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Research Article

A RETROSPECTIVE STUDY OF ADVERSE DRUG REACTION IN MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS AT TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The objective of the study was to the analysis of different parameters including admission type, demographics, type of reaction, the seriousness of reaction, classification of organ system, drugs involved, action taken and outcome of reactions, causality assessment, severity assessment, and the preventability of ADRs for multidrug-resistant tuberculosis patients.

Methods: This retrospective observational study was conducted during the period of September 2017 to June 2020 (34 months) at ADR Monitoring Centre, Department of Pharmacology, Jawaharlal Nehru Medical College, Ajmer, Rajasthan. All spontaneously reported ADRs were evaluated using various parameters such as type of reaction, causality assessment, preventability, and severity.

Results: In the present study, 92 (9.29%) ADRs were reported in relation to 68 MDR-TB patients. The majority of ADRs were considered probable (73.92%), moderate (41.30%), and definitely preventable (42.39%) in nature. In our study, most of the suspected drug names were included: 23 (25%) pyrazinamide, followed by 22 (23.91%) kanamycin, 12 (13.04%) cycloserine, and 11 (11.96%) linezolid. The majority of ADRs were non-serious (67.39%) in nature. ADRs were most commonly reported, with 17 (18.48%) reporting ototoxicity and 17 (18.48%) reporting joint pain, followed by 4 (4.35%) reporting burning feet syndrome, 4 (4.35%) reporting generalized itching, and 4 (4.35%) reporting psychosis.

Conclusion: Our study included 36 different types of suspected ADRs that were reported with multiple frequencies due to 16 categories of drugs and combinations of drugs. The majority of patients were recovering and recovered from concerns associated with ADR after necessary medical intervention and management. Our purpose is to rationale the use of medicines for drug safety as well as patient safety.

Keywords: Multidrug-resistant tuberculosis, Adverse drug reaction, National TB elimination program, Rifampicin resistant.

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INTRODUCTION

In the year 1993, the WHO declared tuberculosis (TB) a global emergency. In the same period, a statement was released by the Director General (Dr. Hiroshi Nakajimo) of the World Health Organization about TB: The disease cannot be controlled in the industrialized countries unless it is sharply reduced as a health threat in the developing countries of Asia, Africa, and Latin America [1]. TB is a communicable disease, caused by the bacillus *Mycobacterium tuberculosis*. It is carried on droplets in the air and can be spread by coughing or sneezing, entering the body through the airway.

As per the global TB report 2021, the total number of incident TB patients notified during 2021 was 1,933,381, which was 19% higher than that of 2020 (16,28,161) [2]. Globally, about a half-million new cases of rifampicin-resistant TB (RR-TB) occurred in 2019, with 78% of them having confirmed MDR-TB as per the guidelines for programmatic management of drug-resistant TB in India by 2021. In India, the estimated number of MDR/RR-TB cases was 124000 (9.1/lakh population). The national anti-tuberculosis drug resistance survey (NDRS) published data about 28% of TB patients were resistant to any drugs and 6.19% had MDR-TB [3].

Daily monitoring and management of adverse events were required for the safe use of drug therapy, which was the ultimate goal for patient safety. Multidrug-resistant (MDR) TB has been recognized as a major problem because it is difficult to treat, costly, and more challenging due to the strains' being resistant to commonly used antituberculosis drugs, including rifampicin (R) and isoniazid (INH). In India, the estimated number of MDR cases to have been put on treatment as per the global TB report in 2021 was 4 per 100,000. A significant reduction was observed in the total number of drug-resistant tuberculosis (DR-TB) patients who started treatment as compared to 2019 [2]. Worldwide, 150,359 people with MDR/RR-TB were enrolled in treatment in 2020, down 15% from the total of 177,100 in 2019 [3]. For each tuberculosis patient, including MDR-TB patients, timely detection, assessment, understanding, and prevention of ADRs are essential for the ultimate goal of rational medicine use.

METHODS

Study design

A retrospective analysis was carried out at the Department of Pharmacology, pharmacovigilance unit of the Adverse Drug Monitoring Centre at Jawaharlal Nehru Medical College and Associated Hospital, Ajmer, Rajasthan (India). We utilized the spontaneously reported voluntary ADR reports of outpatients and inpatients from September 2017 to June 2020. This study was approved by the Institutional Ethical Committee, letter No.1533Acad-III/MCA/2020 dated August 30, 2020.

Data collection methodology

Adverse drug reactions were monitored by the medical team of the MDR-TB center on a daily basis at Jawaharlal Nehru Hospital. Patients were visited (both OPD and IPD) at the MDR-TB center for the initial treatment after the pre-treatment investigations, including sputum for acid-fast bacilli, culture, drug sensitivity test, chest X-ray, renal and liver function tests, HIV test, and other necessary tests as per patients' needs. After that, the second-line treatment started [4]. During follow-up of the second-line treatment, if patients suffered from any serious events and were admitted to the MDR-TB center, the committee members decided on further management of the patient. Active management of ADRs improved the patient's adherence to treatment, reduced

mortality, and enhanced treatment outcome. Serious drug reactions were managed at the health center and reported in Nikshay within 24 h by the health center [4]. The suspected ADR form was recorded by the medical team at the time of an adverse drug reaction identified related to drugs, including all the relevant data such as patient details such as initials, age at the time of event or date of birth, sex, weight, date of reaction started and recovery date, description of reaction details, suspected medications including dose, route, frequency, date of therapy started and stopped, and indication, outcomes of event, and reporter information [5].

Evaluation of ADR data

The collected suspected ADR forms were verified by the causality assessment committee for clinical basis, analyzed, and evaluated to understand the pattern of the ADRs with respect to patient demographics, characteristics of the reaction, type of reaction, characteristics or classification of the drugs involved, management and outcome of reactions, causality assessment, severity assessment, and preventability were analyzed, for inpatients and outpatients at a tertiary care hospital.

Patient characteristics ADRs by age and sex were included for evaluation. Patients were divided into different age groups: 0–4 years, 5–19 years, 20–44 years, 45–65 years, 66–74 years, and >75 years. We utilized the classification of drug reactions given by Rawlins and Thompson [6]. The organ classes were classified using the Medical Dictionary for Regulatory Activities (MedDRA) [7]. The seriousness of ADRs was classified using the ICH E2A guideline criteria [8]. Drugs were classified according to the Anatomical Therapeutic Chemical [ATC] classification system as per the WHO-ATC Index [9]. Action taken was categorized as drug withdrawn, dose reduced; dose not changed, and additional treatment for ADR. The outcome was finalized after confirmation of the dechallenge and rechallenge information. Causality assessment was analyzed using the WHO-UMC assessment scale [10]. The severity of ADRs was classified according to the modified Hartwig Siegel scale [11]. The Schumock and Thornton scale was used to modify the criteria for assessing the preventability of ADRs [12,13].

RESULTS

A total of 990 ADRs occurred in 749 patients between September 2017 and June 2020 (34 months), in which 92 (9.29%) adverse events were reported during treatment of MDR-TB patients with respect to 68 (9.08%) patients including OPD and IPD. The majority of the adverse events were reported by OPD 62 (91.18%) patients, and 6 (8.82%) were reported by IPD patients at the MDR-TB center, as per Table 1.

On the evaluation of the demographic male-to-female ratio, there were 46 (67.65%) males and 22 (32.35%) females mentioned in Table 2.

Out of 92 ADR, 48 (52.17%) belonged to the age group of 20–44 years, followed by 34 (36.96%) belonged to the age group 45–65 years, 9 (9.78%) belonged to the age group 5–19 years, and 1 (1.09%) belonged to the age group 66–74 years. Details are given in Table 3.

The majority of ADR in this study were Type A 81 (88.04%) and Type B 11 (11.96%) reactions. According to the WHO causality assessment criteria, most of the ADRs were probable 68 (73.92%), followed by 12 (13.04%), certain, and 12 (13.04%) possible in nature. As per the reaction, the severity scale accounted for 38 (41.30%) ADRs being mild followed by 37 (40.22%) moderate and 17 (18.48%) severe. On the evaluation of the preventability of ADR, 39 (42.39%) were definitely preventable, followed by 35 (38.04%) probably preventable, and 18 (19.57%) not preventable as per the modified Schumock and Thornton scale. The results are tabulated in Table 4.

The organ systems most commonly affected were ear and labyrinth disorders 20 (21.74%), followed by musculoskeletal and connective tissue disorders 17 (18.48%), followed by nervous system disorders 13 (14.14%), and skin and subcutaneous tissue disorders 13 (14.14%), psychiatric disorders 11 (11.96%), and 6 (6.52%) gastrointestinal disorders. All types of ADR were managed symptomatically and, in the case of serious cases, the suspected drug was replaced as per NTEP guidelines. The results are tabulated in Table 5.

In the present study, 36 different types of suspected ADRs were reported with multiple frequencies due to 16 categories of drugs and a combination of drugs of treatment for MDR-TB patients. The majority of ADRs were reported due to pyrazinamide 23 (25%), followed by kanamycin 22 (23.91%), cycloserine 12 (13.04%), and 11 (11.96%) linezolid. The majority of ADRs were reported, including 17 (18.48%) ototoxicity and 17 (18.48%) joint pain, followed by 4 (4.35%) burning feet syndrome, 4 (4.35%) generalized itching, and 4 (4.35%) psychosis. In our study, one patient was suffering from an HIV infection with MDR-TB. The patient has reported an adverse event, suspected to be due to HIV treatment. Details are given in Table 6.

Table 1: Hospital admission type

Admission type	Number of patients associated with ADRs	% of patients associated with ADRs
OPD	62	91.18
IPD	6	8.82
Grand total	68	100

Table 2: Gender-wise distribution of ADRs reports

Gender	Number of patients associated with ADRs	% of patients associated with ADRs
Female	22	32.35
Male	46	67.65
Grand total	68	100

Table 3: Age-wise distribution of patients with ADRs (i.e., ADRs 92)

Age group	Number of ADR reports	% of ADR reports
0–4	0	0
5–19	9	9.78
20–44	48	52.17
45–65	34	36.96
66–74	1	1.09
Grand total	92	100

Table 4: Analysis of ADRs (reaction type, causality assessment, severity, and preventability)

	Number of ADRs	(%) of ADRs
Reaction type		
Type-A (augmented)	81	88.04
Type-B (bizarre)	11	11.96
Grand total	92	100
Causality assessment		
Probable	68	73.92
Certain	12	13.04
Possible	12	13.04
Unlikely	0	0
Grand total	92	100
Severity		
Mild	38	41.30
Moderate	37	40.22
Severe	17	18.48
Grand total	92	100
Preventability		
Definitely preventable	39	42.39
Probably preventable	35	38.04
Non-preventable	18	19.57
Grand total	92	100

Table 5: Organ system-related disorder due to ADRs

Organ system	Number of ADRs	(%) of ADRs
Ear and labyrinth disorders	20	21.74
Musculoskeletal and connective tissue disorders	17	18.48
Nervous system disorders	13	14.14
Skin and subcutaneous tissue disorders	13	14.14
Psychiatric disorders	11	11.96
Gastrointestinal disorders	6	6.52
Eye disorders	3	3.26
Hepatobiliary disorders	3	3.26
Metabolism and nutrition disorders	3	3.26
Blood and lymphatic system disorders	1	1.08
Investigations	1	1.08
Respiratory, thoracic, and mediastinal disorders	1	1.08
Grand total	92	100

In this study, a total of 62 (67.39%) ADR were found non-serious and 30 (32.61%) ADR were found serious. As per ICH seriousness criteria, out of 30 serious ADRs, 17 (56.67%) were found disabling/incapacitating, followed by 9 (30%) prolonged hospitalization, and 3 (10%) reported other medically important conditions, and no death case was reported. Details are given in Tables 7A and B.

In this study, the drug was withdrawn in the majority of 58 (63.05%) ADR cases followed by 29 (31.52%) that did not change and 5 (5.43%) dose reductions for management. Details are given in Table 8.

In the present study, 9 (9.78%) of ADR were recovered followed by 44 (47.83%) under recovering and 39 (42.39%) of cases not recovered at the time of reporting of ADR. Details are given in Table 9.

DISCUSSION

Active drug safety monitoring and management are an essential component of the patient's safety. The treating physician at the MDR-TB center and medical officer at the periphery observed patients for any adverse events and managed them as per NTEP guidelines and reported them to the ADR Monitoring Centre (AMC). A causality assessment was done by the physician at the MDR-TB center in coordination with AMC. The AMC team reviewed and confirmed the causality of all adverse events in relation to drug treatment after that report was entered into the WHO global database (VigiFlow software). Management of MDR-TB cases is the biggest challenge facing health-care professionals. The government has taken a high level of the plan to control MDR-TB cases in India.

In our study, ADR was observed in 9.08% of MDR-TB patients, which was less as compared to Rathod *et al*. (33.96%) [14] and Hire *et al*. (50%) [15].

Out of 68 patients, the majority of ADRs were reported by OPD patients (91.18%) as compared to the IPD patients (8.82%) due to most of the patients visiting the MDR-TB center for follow-up on an OPD basis at that time. The medical officer took detailed follow-ups including ADR, mostly ADR was non-serious, with no need for hospitalization.

In our study, male (67.65%) patients were more affected due to adverse drug reactions as compared to females (32.35%) which were similar to the study conducted by Rathod *et al*. [14] and Fatima *et al*. [16].

Out of 92 ADRs were reported, respectively, 52.17% and 36.96% belonged to the age groups of 20–44 years and 45–65 years in the

Table 6: Description of suspected drugs, individual reaction with frequency, and total number if ADRs associated with drugs

Suspected drug/active ingredients	ADRs (frequency of occurrence)	Number of ADRs
Ethionamide	Depression Hallucinations Pruritus	3
Levofloxacin	Pruritus	1
Clofazimine	Skin discoloration	1
Cycloserine	Abnormal behavior Burning feet syndrome Depression Hallucinations Pruritus Psychosis (3) Speech disorder (2) Suicidal tendency (2)	12
Efavirenz+Lamivudine +Tenofovir disoproxil fumarate	Breathlessness	1
Ethambutol	Hair loss Vitiligo Generalized itching Burning feet syndrome	4
Ethambutol dihydrochloride +Lomefloxacin hydrochloride + Protionamide +Pyrazinamide	Gastritis Hepatorenal failure	2
Ethionamide	Anorexia Burning feet syndrome TSH increase	3
Isoniazid	Function liver abnormal Generalized pruritus Psychosis	3
Isoniazid+Pyrazinamide +Rifampicin	Generalized itching	1
Kanamycin	Hearing impaired Hypokalemia Numbness of limbs Ototoxicity (17) Vertigo (2)	22
Levofloxacin	Burning feet syndrome	1
Linezolid	Anorexia Blurring of vision (2) Deficiency anemia Neuropathy peripheral (3) Numbness Numbness in leg Optic neuropathy Peripheral neuropathy	11
Pyrazinamide	Epigastric pain Function liver abnormal Generalized pruritus Generalized itching (2) Joint pain (17) Vomiting	23
Pyridoxine	Itchy rash	1
Rifampicin	Nausea Vomiting (2)	3
Grand total		92

Table 7A: Distribution of ADRs according to seriousness

Seriousness of reaction	Number of ADRs	% of ADRs
Non-serious	62	67.39
Serious	30	32.61
Grand total	92	100

Table 7B: Distribution of ADRs based on seriousness criteria as per ICH guideline

Seriousness criteria	Number of ADRs	(%) of ADRs
Disabling/incapacitating	17	56.67
Caused/prolonged hospitalization	9	30
Other medically important condition	3	10
Life threatening	1	3.33
Death	0	0
Congenital anomaly	0	0
Grand total	30	100

Table 8: Management of ADRs reports

Action taken	Number of ADRs	(%) of ADRs
Drug withdrawn	58	63.05
Dose not changed	29	31.52
Dose reduced	5	5.43
Not applicable	0	0
Grand total	92	100

Table 9: Final outcome of ADRs

Final outcome	Number of ADRs	(%) of ADRs
Recovered	9	9.78
Recovering	44	47.83
Not recovered	39	42.39
Fatal/death	0	0
Grand total	92	100

present study as compared to the study conducted by Dela *et al*. [17] result which was different, respectively, 35.2% and 15.2% belonged to the age group of 21–40 years and 41–60 years.

In the present study, most of the ADRs were found to be Type A reactions (88.04%). Type A reactions were predictable and dose dependent and occurred due to the extension of the pharmacological action of the drug, for example, hearing impairment, peripheral neuropathy, joint pain, epigastric pain, psychosis, etc. Only 11.96% of ADRs were Type B reactions. Type B reactions are immunological and non-predictable in nature, for example, generalized itching and generalized pruritus.

In this study, the majority of ADRs were in the probable (73.92%) category, followed by certain and possible, as per the WHO causality assessment scale. As compared with other studies, most of the ADRs were in the possible (81.95%) category in this study conducted by Dela *et al*. [17].

In the present study, the majority of ADRs were found mild (41.30%) and moderate (40.22%) followed by severe (18.48%). These results were dissimilar to those obtained in the study conducted by Fatima *et al*. [16].

In our study, the majority of the ADRs were found to be definitely preventable (42.39%) and probable preventable (38.04%) due to the fact that most of the ADRs were reported to the medical officer on time to take necessary medical treatment to prevent ADR. Another study result totally reversed that 84.74% of ADRs were not preventable. This study was done by Fatima *et al*. [16].

In this study, the most commonly encountered ADRs were ear and labyrinth disorders (21.74%) (e.g., ototoxicity and vertigo), followed by musculoskeletal and connective tissue disorders (18.48%) (e.g., joint pain), and followed by nervous system disorders (14.14%) (e.g., peripheral neuropathy, speech disorders, numbness of limbs, and burning feet syndrome) and skin and subcutaneous tissue disorders (14.14%) (e.g., hair loss, vitiligo, generalized itching, generalized pruritus, and skin discoloration). Another study result showed that the majority of ADRs were gastrointestinal disorders (33.96%) study done by Rathod *et al*. [14].

In this study, 18.48% of ototoxicity was reported due to kanamycin. A similar study was done by Kapadia *et al*. [18].

In this study, the majority of ADRs were non-serious (67.39%) in nature and managed by symptomatic therapy, which is similar to the study conducted by Patel *et al*. [19].

The majority of ADRs were reported due to pyrazinamide, kanamycin, cycloserine, and linezolid, which is similar to a study conducted by Dela *et al*. [17].

In the present study, the drug was withdrawn for the management of 63.05% of suspected ADR cases, which was similar to the study done by Joseph *et al*. [20].

In this study, 9.78% of ADRs were recovered (e.g., generalized itching, psychosis, and numbness in the leg) and the majority of 47.83% of ADRs were under recovering (e.g., peripheral neuropathy, joint pain, hallucinations, abnormal behavior, skin discoloration, and burning feet syndrome) and 42.39% of ADRs cases were not recovered at a time of ADRs reported as per clinical outcome (e.g., ototoxicity and hair loss).

CONCLUSION

Our study showed that the majority of ADRs were reported in males as compared to females. The higher number of ADRs was reported in the age group of 20–44 years. The majority of ADRs were found to be non-serious, probable, mild, and preventable in nature. This study reported ADRs, including serious and non-serious, that were similar to those observed in other studies except for minor variations. Clinical findings were more accurate and rapid management to prevent the ADRs. The physician advised patients to take a high-protein diet, healthy food, and timely medicine to improve their tolerance to drugs and reduce adverse events.

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AUTHORS' CONTRIBUTIONS

Dr. Amul Mishra: Study design, data review, and data analysis, Dr. Sunil Kumar Mathur: Support for ADR reporting from hospital, causality assessment of each ADR cases, clinically data review, and data analysis. Saurabh Kumar Jain: Study design, collection of ADR data and analysis, manuscript preparation.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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