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Original Research Article

A prospective observational pharmacovigilance study of adverse drug reaction monitoring in patients of MDR - TB at tertiary care hospital

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ABSTRACT

Background: The emergence of drug resistant mycobacteria has become a significant public health problem world over creating an obstacle to effective TB control. ADRs are common in patients of MDR-TB on DOTs-Plus drug regimen. Present study was carried out in tertiary care hospital. Identification 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 Department of TB- Chest and Medicine, Govt. Medical College, Aurangabad, Maharashtra, India. All the MDR-TB patients admitted at the directly observed treatment, short course plus (DOTS plus) Center at Medical College Hospital were enrolled and were monitored for ADRs. The causality and severity of the reactions were determined using Naranjo algorithm and Hartwig questionnaire, respectively.

Results: A total of 121 tuberculosis patients of MDR-TB on DOTS therapy were enrolled for the study. Out of 121 patients, 13 were dropouts, 6 died, 7 defaulted so 108 patients assessed for ADRs, 48 patients developed 61 (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 32 (52.45%), followed by Ototoxicity 7 (11.48%) and Psychiatric Manifestations 6 (9.84%) and skin problems 3 (4.92%). On evaluation of the causality of ADRs, majority were found to be Possible (59.02%). The severity assessment showed that most of the patients ADRs were of moderate level (50.82%).Some patients required treatment withdrawal and replacement with other drug and most of the patients were managed with supportive medication without removing anti-tubercular drug from their treatment regimen.

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.

Keywords: Adverse drug reactions, Antitubercular drugs, Causality assessment, Severity assessment

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem, with most cases arising from a mixture of physician error and patient non-compliance during treatment of susceptible TB. The extent and burden of MDR-TB varies significantly from country to country and region to region. It should be stressed that MDR-TB is a man-made phenomenon - poor treatment, poor drugs and poor adherence lead to the development of MDR-TB. Use of inadequate treatment in patients with drug-resistant TB strains will fail to cure a significant proportion of such cases and can create even more resistance to the drugs in use. Ongoing transmission of established drug-resistant

strains in health care facilities is also believed to be a major source of new drug resistant cases.[1]

Globally in 2016, following WHO guidance issued in May 2016, all cases of rifampicin-resistant TB (RR-TB), including those with multidrug-resistant TB (MDR-TB), should be treated with a second-line MDR-TB treatment regimen. Globally in 2015, there were an estimated 480 000 new cases of MDR-TB and an additional 100 000 people with rifampicin-resistant TB who were also newly eligible for MDR-TB treatment; India, China and the Russian Federation accounted for 45% of these cases.[2]

India is one of the high burden countries for tuberculosis as well as drug-resistant tuberculosis. As per WHO's "Global Tuberculosis Report, 2015", India account for an estimated 480,000 new cases of MDR-TB and an additional 100,000 people with rifampicin resistant TB (RR-TB). People with rifampicin resistant TB are now eligible for the same treatment as people with MDR TB.[3]

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin.[4]

Treatment of MDR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. Reserve drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and change of regimen.

Therefore, it is imperative to monitor and treat adverse drug reactions developed by the patients. This approach ensures better compliance of patients and good treatment outcome. At the same time, data regarding ADRs of second-line anti-tubercular drugs in India are scanty. Hence, the aim of this study was to assess the adverse drug reactions of second-line anti-tubercular drugs used to treat MDR-TB in India.[5]

Aims and objectives

- Adverse drug reaction monitoring in patients of MDR-TB at Tertiary Care Hospital.
- 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.

METHODS

Present study was carried out at Drug Resistance Tuberculosis Centre of Govt. Medical College, Aurangabad, Maharashtra, with prior approval of institutional Ethics Committee.

It was a prospective, observational, open label, longitudinal, descriptive clinical study.

Inclusion criteria

- Patient of either sex of age more than 18 years – 45 years with tuberculosis.
- Diagnosed cases of MDR- TB, enrolled under RNTCP program.
- Agreed to adhere tuberculosis treatment regime 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.
- Patients those were transferred to XDR-TB/whose diagnosis was changed.
- 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 and admitted in Drug Resistance Tuberculosis Centre, in Govt. Medical College Aurangabad.
- Data was collected from January 2015 to December 2016.
- All study subjects were evaluated after written informed consent.
- Thorough detailed history was taken regarding the demographic profile, present complaints, past history of tuberculosis, history of any addiction, family history of Tuberculosis.
- Detailed general and systemic examination was done to find out any abnormalities.
- Body mass index (BMI) was calculated in all the patients.
- Pre-treatment investigations done included informed consent, urine for albumin, sugar and pregnancy test for female patients (if 18 to 45 yrs. old), complete haemogram, renal and liver function test, Thyroid function test, psychiatric evaluation, Audiometry (SOS), Vision Acuity Test (SOS).

Treatment regimen

The standardized regimen consisted of an intensive phase (IP) of 6-9 months with 6 drugs, namely kanamycin (Km), ofloxacin (Ofx) (now levofloxacin), ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and cycloserine (Cs) given daily. This was followed by a continuation phase (CP) of 18 months of 4 drugs, namely Ofx (now levofloxacin), Eto, E and Cs. At the end of 6 months of

treatment, if the fourth month culture remained positive, the IP was extended for a further 3 months. Doses of the drugs were chosen according the weight range to which patient belonged.

All patients enrolled to the study were treated with a daily supervised regimen. All patients were monitored daily for adverse drug reactions after starting regimen till the patients remains admitted in hospital and later followed up personally or telephonically at regular intervals of 2 monthly bases and will be asked questions regarding possible adverse drug reactions of the drug which are prescribed to them. In between the 2 monthly follow up in OPD, telephonic questioning regarding adverse drug reactions will be asked on the any day of first week of every month. Anticipated ADRs will be identified and assessed.

The causality of adverse drug reactions will be assessed as per Naranjo's causality assessment scale, for severity of the adverse drug reactions as per Modified Hartwig-Siegel Scale. At the end of the study, these adverse event records will be analyzed and statistically interpreted.

Parameters were studied

1. Incidence of adverse drug reactions in anti-TB (AKT) agents.
2. Severity of adverse drug reaction using Modified hartwig-siegel scale.
3. Causality of adverse drug reaction using Naranjo's scale.

RESULTS

Table 1: Demographic profile of patents.

Parameters		Number	Percentage (%)
Gender	Male	71	65.74
	Female	37	34.25
Age group (in years)	<20	13	12.03
	21-30	37	34.25
	31-40	42	38.89
	41-45	14	12.96
Weight bands (Kg)	<16	00	00
	16-25	00	00
	26-45	68	62.96
	46-70	37	34.25
	>70	03	2.77
Addictions	Alcoholic	20	18.51
	smokers	16	14.81
	Tobacco chewer	28	25.92

A total number of n=108 patients who were on DOTS plus therapy were included in this study around 71 (65.74%) were male and 37 (34.25%) were female. Patients of different age group ranging from 18-45 years were reported in the study. 13 patients were under 20 years of age (12.03%) followed by 42 resides in the age of 31-40 (38.89%), 21-30 of 37 patients (34.25%). Rest were in 41-45 years age group (12.96%) (Table 1).

Table 2: Incidence of Adverse Drug reactions.

Type of ADR	No. of patients	Percentage (%)
Gastrointestinal	32	52.45
Nausea, vomiting	21	34.43
Anorexia	02	3.28
Epigastric discomfort	05	4.39
Change of taste	02	3.28
Diarrhea	02	3.28
Hepatitis	01	1.64
Ototoxicity	07	11.48
Decreased hearing (B/L SNHL+Tinnitus)	05	8.20
Tinnitus +Vertigo	02	1.64
Psychiatric manifestations		
Insomina+Suicidal Tendencies	06	9.84
Depression	02	3.28
Altered behavior	01	1.64
Insomnia+ Suicidal	01	1.64
Tendencies+Depression	01	1.64
Hallucination + Suicidal Tendency	01	1.64
Peripheral neuropathy	02	3.28
Vision defect	02	3.28
Impaired visual acuity	02	3.28
Color discrimination	00	00
Skin	03	4.92
Pruritus with rash	02	3.28
Pruritus without rash	01	1.64
Injection site pain and swelling	04	6.55
Renal dysfunction	02	3.28
Deranged RFT	02	3.28
Musculoskeletal	03	4.92
Arthralgia	03	4.92
Total	61	100

Out of these 108 patients 48 patients developed 61 ADRs of various types (Table 2). Among the 61 reported ADRs, most were observed in males (30/62.50%) and remaining (18/37.50%) were females. The overall incidence of ADRs was 56.48%. 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 (32 cases/52.45%) followed by ototoxicity (7cases/11.48%), Psychiatric Manifestations (06 Cases/9.84%), other systems (16 cases). Nausea and

Vomiting was the most common ADR (21/34.43%) followed by Ototoxicity (6/9.84%), Inj. site pain swelling (4/6.55%).

Out of the 108 drug resistance tuberculosis patients, patients were divided in the different weight bands according to it 68 (62.96%) patients in weight band 26-45kg followed by 37 (34.25%) patients in weight band 46-70kg. Drug resistance pattern in out of 108 patients, 57 (52.78%) patients showing rifampicin mono-resistance while 51 (47.22%) 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).

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

Sr. no	Type	No. of patients	Percentage
1	Probable	25	40.98
2	Possible	36	59.02
3	Certain	00	00
Total		61	100

The causality assessment of ADRs revealed that 13 (21.31%) cases were detected as Definite, 19 (31.14%) as possible and 29 (47.54%) as probable reactions. The Severity assessment of ADRs revealed that 31 (50.82%) cases were mild, 24 (39.34%) were Moderate and 06 (9.84%) sever ADR observed (Table 4).

Table 4: Severity of ADRs induced by anti TB drugs according to Modified Hartwig-sigel Scale.

Sr. no.	Type	No. of patients	Percentage
1	Mild	25	40.98
2	Moderate	31	50.82
3	Severe	05	8.91
Total		61	100

DISCUSSION

The present observational study has evaluated a DOTS-Plus programme, 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 108 patients, the age group ranged from 18 to 45 years. Maximum number of cases were in the age group 31-40yrs (38.89%) followed by 21-30yrs (34. 25%). 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.[7]

In the present study, majority of the patients were males71 (65.74%) and Females 37 (34.25%). In the present study, majority of the patients were males 71 (65.74%) and Females 37 (34.25%). similar observations were noted by authors in a study (males 65.79% and females 34.21%).[2] and proportion of males to females was 54.54% and 45.46% respectively.[6]

Weight band: Of the 108 drug resistance tuberculosis patients in this study, majority of patients were in the weight band of 26 to 45 Kg (62.96%). Whereas, a study observed that majority patients were above 4Kg (51.43%). 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 56.48% patient's, a finding comparable to present study reports notified in different studies.[7-9]

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 32(52.45%) similar to other studies.[9-11] on the contrary other studies have found observed gastrointestinal ADRs in 42%, 60% and 100% patients respectively.[7,8,12,13] Hepatotoxicity was noted in 1(1.64%) patient only. Similarly finding were reported other authors.[11,13]

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 (11.68%) 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.[2,11,14] whereas another study reported ototoxicity in 15% patients.[12] Kanamycin was withdrawn in 80% of these patients and substituted with PAS (p- amino salicylic acid).

Psychiatric 06 (9.84%) 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 4 (6.55%) 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.[8] None of the patients required withdrawal of injection Kanamycin.

Arthralgia 3 (4.92%) 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 (4.92%) 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%.[7,11,16] On the one of the study reported cutaneous reactions in 43.3% patients.[13]

Renal involvement was seen 2(3.28%) 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 (3.28%), Peripheral Neuropathy 2(3.28). similar findings seen in a study with frequency of visual disturbance 1(0.9%) and peripheral neuropathy 3 (2.7%).[9]

In present study Causality assessment of 61 ADRs was done by Naranjo's Causality Scale, out of 61 ADRs,36(59.02%)into possible category, And 25(40.98%) 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 61 ADRs as Mild 40.98%, moderate 50.82% and sever 8.91%, 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 challenge 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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