Journal of Innovations in Applied Pharmaceutical Science
(JIAPS)

Content available at: www.saap.org.in ISSN: 2455-5177

Pharmacovigilance among patients with multi drug resistance tuberculosis (MDR-TB) treatment-a prospective study

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Article History

Received: 18-02-2022
Revised: 28-02-2022
Accepted: 25-03-2022

Keywords: ADRs; Causality and severity, DOTS therapy; Drug resistance; MDR-TB.

Abstract

Background: ADRs are frequent in patients of MDR-TB on DOTs-Plus drug regimen. Current study was carried out in tertiary care hospital. Recognition of types and frequency of adverse drug reactions in Intensive and continuation phase of MDR- TB Patients.

Methods: It was a prospective observational study conducted in Damien Foundation Urban Leprosy & TB Centre, Nellore. All the MDR-TB patients admitted at the directly observed treatment, short course plus (DOTS plus) Center were enrolled and were monitored for ADRs. The causality and severity of the reactions were determined using Naranjo algorithm.

Results: A total of 200 tuberculosis patients of MDR-TB on DOTS therapy were enrolled for the study. Out of 200 patients, 10 were dropouts, 10 defaulted so 190 patients assessed for ADRs, 129 patients developed 109 (56.48%) adverse drug reactions. The higher numbers of ADRs were observed in age group 31- 40yrs followed by 21-30yrs which were more common in men. Majority of adverse drug reactions were Gastrointestinal (GI) problems 48 (37.20%), followed by Ototoxicity 7 (5.42%) and Psychiatric Manifestations 3 (2.321 %) and skin problems 3 (2.32%). On evaluation of the causality of ADRs, majority were found to be Possible (57.95%). The severity assessment showed that most of the patients ADRs were of moderate level (42.04%).

Conclusions: ADRs are major factor limiting completion of drug therapy under RNTCP and occurrence of drug resistance which requires attention of all health care professionals.

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https://doi.org/10.37022/jiaps.v7i1.306

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Introduction

Tuberculosis (TB) is an infectious disease (potentially fatal contagious) usually caused by Mycobacterium tuberculosis (MTB) bacteria. Tuberculosis generally affects the lungs, but can also affect other parts of the body [1].

Tuberculosis (TB) is an ancient disease that has affected mankind for more than 4,000 years. It is a chronic disease caused by the bacillus *Mycobacterium tuberculosis* and spreads from person to person through air [2]. TB usually affects the lungs but it can also affect other parts of the body, such as respiratory system, the gastrointestinal (GI) system, the lymphoreticular system, the skin, the central nervous system, the musculoskeletal system, the reproductive system, and the liver brain, intestines, kidneys, or the spine. Symptoms of TB depend on the body the TB bacteria are growing. In the cases of pulmonary TB, it may cause symptoms, such as chronic cough, pain in the chest, haemoptysis, weakness or fatigue, weight loss, fever, and night-sweats.

Classification based on drug resistance:

- Mono-resistant (MR): A TB patient, whose biological specimen is resistant to one first line anti-TB drug only.

• Poly-Drug Resistant (PDR): A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both INH and Rifampicin.

• Multi Drug Resistant (MDR): A TB patient, whose biological specimen is resistant to both isoniazid and rifampicin with or without resistance to other first line drugs, based on the results from a quality assured laboratory.

• Rifampicin Resistant (RR): resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs excluding INH. Patients, who have any Rifampicin resistance, should also be managed as if they are an MDR TB case.

Prevention of TB involves screening those at high risk, early detection and treatment of cases , and vaccination with the Bacillus Calmette-Guerin (BCG) vaccine [4].Those at high risk include household , workplace , and social contacts of people with active TB [5]. Treatment requires the use of multiple antibiotics over a long period of time Antibiotic resistance is a growing problem with increasing rates of multiple drug resistance tuberculosis (MDR-TB) [6].

Evidence of TB has been reported in human remains dated thousands of years (Hershkovitz et al., 2017, K Zaman 2010). For a human pathogen with no known environmental reservoir, Mycobacterium tuberculosis has honed the art of survival and has persisted in human communities from antiquity through modern time. In the past few decades, there has been a concerted global effort to eradicate TB. These efforts had yielded some positive dividends especially since 2000 when the World Health Organization (WHO, 2017) estimated that that global incidence rate for tuberculosis has fallen by 1.5% every year. Furthermore, mortality arising from tuberculosis has significantly and steadily declined. The World Health Organization (WHO, 2016) reports a 22% drop in global TB mortality from 2000 through 2015.

AIM AND OBJECTIVES

Adverse drug reaction monitoring in patients of MDR at TB centre.

- Identification of types and frequency of adverse drug reactions in Intensive and continuation phase.
- To evaluate the incidence of treatment discontinuation in relation to ADRs.
- To assess casualty and severity of the reported adverse drug reactions.

Ethodology

Present study was carried out at Drug Resistance Tuberculosis at TB Research Centre, Nellore, and A.P.

It was a prospective, observational study.

Inclusion criteria

- Patient of either sex of age more than 18 years – 50 years with tuberculosis.
- Diagnosed cases of MDR- TB, enrolled under NTEP (RNTCP) program.
- Agreed to adhere tuberculosis treatment regimen prescribed.
- Patient who provide written informed consent and ready to give follow up

Exclusion criteria

- History of Patients receiving ART Treatment
- Patients with deranged Liver and Kidney function tests.
- • History of patient suffering from any other chronic disease condition requiring any concomitant medication.
- Not ready to give informed consent.
- Not ready to give follow up.

Procedure

Patients for this study were included from all patients diagnosed to have MDR-TB (Isoniazid and Rifampicin resistance) and rifampicin resistance by DST (Drug susceptibility test) and admitted in Drug Resistance Tuberculosis at TB Research Centre, Nellore.

Results

Table 1: Demographic profile of patents.

Parameters		Number	Percentage (%)
Gender	Male	132	67.85
	Female	68	32.14
Age group (in years)	<20	20	17.14
	21-30	25	21.42
	31-40	95	41.07
	41-50	60	20.35
Weight (Kg)	16-29	00	00
	26-45	35	26.78
	46-70	138	57.85
	>70	27	15.35

A total number of n=200 patients who were on DOTS plus therapy were included in this study around 132 (66.00%) were male and 68 (34.00%) were female. Patients of different age group ranging from 18-50 years were reported in the study. 20 patients were under 20 years of age (10.00%), 21-30 of 25 patients (12.50%)., followed by 95 resides in the age of 31-40 (47.50%), Rest were in41- 50 years age group (30.00%) (Table 1).

Table 2: Incidence of Adverse Drug reactions.

Type of ADR	No. of patients	Percentage (%)
Gastrointestinal	48	37.20
Nausea, vomiting	26	20.15
Anorexia	02	1.55
Epigastric discomfort	05	3.87
Change of taste	04	3.10
Diarrhea	04	3.10
Hepatitis	03	2.32
Psychiatric Manifestations	03	2.32
Ototoxicity	07	5.42
Tinnitus +Vertigo	02	1.55
Insomina+Suicidal Tendencies	03	2.32
Depression	02	1.55
Altered behavior	01	0.77
Peripheral neuropathy	02	1.55
Vision defect Impaired visual acuity	02	1.55
Pruritus with rash	02	1.55
Pruritus without rash	01	0.77
Injection site pain and swelling	07	5.42
Renal dysfunction Deranged RFT	02	1.55
Musculoskeletal Arthralgia	03	2.32
Total	129	100

Out of these 200 patients 129 patients developed ADRs of various types (Table 2). Among this ADRs, most were observed in males (132/66.00%) and remaining (68/34.00%) were females. The overall incidence of ADRs was 64.50%. ADRs in this study were categorized according to the systems affected like gastrointestinal system, ototoxicity, psychiatric manifestations and other systems like skin, vestibular, musculoskeletal etc. Majority of ADRs were related to gastrointestinal system (48 cases/37.20%) followed by ototoxicity (7cases/5.42%), Psychiatric Manifestations (03 Cases/2.32%), other systems (35 cases). Nausea and Vomiting was the most common ADR (26/20.15%) followed by Inj. site pain swelling (07/5.42%).

Out of the 200 drug resistance tuberculosis patients, patients were divided in the different weight bands according to it 35 (26.78%) patients in weight band 26- 45kg followed by 138 (58.66%) patients in weight band above 70kg followed by 27 (9.33%) patients in weight band 26-45kg . Drug resistance pattern in out of 200 patients, 95 (47.50%) patients showing rifampicin mono-resistance while 105 (52.50%) patients showing Isoniazid and Rifampicin Resistance.

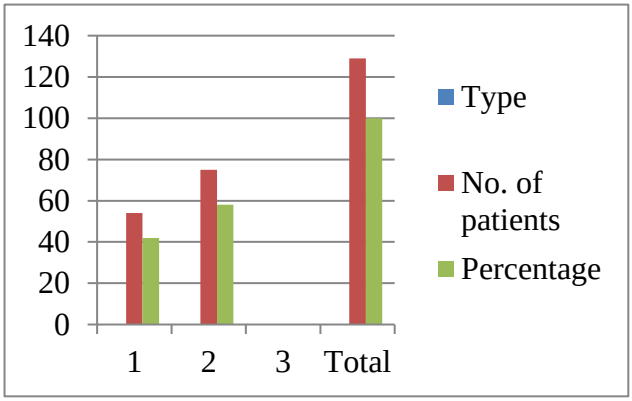
The main action taken in patients with detected ADR was Withhold and Replacement of drug seen. The action mainly was taken when patients with psychiatric ADRs required withdrawal of cycloserine which was replaced with PAS. One patients required pyrazinamide withdrawal for peripheral neuropathy. While Kanamycin was replaced with PAS in patients suffers from ototoxicity.

Table 3: Causality of ADRs induced by anti TB drugs according to Naranjo algorithm.

Sr. no	Type	No. of patients	Percentage
1	Probable	54	41.86
2	Possible	75	58.13
3	Certain	00	00
Total		129	100

Discussion

The present observational study has evaluated a DOTS- Plus program, with special reference to Adverse Drug effects in



which standard treatment of drug resistant tuberculosis cases as per RNTCP guidelines has been started in this DR-TB Centre. In the present study of 200 patients, the age group ranged from 20 to 50 years. Maximum number of cases was in the age group 31-40yrs (41.07%) followed by 21-30yrs (21.42%). The median age of the patients in present study was 31.78 years, as compared to the reports in which the median age was 28 years.6 and in another study it was reported as 26 years respectively. In the present study, majority of the patients were males 132 (66.00%) and Females 68 (34.00%). similar observations were noted by authors in a study (males 66.00% and females 34.00%).and proportion of males to females was 54.54% and 45.46% respectively. Weight band: Of the 129 drug resistance tuberculosis patients in this study, majority of patients were in the weight band of 26 to 70 Kg (84.63%). Whereas, a study observed that majority patients were above 40 Kg. Majority of the drug resistance tuberculosis patients were underweight before the start of treatment. In Present study, rifampicin mono resistance was found in 52.78%, while both isoniazid and rifampicin resistance were found in 47.22% patients. Initially, when our DR-TB center started only solid cultures were available in the program due to which both rifampicin and isoniazid resistance was reported together. As line probe assay became available, rifampicin mono resistance cases started getting picked up.

In this study ADRs were observed in 58.66% patients, a finding comparable to present study reports notified in different studie. The ADR reported in present study were, Gastrointestinal, Ototoxicity, Psychiatric manifestations, Injection site swelling/pain, Arthralgia, Skin, Renal Involvement, Vision defect, peripheral neuropathy.

Gastro intestinal symptoms were most common adverse reaction observed in this study that is 48(37.20%) similar to other studies. on the contrary other studies have found observed gastrointestinal ADRs in 42%, 60% and 100% patients respectively. Hepatotoxicity was noted in 3(2.32%) patients only. Similarly finding were reported other authors. They were mild but required immediate treatment. These gastrointestinal symptoms occurred mostly within a week of starting treatment. No patient required alteration in DOTS-Plus treatment due to gastrointestinal ADRs. Ototoxicity 7 (5.42%) was second most common ADR observed in this study of which decreased hearing 5 and tinnitus and vertigo in 2 patients These findings were similar to observations in a study which reported ototoxicity as second most common ADR after gastrointestinal ADR and frequency of ototoxicity. Whereas another study reported ototoxicity in 5.42% patients.14 Kanamycin was withdrawn in 80% of

These patients and substituted with PAS (p- amino salicylic acid). Psychiatric 3 (2.32%) manifestations were the third most common adverse reaction in this study of which insomnia was the most common followed by suicidal tendency, depression and altered behavior in descending order. Psychiatric ADRs were less common in this study as compared to 15.9%.7 and 15%.15 in other studies. All patients with psychiatric manifestation required withdrawal of cycloserine which was replaced with PAS (P-amino salicylic acid).

Injection site swelling/pain 7 (5.42%) was fourth common ADR observed in this study. In contrast, it was reported in a study that injection site swelling/pain seen in 21.05% patients.None of the patients required withdrawal of injection Kanamycin. Arthralgia 3 (2.32%) was fifth common ADR observed in this study. Similar observation was seen in 4.5% and 7.94% respectively.9,11 In contrast, it was observed in the studies that arthralgia was seen in 31% and 23.68% patients.[8,14] Skin Adverse drug reactions ADR observed in this study was 3 (2.32%) of which pruritus without rash in 1 and pruritus with rash in 2 patient. Frequency of skin reaction found in this study is similar 4%, 1.58% and 4.5%.On the one of the study reported cutaneous reactions in 43.3% patients.

Renal involvement was seen 2(1.55%) patients in this study which is similar to observation noted in different other studies 1.58%, 2.7% and 2% respectively.9,11,12 Renal involvements were seen in the form of borderline derangement of serum creatinine (2mg%) which improved in few weeks and none required withdrawal of injection kanamycin. Other ADR including Visual defect in 2 (1.55%), Peripheral Neuropathy 2(1.55%). similar findings seen in a study with frequency of visual disturbance 1(0.9%) and peripheral neuropathy 3 (2.7%).

In present study Causality assessment of 129 ADRs was done by Naranjo's Causality Scale, out of 129 ADRs,75(58.13%)into possible category and 54(41.86%) fall into Probable category. None of categorized into 'Certain' category. The severity of ADRs in the present study was assessed by Modified Hartwig and sigel scale. The distribution of 88 ADRs as Mild 43.18%, moderate 54.54% and sever 2.27%, as the study population the patients was hospitalized for ADRs, higher number of ADRs belonged to "Moderate "grade.

Conclusion

Drugs for treating MDR-TB strains involve a long-term exposure and have greater toxicity effects. A high frequency of adverse drug reactions is one of the major challenges in the treatment of MDR-TB Pharmacovigilance now become important component of drug treatment, Drug therapy and active Pharmacovigilance goes hand in hand. The present

Study evaluated pattern and frequency of adverse drug reactions in patients receiving treatment for Multi-drug resistant tuberculosis and assessed their severity and causality. A majority of ADRs is possible in causality

assessment and more of them are seems to be treatable and preventable.

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