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Original Research Article

A Rational Pharmacotherapeutic Research Study on the Prescription Patterns of Anti-Tubercular Drugs Monotherapy or Combination Therapies in Multi Drug-Resistant Tuberculosis Patients at Tertiary Patientcare Hospitals

Moumita Hazra

Associate Professor, Head of Department In Charge, Department of Pharmacology, Mamata Medical College and Hospitals, Telangana, India

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Corresponding author: Dr. Moumita Hazra
Conflict of interest: Nil

Abstract

Background: This rational pharmacotherapeutic appraisal study was conducted to assess the maintenance of the various aspects of rational pharmacotherapeutics, including appropriateness, efficacy, safety, availability, and ease of administration in prescribing different anti-tubercular drugs, like ofloxacin, delamanid or bedaquiline, which reflected upon the prescription percentages of these drugs, thus delineating the choice of drugs, treatment regimens and the routine prescription patterns of anti-tubercular monotherapy or combination therapies, among multi-drug resistant tuberculosis patients, in multi-centre tertiary patientcare hospitals.

Aim and Objectives: This rational pharmacotherapeutic research study was conducted to interprete the prescription patterns of anti-tubercular drugs monotherapy or combination therapies, among multi drug-resistant tuberculosis patients at tertiary patientcare hospitals.

Materials and Methods: From the clinical prescriptions of 102 multi drug-resistant patients, thorough patients' history with complete examination details and the prescription patterns were obtained with the study proforma, and the study data were observed, thoroughly analysed and recorded. For 24-48 weeks, these patients had been prescribed anti-tubercular drugs, like delamanid 100 mg twice daily, ofloxacin 400 mg twice daily, and bedaquiline 400 mg four times daily followed by 200 mg thrice weekly, as part of MDR-TB treatment regimens. The number of prescriptions for each drug were recorded, and the corresponding prescription rates were statistically derived in percentages.

Results: The prescription frequency of delamanid was followed by ofloxacin and bedaquiline.

Conclusion: Delamanid was more commonly prescribed anti-tubercular drug, followed by ofloxacin, which was less commonly prescribed, and finally followed by bedaquiline, which was the least prescribed anti-tubercular drug.

Keywords: Rational Pharmacotherapeutics, Prescription Patterns, Anti-Tubercular Drugs, Ofloxacin, Delamanid, Bedaquiline, Monotherapy, Combination Therapies, Multi-Drug Resistant Tuberculosis.

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Introduction

World Health Organisation 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.

Delamanid, a nitro-dihydro-imidazooxazole, is a bactericidal cell wall methoxy-mycolic and keto-mycolic acids biosynthesis inhibitor in actively replicating, dormant, and intracellular 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*.

Ofloxacin is bactericidal to *M. tuberculosis*, MAC, *M. fortuitum*, and other atypical mycobacteria, with inhibitory effect on DNA gyrase, DNA topoisomerase IV and IL-1α, IL-6, IL-8. Bedaquiline, a novel diarylquinoline, inhibits mycobacterial adenosine triphosphate synthase of *M. tuberculosis*, disrupting mycobacterial energy metabolism and replication. Bedaquiline's initial bacteriostatic action is followed by a bactericidal effect after 5-7 days[1-11]

Objectives:

The objective of this rational pharmacotherapeutic research study was to interprete the prescription patterns of anti-tubercular drugs monotherapy or combination therapies, among multi drug-resistant tuberculosis patients at tertiary patientcare hospitals.

Methodology:

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. Written permissions to access the relevant medical records were obtained from the hospitals, outlining the aims of the study. The study involved almost negligible risk, of any type, to the patients. The design provided an equal opportunity to all the eligible patients to be included in the study. The patients who were included in the study were assured confidentiality, and an informed consent was obtained from each individual.

Selection Criteria of the patients:

Inclusion Criteria:

The inclusion criteria are 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) World Health Organisation 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:

The Exclusion Criteria of the patients are 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 Design:

A multi-centre, retrospective, observational and analytical study of the clinical prescriptions was performed.

Study Population:

The study population consisted of 102 treated multi drug-resistant tuberculosis patients.

Study Period:

The study period was 1 year, that is from September, 2014 to December, 2014, and from July, 2021 to February, 2022.

Place of Study:

The place of study, comprising of this research study and the compilation of the study literature, was the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, and Tuberculosis, Chest Diseases and Respiratory Medicine, in global multi-centre tertiary patientcare hospitals.

Study Procedure:

From the clinical prescriptions of 102 multi drug-resistant 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 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 World Health Organisation's definitions of treatment outcomes requiring at least five consecutive negative culture results during the final 12 months of treatment to be classified as cured, and either 72 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 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.

For 24-48 weeks, these patients had been prescribed anti-tubercular drugs, like delamanid 100 mg twice daily, ofloxacin 400 mg twice daily, and bedaquiline 400 mg four times daily followed by 200 mg thrice weekly, 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[12].

The number of prescriptions for each drug were recorded, and the corresponding prescription rates were statistically derived in percentages.

The prescription patterns of all 3 drugs were analysed. The number of prescriptions of 102 patients treated with each drug: delamanid, ofloxacin and bedaquiline was recorded, and the percentage of prescriptions for each drug was calculated. The prescription content analysis, of all the 102 prescriptions, was also done.

Statistical Analysis:

The study data were statistically analysed with different percentages.

Results:

102 patients were treated for multi-drug tuberculosis. All the patients completed the treatment thoroughly. There were no dropout patients due to adverse effects, none was lost to follow-up and none of the patients withdrew voluntarily. The patients' adherence to treatment was very high. The demographic characteristics for delamanid, ofloxacin or bedaquiline were comparable.

Among the anti-tubercular drugs prescribed in 102 prescriptions under study, delamanid was most commonly prescribed significantly (47 prescriptions, 46.08%), followed by ofloxacin (29 prescriptions, 28.43%), bedaquiline (26 prescriptions, 25.49%); (delamanid > ofloxacin > bedaquiline), as depicted in Table 1 and Figure 1.

Table 1: The Patterns of Prescription Frequencies of Different Anti-Tubercular Drugs

Anti-Tubercular Drugs	Number of Prescriptions	Prescription Percentages
Delamanid	**47**	**46.08%**
Ofloxacin	**29**	**28.43%**
Bedaquiline	**26**	**25.49%**

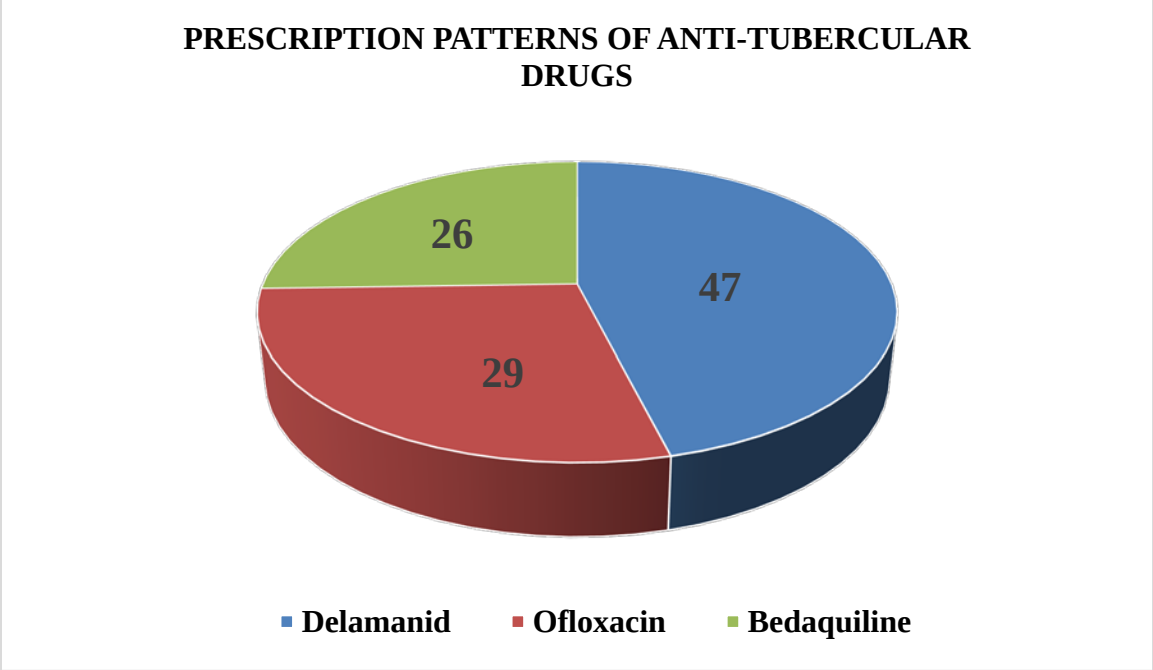

Figure 1: Prescription Frequencies of Different Anti-Tubercular Drugs

Discussion:

In this study, 102 patients were treated for multi-drug tuberculosis. All the patients completed the treatment thoroughly. There were no dropout patients due to adverse effects, none was lost to follow-up and none of the patients withdrew voluntarily. The patients' adherence to treatment was very high. The demographic characteristics for delamanid, ofloxacin or bedaquiline were comparable.

Among the anti-tubercular drugs prescribed in 102 prescriptions under study, delamanid was most commonly prescribed significantly (47 prescriptions, 46.08%), followed by ofloxacin (29 prescriptions, 28.43%), bedaquiline (26 prescriptions, 25.49%); (delamanid > ofloxacin > bedaquiline).

This rational pharmacotherapeutic appraisal study was conducted to assess the maintenance of the various aspects of rational pharmacotherapeutics, including appropriateness, efficacy, safety, availability, and ease of administration in prescribing different anti-tubercular drugs, like ofloxacin, delamanid or bedaquiline, which reflected upon the prescription percentages of these drugs, thus delineating the choice of drugs, treatment regimens and the routine prescription patterns of anti-tubercular monotherapy or combination therapies, among multi-drug resistant tuberculosis patients, in multi-centre tertiary patientcare hospitals.

Many phase II clinical trials had been performed with delpazolid, SQ-109, sutezolid, linezolid, and nitazoxanide, for drug-sensitive anti-tubercular treatment. Phase II and III clinical trials had been done with high dose rifampicin, for the treatment of drug-sensitive tuberculosis. Rifapentine is also studied for the treatment of drug-sensitive tuberculosis. A phase II trial with bedaquiline, as a combination therapy with existing and re-purposed anti-TB drugs, was conducted for analysing multi-drug resistant tuberculosis. Another phase II trial was done with the combination therapy of delamanid, linezolid, levofloxacin and pyrazinamide to analyse the pharmacotherapeutic effects in quinolone-sensitive multi-drug resistant tuberculosis. In yet another phase II clinical trial, the pharmacotherapeutics of levofloxacin with

optimised background regimen, were analysed for multi-drug resistant tuberculosis.

Several phase III clinical trials had been conducted with anti-tubercular pharmacotherapeutic drugs, like bedaquiline, delamanid, clofazimine, in the treatment of drug-sensitive tuberculosis. A phase III clinical trial has been done with a combination therapy regimen of bedaquiline, linezolid and other anti-tubercular drugs.

In a phase III clinical trial, involving two optimised background anti-tubercular regimens of bedaquiline, that is, 09 months for oral treatment and 06 months for injection treatment, had also been conducted. One phase III clinical trial was performed with the combination therapy of bedaquiline, linezolid and levofloxacin with optimised background regimen for the treatment of multi-drug resistant tuberculosis. Bedaquiline and delamanid with various existing regimens were studied for the treatment of both multi-drug resistant and extensively drug-resistant tuberculosis. The combination pharmacotherapeutic regimen of moxifloxacin, pyrazinamide and other anti-tubercular drugs were also studied in a phase III clinical trial. A tuberculosis trial consortium study was also performed to study the combination therapy of rifapentin and moxifloxacin, in drug-sensitive anti-tubercular therapy[1-12].

Conclusion:

The prescription frequency of delamanid was followed by ofloxacin and bedaquiline. Therefore, it is being concluded that delamanid was more commonly prescribed anti-tubercular drug, followed by ofloxacin, which was less commonly prescribed, and finally followed by bedaquiline, which was the least prescribed anti-tubercular drug.

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Declarations:

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