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Research Article

A PHARMACOVIGILANCE SAFETY ASSESSMENT AND PRESCRIPTION PATTERNS ANALYSIS OF DELAMANID AMONG GLOBAL TERTIARY CARE MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS: A STUDY, IN RATIONAL PHARMACOTHERAPEUTICAPPRAISAL

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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 *M.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*.

Objectives: The objective of this rational pharmacotherapeutic appraisal study was the pharmacovigilance safety assessment and prescription patterns analysis of delamanid among global tertiary care multi-drug resistant tuberculosis patients.

Methods: A multi-centre, prospective, open-labelled study of 100 multi-drug resistant tuberculosis patients, was performed. For 24 – 48 weeks, the patients were prescribed oral delamanid 100 mg twice daily, in accordance with the followed anti multi-drug resistant tubercular treatment regimens and the respective tuberculosis patient category. The anti-tubercular pharmacotherapeutic occurrence of adverse effects, due to oral delamanid therapy, was thoroughly analysed. The pharmacovigilance safety assessment was done by the monitoring of adverse drug reactions, like nausea, vomiting, headache, insomnia, dizziness, tinnitus, hypokalaemia, gastritis, decreased appetite and asthenia, among the patients, 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. A thorough evaluation of the prescription contents of all the patients was also done.

Results: The safety assessment showed that the occurrence of adverse effects was statistically non-significant. The completeness of prescription contents was observed in 100% of prescriptions.

Conclusions: Delamanid was safe and tolerable among multi-drug resistant tuberculosis patients. Prescription content analysis showed 100% completeness.

INTRODUCTION

The treatment of multi-drug resistant or extensive drug-resistant tuberculosis 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 extensive drug reistance), mostly due to the insufficient number of active

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drugs during both intensive and continuation phases. 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 *M. 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.*[1, 2, 3, 4,5, 6, 7, 8, 9, 10, 11.]

Objective

The objective of this rational pharmacotherapeutic appraisal study was the pharmacovigilance safety assessment and prescription patterns analysis of delamanid among global tertiary care multi-drug resistant tuberculosis patients.

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

Study Design

The study was global, multi-centre, prospective, and open-labelled; and also an analytical study.

Study Population

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

Selection Criteria of the study population

Inclusion Criteria

(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) World Health Organisation (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.

Exclusion Criteria

(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 1.5 years, from June, 2015 to December, 2015; and January, 2021 to February, 2022.

Place of Study

The research study and the compilation of the study literature was 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 multi-centre 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, All India Institute of Medical Sciences, and GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories.

Study Procedure

In this study, 100 global multi-drug resistant tuberculosis patients were prescribed anti-tubercular drug oral delamanid 100 mg twice daily, for 24 - 48 weeks,in accordance with the 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, and the respective tuberculosis patient category.[12, 13] From the 100 multi drug-resistant tuberculosis patients, thorough patients' history with complete examination details, before and after the administration of the study drugs therapy, were obtained with the study proforma, and thoroughly analysed; 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 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, including body mass index, pulse rate, respiratory rate, oxygen saturation, 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 three 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 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, 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, clinical outcomes, were recorded and thoroughly analysed.

The anti-tubercular pharmacotherapeutic occurrence of adverse effects, due to oral delamanid therapy was evaluated by the pharmacovigilance safety assessment including monitoring of adverse drug reactions, like nausea, vomiting, headache, insomnia, dizziness, tinnitus, hypokalaemia, gastritis, decreased appetite and asthenia among the patients, 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 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). The analysis of different attributes of patient compliance was also performed.

The prescription content analysis was conducted by analyzing the different aspects of the prescription contents, like (i) the completeness of the prescription contents, (ii) the dose of drug, (iii) the duration of treatment, (iv) the instructions of medication, (v) the frequency of drug intake, (vi) the name of the drug and (vii) the dosage form of the drug were thoroughly analysed and recorded, and the various observations were statistically recorded as the prescription content analysis percentages.

Statistical analysis

The statistical analyses were made by test of significance with p values, and with percentages and 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 anti-tubercular treatment was very high. The demographic characteristics of the patients receiving anti-tubercular delamanid and ofloxacin therapies, were comparable.

The adverse drug reactions were negligible with delamanid treatment. Thus, the safety assessment showed that the occurrence of adverse effects was statistically non-significant, as depicted in Table 1. Tolerability was good for delamanid, among multi-drug resistant tuberculosis patients.

Table 1 the Occurrence of Adverse Drug Reactions With Delamanid Therapy

Serial No.	Adverse drug reactions of delamanid therapy	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.	Hypokalaemia	0	-	Non-significant
8.	Gastritis	0	-	Non-significant
9.	Decreased appetite	0	-	Non-significant
10.	Asthenia	0	-	Non-significant

The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions, as depicted in Table 2.

Table 2 Prescription Content Analysis For Different Anti-Tubercular Drugs

Prescription Contents	Results (%)
Completeness of prescription contents	100 (100%)
Dose of drug	100 (100%)
Duration of treatment	100 (100%)
Instructions of medication	100 (100%)
Frequency of drug intake	100 (100%)
Name of the drug	100 (100%)
Dosage form of the drug	100 (100%)

DISCUSSION

Delamanid needsmycobacterial F420 system for its activation. This system is the analog of flavin mononucleotide complex and composed of two enzymes, deazaflavin-dependentnitroreductase (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 theDdn enzyme for converting into its active and inactive forms, anunknown reactive intermediate metabolite that is active against *Mycobacterium tuberculosis* and a desnitro (inactive) form, respectively. The mainfunction of delamanid in preventing mycolic acid biosynthesis is attributed to the reactive intermediate metabolite. The removal of this major compound from the *Mycobacterium* cell wall leads to the destruction of this bacterium. G6PD is also responsible for returning the F420 to the reduced form. Duringdose-escalation

studies, administration of higher oral doses was associated with a less than proportional increase in plasmaexposure.[14]

Delamanid's activity requires the mycobacterial deazaflavin F420-dependent glucose-6-phosphate dehydrogenase (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 des-nitro 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 (EBA) 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.[6]

In another study, it was found that mutations in *fbi*C and *ddn*gene may be conferred to delamanid resistance on *M. tuberculosis* isolates.[15] In this study, the safety assessment showed that the occurrence of adverse effects among the patients, were statistically non-significant. The completeness of prescription contents was observed in 100% of prescriptions. The molecular pharmacological analysis of delamanid depicted its molecular efficiency in multi-drug resistant anti-tubercular pharmacotherapeutic applications.[16, 17]

CONCLUSIONS

Delamanid were safe and tolerable among multi-drug resistant tuberculosis patients. Prescription content analysis showed 100% completeness.

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