pharmacological analytical study.

Study Population

The study population consisted of 100 global multidrug-resistant tuberculosis patients.

Selection Criteria of the Study Population

Inclusion criteria

The following criteria were included in the study:
(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) the WHO definitions, criteria, and categorizations for tuberculosis, (v) cooperative 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 antitubercular drug, and (ix) patients not taking any concomitant medication.

Exclusion criteria

The following criteria were excluded from the study:
(i) Uncooperative or unconscious patients, (ii) patients below 18 and above 55 years, (iii) patients presenting with any category other than multidrug-resistant tuberculosis, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high-risk diseases or comorbidities, (vi) cardiac, renal, or any other associated complications or comorbidities, (vii) any chronic disease intervening with the study data, (viii) immunocompromised patients, (ix) patients suffering from gastrointestinal diseases such as 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, and (xiii) female patients using hormonal contraceptives.

Study Period

The study period, comprising the periods for the research study and the compilation of the study literature, was 2 years 1 month, from September 1998 to December 1998; December 2012 to April 2013; December 2016; and October 2020 to December 2021.

Place of Study

The research study and the compilation of the study literature were done in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Pathology, Clinical Pathology, Molecular Diagnostics, Internal Medicine, Tuberculosis, Chest Diseases and Respiratory Medicine, Cardiology, Clinical Research, in global multicenter tertiary care hospitals: Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, J. J. M. Medical College and Hospitals, Presidency College, All India Institute of Medical Sciences, and GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories.

Study Procedure

In this study, 100 global MDR tuberculosis patients were randomly allocated into Group A (delamanid therapy) = 50 patients and Group B (levofloxacin therapy) = 50 patients. The study patients were single blinded, regarding the allotted drug therapy being administered. For 24–48 weeks, Group A patients were prescribed antitubercular drug oral delamanid 100 mg twice daily, and Group B patients were prescribed antitubercular drug oral ofloxacin 400 mg twice daily, in accordance with the MDR-TB treatment regimens, recommended by the 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 methodology, and the respective tuberculosis patient category.[12,13] From the 100 multidrug-resistant tuberculosis patients, thorough patients' history with complete examination details, before and after the administration of the study drugs therapy, was obtained with the study pro forma, thoroughly analyzed and the following details were 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, 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 antituberculosis 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 comorbidities, family history, personal history, socioeconomic history, reproductive history, concomitant medication history, surgical history, and the symptomatic effect of treatment on tuberculosis. Details of complete general physical examination, including body mass index, pulse rate, respiratory rate, oxygen saturation, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory, and cardiopulmonary 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 two positive results among the five cultures recorded in the final 12 months, one positive in any one of the final three cultures, or a clinical decision, was to be considered, to continue or discontinue treatment depending on the treatment success or failure respectively. Favorable outcome was defined as a combination of cured and treatment completed, and unfavorable outcome as a combination of death and failure. Multidrug resistance was defined as resistance to at least rifampicin and isoniazid that had been detected at baseline. 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./lot no. of the drug, drug manufacturer's name, brand/generic name of the drug, indications for the usage of the suspected drug, any concomitant medicines, and 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, were recorded and thoroughly analyzed.

The comparative antitubercular pharmacotherapeutic occurrence of adverse effects, due to oral delamanid therapy and oral ofloxacin therapy, was thoroughly analyzed, with adequate consideration of causality assessment grading and staging. The causality assessment score estimation was deduced from the grading and staging of the adverse drug reactions, sequentially (Sources of Excerpts: Naranjo Algorithm – Adverse Drug Reactions Probability Scale [Table 1] and WHO – Uppsala Monitoring Centre Causality Categories [Table 2] modified and adapted, in the compilation of Causality Assessment Score Estimation Methodology, by Grading and Staging of the Causality of Adverse Drug Reactions).[14,15] The causality assessment attributes analyzed and graded were as follows: (i) History of hypersensitivity to the same drug administered; (ii) history of hypersensitivity to the same generic category of drug administered; (iii) history of adverse drug reaction-like symptoms previously; (iv) occurrence of adverse drug reaction after the suspected drug administration; (v) improvement of adverse drug effects after discontinuation of the drug, modification of drug dose, alternate drug administration, or specific antagonist administration; (vi) appearance of adverse drug effects after recontinuation of the drug, reversal to previous drug dose on patient stabilization, reversal to previous drug administration, or discontinuation of antagonist administration; (vii) alternative coexisting sources, like disease or medications, causing adverse drug effect-like reaction; (viii) false adverse drug effect mimicking reactions; (ix) appearance of adverse drug effect with a placebo; (x) detection of the suspected drug in body fluids in toxic concentrations; (xi) severity of adverse drug reactions with increase or decrease of drug dose; and (xii) occurrence of adverse drug reactions with the suspected drug in a time-variant or place-variant manner, along with the grading of "Yes" = +1, "No" = -1, and "Uncertain" = 0. The causality assessment grades were subsequently staged into none, mild, moderate, or severe stages. Then, the causality assessment scores were derived from the recorded grading and staging, as follows:

a. ≥9, severe on average = Definite causality of adverse drug reaction
b. 5–8, moderate-severe on average = Probable causality of adverse drug reaction
c. 1–4, mild-moderate on average = Possible causality of adverse drug reaction
d. ≤0, mild or none on average = Doubtful/unlikely causality of adverse drug reaction
e. ≤0–>0 variable, variable on average = Conditional/unclassified causality of adverse drug reaction
f. ≥0 variable, variable on average = Unassessable/unclassifiable causality of adverse drug reaction

Finally, the pharmacovigilance safety assessment was done by the monitoring of adverse drug reactions, such as nausea, vomiting, headache, insomnia, dizziness, tinnitus,

Table 1: Naranjo algorithm – adverse drug reaction probability scale[14]

Score	Adverse drug reaction categories	Interpretation of scores
Total score: ≥9	Definite	The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure
Total score: 5–8	Probable	The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state
Total score: 1–4	Possible	The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease
Total score: ≤0	Doubtful	The reaction was likely related to factors other than a drug

hypokalemia, gastritis, decreased appetite, and asthenia among Group A patients (delamanid therapy), and monitoring of adverse drug reactions, such as nausea, vomiting, diarrhea, pruritis, insomnia, headache, vaginitis, and dizziness, among Group B patients (ofloxacin therapy), with Adverse Event Case Report Forms, on days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 and on further follow-ups. 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–<1/10), uncommon (≥1/1000–<1/100), rare (≥1/10,000–<1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data). The analysis of different attributes of patient compliance was also performed.

The molecular pharmacological basis of the antitubercular pharmacotherapeutic drug delamanid was also thoroughly analyzed from wide ranged molecular pharmacological research, review, and case presentation study literature to illuminate on the antimycobacterial rationale of the clinical pharmacotherapeutic use of this nitroimidazole delamanid, among MDR tuberculosis patients.

Statistical Analysis

The statistical analyses were made by unpaired *t*-test, Chi-square test, one-way ANOVA test, two samples Z-test, and test of significance with p values, with subsequent tabular representations.

RESULTS

All the patients completed the treatment thoroughly. There were no dropout patients due to adverse effects, no patients were lost to follow-up and no patients voluntarily withdrew. The patients' adherence to antitubercular treatment was very high. The demographic characteristics of the patients receiving antitubercular delamanid and ofloxacin therapies were comparable. Adverse effects were negligible in either group. Thus, the safety assessment showed that both in Group A [Table 3] and Group B [Table 4] patients, the occurrence of adverse effects was statistically non-significant. Tolerability was good for both delamanid and ofloxacin, among MDR tuberculosis patients.

Table 5 depicts that for both delamanid and ofloxacin, the causality grading was "No" = –1, with causality staging of "None," for all the causality assessment attributes, as there were no occurrence of any adverse effect, with delamanid or ofloxacin. Therefore, the causality assessment scorings were as follows:

- Causality assessment scoring for delamanid: –12, none on average = unlikely causality of adverse drug reaction
- Causality assessment scoring for ofloxacin: –12, none on average = unlikely causality of adverse drug reaction.

Causality Grading

Yes = +1, no = −1, uncertain = 0.

Table 2: World Health Organization – Uppsala monitoring center causality categories[15]

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Table 3: Group A: The occurrence of adverse effects with delamanid therapy

Serial No.	Adverse effects	Number of patient occurrence	Z-value	*P*-value
1.	Nausea	0	-	Non-significant
2.	Vomiting	0	-	Non-significant
3.	Headache	0	-	Non-significant
4.	Insomnia	0	-	Non-significant
5.	Dizziness	0	-	Non-significant
6.	Tinnitus	0	-	Non-significant
7.	Hypokalemia	0	-	Non-significant
8.	Gastritis	0	-	Non-significant
9.	Decreased appetite	0	-	Non-significant
10.	Asthenia	0	-	Non-significant

Staging of Causality Grades

None, mild, moderate, and severe.

Causality Assessment Scoring

- ≥9, severe on average = Definite causality of adverse drug reaction
- 5–8, moderate-severe on average = Probable causality of adverse drug reaction
- 1–4, mild-moderate on average = Possible causality of adverse drug reaction
- ≤0, mild or none on average = Doubtful/unlikely causality of adverse drug reaction
- ≤0–>0 variable, variable on average = Conditional/unclassified causality of adverse drug reaction
- ≥0 variable, variable on average = Unassessable/unclassifiable causality of adverse drug reaction.

Table 4: Group B: The occurrence of adverse effects with ofloxacin therapy

Serial No.	Adverse effects	Number of patient occurrence	Z-value	*P*-value
1.	Nausea	0	-	Non-significant
2.	Vomiting	0	-	Non-significant
3.	Diarrhea	0	-	Non-significant
4.	Headache	0	-	Non-significant
5.	Dizziness	0	-	Non-significant
6.	Skin rash	0	-	Non-significant
7.	Arthralgia	0	-	Non-significant

The molecular pharmacological analysis of delamanid, as derived from the evidence-based medical databases, illuminated on its systematic functional synchrony in the antimycobacterial pharmacodynamic and pharmacotherapeutic response mechanisms, and established that the clinical pharmacotherapeutic applications of delamanid are very beneficial among MDR and extensively drug-resistant tuberculosis patients, mostly, because of its unique activities of facilitation of better bacterial drug penetration, owing to decreased hydrophobicity; accompanied by its promotion of intracellular generation of microbiocidal nitrogen oxidative intermediaries, which supplements its efficacy, among MDR and extensively drug-resistant tuberculosis patients.

DISCUSSION

Delamanid needs mycobacterial F420 system for its activation. This system is the analog of flavin mononucleotide complex and composed of two enzymes, deazaflavin-dependent nitroreductase (Ddn, Rv3547) and F420-dependent glucose-6-phosphate dehydrogenase (G6PD; FGD1, Rv0407), as well as four coenzymes, *Fbi*A (Rv3361), *Fbi*B (Rv3261), *Fbi*C (Rv1173), and Rv0132c. All of these genes and coenzymes are involved in the synthesis and recycling of cofactor F-420. Delamanid has undergone the influence of the Ddn enzyme for converting into its active and inactive forms, an unknown reactive intermediate metabolite that is active against

Table 5: Pharmacovigilance causality assessment grading and staging scores

Serial No.	Causality assessment attributes	Causality grading for delamanid	Causality grading for ofloxacin	Staging of causality grades for delamanid	Staging of causality grades for ofloxacin
1.	History of hypersensitivity to the same drug administered	–1	–1	None	None
2.	History of hypersensitivity to the same generic category of drug administered	–1	–1	None	None
3.	History of adverse drug reaction-like symptoms previously	–1	–1	None	None
4.	Occurrence of adverse drug reaction after the suspected drug administration	–1	–1	None	None
5.	Improvement of adverse drug effects after discontinuation of drug, modification of drug dose, alternate drug administration, or specific antagonist administration	–1	–1	None	None
6.	Appearance of adverse drug effects after recontinuation of drug, reversal to previous drug dose on patient stabilization, reversal to previous drug administration, or discontinuation of antagonist administration	–1	–1	None	None
7.	Alternative coexisting sources, such as disease or medications, causing adverse drug effect-like reaction	–1	–1	None	None
8.	False adverse drug effect mimicking reactions	–1	–1	None	None
9.	Appearance of adverse drug effect with a placebo	–1	–1	None	None
10.	Detection of the suspected drug in body fluids in toxic concentrations	–1	–1	None	None
11.	Severity of adverse drug reactions with increase or decrease of drug dose	–1	–1	None	None
12.	Occurrence of adverse drug reactions with the suspected drug in a time-variant or place-variant manner	–1	–1	None	None

M. tuberculosis and a desnitro (inactive) form, respectively. The main function of delamanid in preventing mycolic acid biosynthesis is attributed to the reactive intermediate metabolite. The removal of this major compound from *Mycobacterium* cell wall leads to the destruction of this bacterium. G6PD is also responsible for returning the F420 to the reduced form.

During dose-escalation studies, administration of higher oral doses was associated with a less than proportional increase in plasma exposure.[16]

In one study, the safety assessments were performed by the different safety tests, including the following: Monthly physical examinations, weekly assessment of vital signs, standard 12-lead ECG, clinical laboratory tests (including a hematologic profile, coagulation measurements, a urinalysis, and measurements of hepatic aminotransferase and thyroid and adrenal hormone levels), and baseline audiometry. The QT interval duration for each ECG was corrected with the use of Fridericia's formula: Corrected QT interval = QT × (1000 ÷ RR interval in milliseconds) 0.33. Use of concomitant medications was recorded daily, and adverse events were documented; immediately reportable events and clinically significant abnormal laboratory results were evaluated as appropriate. The microbiologic assessments were performed with morning sputum specimens obtained during the 8-week treatment period and during the 4-week post-treatment period on days 0.1, 1, 8, 15, 22, 29, 36, 43 50, 57, 63, 70, 77, and 84. If patients were unable to expectorate sputum, attempts were made to induce sputum expectoration with the use of aerosol inhalation. Sputum samples were deemed unobtainable if no sputum could be obtained after induction. Samples were cultured in liquid broth medium (in an automated mycobacterial growth indicator tube system) and in solid mycobacteriological culture medium (with the use of egg-based Lowenstein Jensen medium for 90% of the patients). Mycobacterial cultures were identified according to the growth and morphologic characteristics of the colony and with the use of commercial identification methods, including DNA hybridization systems, DNA amplification methods and GenoType MTBDRplus, or other standardized methods. Microbiological tests were performed in local laboratories in accordance with guidelines from the Clinical and Laboratory Standards Institute for sputum processing, smear microscopy, culture techniques, drug-susceptibility testing, and identification of mycobacteria.[17]

Delamanid's activity requires the mycobacterial deazaflavin F420-dependent G6PD, Fgd 1, and resistance to delamanid is conveyed by mutations of either F420 or Fgd 1. Delamanid is a prodrug that must be reduced by the deazaflavin-dependent nitroreductase to its desnitro metabolite to be active. Mutations of Rv3547, the gene coding for the deazaflavin-dependent nitroreductase, also convey mycobacterial resistance to delamanid. The early bacterial activity of delamanid, 400 mg daily, was modest for the first 4 days but subsequently the number of CFU in cultured sputum decreased progressively to day 14. In another pulmonary TB study in man, the number of MTB colonies declined steadily with all doses of delamanid over 14 days. Although the differences were not statistically significant, there was a trend to a greater effect with increasing daily doses between 100 mg and 300 mg.[5]

In another study, it was found that mutations in *fbi*C and *ddn* gene may be conferred to delamanid resistance on *M. tuberculosis* isolates.[18]

With the advent of quinolones, and later the fluorinated 4-quinolones, the fluoroquinolones, the medical world has certainly taken long strides in treating enormous number of diseases.

Fluoroquinolones are chemical derivatives of quinoline, the prodrome of chloroquine. 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.

Substitution at C-7 or its N-4-piperazinyl moiety was found to affect potency, bioavailability, and physicochemical properties. Furthermore, it can increase the affinity towards mammalian topoisomerases that may shift quinolones from antibacterial to anticancer candidates. Moreover, the presence of DNA topoisomerases in both eukaryotic and prokaryotic cells makes them excellent targets for chemotherapeutic intervention in antibacterial and anticancer therapies.

Fluoroquinolones are quite significantly efficacious for their bactericidal inhibitory effect on:

1. DNA gyrase caused by the binding of fluoroquinolones to the A subunits (gyr A), thus inhibiting the replication and transcription of bacterial DNA, responsible for the proper functioning of the cell, and the subsequent change of conformity of DNA gyrase molecule caused by the binding of fluoroquinolones to the DNA-binding groove between A (gyr A) and B (gyr B) subunits
2. Par C subunits (par C) and Par E subunits (par E) of DNA topoisomerase IV, thus inhibiting decatenation and relaxation of DNA and segregation of replicating chromosomes or plasmids in bacteria
3. Pro-inflammatory cytokines, such as interleukins: IL-1α, IL-6, IL-8, and tumor necrosis factor-α, leading to

attenuation of inflammatory response and exhibiting multiple immunomodulatory actions.

Fluoroquinolones also have superinducing effect on interleukin IL-2.

The first-generation quinolones (e.g., nalidixic acid) achieve minimal serum levels. The second-generation quinolones (e.g., ciprofloxacin) have increased Gram-negative and systemic activity. The third-generation quinolones (e.g., levofloxacin) have expanded activity against Gram-positive bacteria and atypical pathogens. The fourth-generation quinolones (e.g.: trovafloxacin) have significant activity against anaerobes. The fifth-generation quinolones (e.g.: aravofloxacin) have activity against multi-resistant pathogens.

They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and β-lactams.

The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration, and favorable safety and tolerability profiles.[19-24]

In this study, the safety assessment showed that both in Group A and Group B patients, the occurrence of adverse effects was statistically non-significant. For both delamanid and ofloxacin, the causality grading was "No" = –1, with causality staging of "None," for all the causality assessment attributes, as there was no occurrence of any adverse effect, with delamanid or ofloxacin. The causality assessment scoring for delamanid: –12, none on average = unlikely causality of adverse drug reaction, and the causality assessment scoring for ofloxacin: –12, none on average = unlikely causality of adverse drug reaction. All the patients completed the treatment thoroughly, with no dropout patients due to adverse effects, no lost to follow-up patients, and no patients who voluntarily withdrew. The molecular pharmacological analysis of delamanid depicted its molecular efficiency in MDR antitubercular pharmacotherapeutic applications.

CONCLUSIONS

The patients' adherence to antitubercular treatment was very high. Both delamanid and ofloxacin were safe and tolerable among MDR tuberculosis patients; with nil causality association of adverse drug reactions. The molecular pharmacological analysis of delamanid depicted its efficiency in the pharmacotherapeutic application among global MDR and extensively drug-resistant tuberculosis patients.

ACKNOWLEDGMENTS

My profound gratitude to the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Tuberculosis, Chest Diseases, Respiratory Medicine, Cardiology, Internal Medicine, Pathology, Clinical Pathology, Molecular Diagnostics, and Clinical Research, in Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, West Bengal, India, World, J. J. M. Medical College and Hospitals, Karnataka, India, GIOSTAR IORM Institutes, Hospitals and Laboratories, New Delhi, India, United States of America, World, Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India, and Mamata Medical College and Hospitals, Khammam, Telangana, India, for the successful completion of this research project.

REFERENCES

1. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, *et al*. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J 2017;49:1602308.
2. D'Ambrosio L, Centis R, Sotgiu G, Pontali E, Spanevello A, Migliori GB. New anti-tuberculosis drugs and regimens: 2015 update. ERJ Open Res 2015;1:00010.
3. Pontali E, Sotgiu G, Tiberi S, Tadolini M, Visca D, D'Ambrosio L, *et al*. Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: A systematic review. Eur Respir J 2018;52:1800934.
4. Sapkal PM, Pantwalawalkar JR. Tuberculosis drug resistance: An overview. Int J Res Methodol 2015;1:8-18.
5. Field SK. Safety and efficacy of delamanid in the treatment of multidrug-resistant tuberculosis (MDR-TB). Clin Med Insights Ther 2013;5:137-49.
6. Chang KC, Yew WW. Management of difficult multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis: Update 2012. Respirology 2013;18:8-21.
7. Tiberi S, Scardigli A, Centis R, D'Ambrosio L, Muñoz-Torrico M, Salazar-Lezama MÁ, *et al*. Classifying new anti-tuberculosis drugs: Rationale and future perspectives. Int J Infect Dis 2017;56:181-4.
8. Migliori GB, Tiberi S, Zumla A, Petersen E, Chakaya JM, Wesje C, *et al*. MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the global tuberculosis network. Int J Infect Dis 2020;92S: S15-25.
9. Gupta R, Wells CD, Hittel N, Hafkin J, Geiter LJ. Delamanid in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2016;20:S33-7.
10. Sotgiu G, D'Ambrosio L, Centis R, Mura I, Castiglia P, Spanevello A, *et al*. The multidrug-resistant tuberculosis threat: Old problems and new solutions. J Thorac Dis 2015;7:E354-60.
11. Mohammed HH, Abuo-Rahma GE, Abbas SH, Abdelhafez EM. Current trends and future directions of fluoroquinolones. Curr Med Chem 2019;26:3132-49.
12. Nahid P, Mase SR, Miglior GB, Sotgiu G, Bothamley GH, Brozek JL, *et al*. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med 2020;201:500-1.
13. World Health Organization. 2020. Global Tuberculosis Report. Geneva, Switzerland: World Health Organization; 2020. Available form: https://

www.who.int/teams/global-tuberculosis-programme/tb-reports. [Last accessed on 2021 Sep 21].
14. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
15. WHO-UMC System for Standardized Case Causality Assessment. Geneva: World Health Organisation (WHO)-Uppsala Monitoring Centre. Available from: http://www.who-umc.org/Graphics/24734.pdf [Last accessed on 2021 Nov 30].
16. Khoshnood S, Taki E, Sadeghifard N, Kaviar VH, Haddadi MH, Farshadzadeh Z, *et al*. Mechanism of action, resistance, synergism, and clinical implications of delamanid against multidrug-resistant *Mycobacterium tuberculosis*. Front Microbiol 2021;12:717045.
17. Zheng H, He W, Jiao W, Xia H, Sun L, Wang S. Molecular characterization of multidrug resistant tuberculosis against levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, and delamanid in Southwest of China. BMC Infect Dis 2021;21:330.
18. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2021;366:2151-60.
19. Hazra M. A multivariate comparative clinical pharmacotherapeutic efficacy and chronopharmacovigilance assessment study of ofloxacin, one of the commonplace TGFβ1 inducing and telomerase impairing fluoroquinolones, in treating acute gastroenteritis, chronic obstructive pulmonary disease, new drug-sensitive tuberculosis, recurrent mixed cutaneous infections, and post-surgical refractory wound infections, among the global patients, with heterogenous pharmacogeographic and pharmacogenomic constitution. Int J Basic Clin Pharmacol 2021;10:270-80.
20. Karampela I, Dalamaga M. Could respiratory fluoroquinolones, levofloxacin and moxifloxacin, prove to be beneficial as an adjunct treatment in COVID-19? Arch Med Res 2020;51:741-2.
21. Brar RK, Jyoti U, Patil RK, Patil HC. Fluoroquinolone antibiotics: An overview. Adesh Univ J Med Sci Res 2020;2:26-30.
22. World Health Organization. 2020. Differences Among Fluoroquinolones in the Treatment of MDR-TB. Geneva: World Health Organisation Archives. https://www.archives.who.int. [Last accessed on 2021 Sep 21].
23. Tripathi KD. Antitubercular Drugs. In: Tripathi M, editor. Essentials of Medical Pharmacology. 7th ed. New Delhi, London, Philadelphia, PA: Jaypee Brothers Medical Publishers Ltd.; 2013. p. 765-79.
24. Gumbo T. Chemotherapy of tuberculosis, *Mycobacterium avium* complex disease, and leprosy. In: Brunton LB, Hilal-Dandan R, Knollmann BC, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 13th ed. New York, Chicago: McGraw-Hill; 2018. p. 1067-86.

How to cite this article: Hazra M. A Quantitative Comparative Pharmacovigilance Scoring of Causality Assessment Grading and Staging of Delamanid and Ofloxacin, Among Global Multidrug-Resistant Tuberculosis Patients, and a Molecular Pharmacological Analysis of Delamanid, as an Antitubercular Drug. Int J Sci Stud 2021;9(9):80-88.

Source of Support: Nil, **Conflicts of Interest:** None declared.