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Original Research Article

An observational study of adverse drug reactions in hospitalized patients of drug resistance tuberculosis taking PMDT therapy in a tertiary care hospital

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ABSTRACT

Background: Drug resistant tuberculosis is an important public health issue in India. The treatment regimen followed is Programmatic Management of Drug resistant Tuberculosis (PMDT) approach. Adverse drug reactions (ADRs) are a serious issue which increases the risk of defaulter rate if poorly managed. Thus study was undertaken to assess the ADRs caused by PMDT therapy in indoor patients of Department of Respiratory Medicine in a tertiary care hospital at Surat.
Methods: The prospective and observational study was carried out for one year period. The causality was determined by World Health Organization (WHO) Uppasala Monitoring Centre (UMC) scale and severity was determined by Modified Hartwig and Siegel scale. Fisher exact test was applied for statistical analysis.
Results: Among 24 drug resistant tuberculosis patients, 12 (50%) patients developed ADRs due to second line antitubercular drugs. Occurrence of ADRs was more among Category V (100%) as compared to Category IV (36.8%). Occurrence of ADRs was more among females (60%). The commonly involved systems are auditory system (33.3%). Majority of ADRs developed within 61-90 days (66.7%) of initiation of drug therapy. Highest percentage of ADRs causing drugs was pyrazinamide (27.8%). On evaluation of the causality of ADRs, majority were found to be possible (53.3%). The severity assessment showed that most of the patients ADRs were of moderate level (73.3%).
Conclusions: PMDT therapy is complicated but early management and reporting of ADRs decreases default rate.

Keywords: Adverse drug reaction, PMDT, Second line antitubercular drugs

INTRODUCTION

Emergence of drug resistant tuberculosis has become a significant public health problem globally. As per World Health Organization (WHO) Global TB Report 2015, estimated that approximately more than 500,000 MDR-TB and 40,000 XDR-TB cases emerge every year worldwide.[1,2]

The Revised National Tuberculosis Control Programme (RNTCP) launched the internationally recommended strategy to control tuberculosis. Multi drug resistant tuberculosis (MDR-TB), defined as tuberculosis with isolates showing in vitro resistance to at least isoniazid and rifampicin.[3-5] Extensively drug resistant TB (XDR-TB) defined as in vitro drug resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the injectable drugs: capreomycin, kanamycin or amikacin.[6-8]

PMDT therapy includes combinations of various second line drugs regimens.[9] RNTCP is using a standardised treatment regimen (Category IV) for the treatment of MDR-TB cases. Category IV regimen comprises of 6 drugs: kanamycin, ofloxacin (levofloxacin), ethionamide,

pyrazinamide, ethambutol and cycloserine during 6-9 months of the Intensive Phase. While four drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the continuation Phase.[17] The XDR-TB cases are treated with (Category V). Its intensive phase (6-12 months) consists of 7 drugs- Capreomycin, PAS, Moxifloxacin, High dose INH, Clofazimine, Linezolid and amoxyclavulanic acid. The continuation phase (18 months) consists of 6 drugs- PAS, Moxifloxacin, High dose INH, Clofazimine, Linezolid and amoxyclavulanic acid.[9,16]

Treatment of drug resistance tuberculosis is difficult, complicated and much costlier. Second-line antitubercular drugs associated with various adverse drug reactions (ADRs).[10] Thus there is need of frequent interruption and change of regimen. Poor management of adverse effects increases the risk of default or poor adherence to treatment. Considering all these factors the present study was planned to assess the ADRs caused by PMDT therapy in our setup.

METHODS

A prospective and observational study was carried out for one year period in patients who were taking PMDT therapy (indoor patients) in Department of Respiratory Medicine at SMIMER hospital at Surat.

Institutional Ethic Committee permission was obtained before conducting the study. Informed consent was taken from patients and relatives. Strict confidentiality about their details was maintained.

Inclusion criteria

Patients with 18 years and above age group. Indoor patients who gave written informed consent were included in the study. Guardians consent was taken, if patient was unable to give consent.

Exclusion criteria

Patients below 18 years of age group. Pregnant or lactating women. Patient with liver or kidney disease. Uncooperative patients who refuse for verbal and written consent. Alcoholic patients. Patient with other illness like diabetes, hypertension, HIV or on other medication.

Patient's detailed information about their clinical status, past history, adverse effects, management were taken. Drug dosages were decided according to weight band recommendation of PMDT guidelines. Events were considered as ADRs with opinion of pulmonologist and investigator. PAS (Para amino salicylic acid) was reserved for patients who developed adverse drug reaction. The causality of the ADRs was determined using WHO UMC scale. The severity of the ADRs was determined using Modified Hartwig and Siegel scale.

Statistical analysis

Fisher exact test was applied to know association between two variables.

RESULTS

A total of 33 indoor patients on drug resistance tuberculosis therapy were enrolled in the study. Among them 24 patients satisfied our inclusion criteria. Out of these 12 (50%) patients were reported with ADRs.

Table 1: Adverse drug reactions among patients as per PMDT treatment regimen.

Treatment regimen	No. of patients as per inclusion criteria (%)	No. of patients developed ADRs (%)	(%) of occurrence of ADRs
Category IV	19 (79.2)	7 (58.3)	36.8
Category V	5 (20.8)	5 (41.7)	100
Total	24 (100)	12 (100)	50

The above table shows the association between treatment regimen and development of ADR. [P value-0.03 (Fisher exact test)]

Table 2: Adverse drug reactions among patients on PMDT therapy as per gender.

Gender	No. of patients as per inclusion criteria	No. of patients developed ADRs	(%) of occurrence of ADRs
Male	14 (58.3)	6 (50)	42.8
Female	10 (41.7)	6 (50)	60
Total	24 (100)	12 (100)	50

[P value= 0.67(Fisher exact test), OR=0.5]

The proportion of drug resistance tuberculosis patients were more in Category IV 19 (79.2%) as compared to Category V 5 (20.8%). While occurrence of ADRs was more among Category V (100%) as compared to Category IV (36.8%). It shows that there is association between treatment regimen and development of ADR. [P value-0.03 (Fisher exact test)] (Table 1).

The proportion of drug resistance tuberculosis was more in males 14 (58.3%) as compared to females 10 (41.7%). While occurrence of ADRs was more among females (60%) as compared to males (42.8%). Gender is not associated PMDT therapy. (P value= 0.67, OR=0.5) (Table 2).

Table 3: Adverse drug reactions among patients on PMDT therapy as per age.

Age	No. of patients as per inclusion criteria (%)	No. of patients developed ADRs (%)	(%) of occurrence of ADRs
<40 years	15 (62.5)	8 (66.7)	53.3
>40 years	9 (37.5)	4 (33.3)	44.4
Total	24 (100)	12 (100)	50

[P value = 0.6733, OR=1.4]

Table 4: Details of system specific adverse drug reactions.

Types of ADRs	Frequency	Percentage (%)
Gastrointestinal system		
Nausea and vomiting	1	6.7
Haematological system		
Hypokalemia	1	6.7
Liver and biliary system		
Hepatitis	1	6.7
Central and peripheral nervous system		
Insomnia	1	6.7
Peripheral neuropathy	1	6.7
Musculo-skeletal system		
Joints pain	2	13.3
Leg cramps	1	6.7
Auditory system		
Hearing loss	5	33.3
Dermatological disorder		
Rashes	2	13.3

The proportion of the disease was more among patients below 40 years of age 15 (62.5%) as compared to those above 40 years of age 9 (37.5%). Occurrences of ADRs were more among patients below 40 years of age (53.3%) as compared to those above 40 years of age (44.4%). (P value= 0.6733, OR=1.4) (Table 3).

The commonly involved systems are auditory system 5 (33.3%) followed by dermatological disorder 2 (13.3%), musculo-skeletal system 3 (20%), gastrointestinal system 1 (6.7%) haematological system 1 (6.7%), liver and biliary system 1 (6.7%), central and peripheral nervous system 2 (13.3%). Commonly identified ADRs from auditory system included hearing loss (33.3%). (Table 4)

Pyrazinamide presented with highest percentage of ADRs i.e. 5 (27.8%) followed by Kanamycin 3 (16.7%), Ethionamide 3 (16.7%) and other. (Table 5).

Majority of ADRs developed within 61-90 days 8 (66.7%) followed by within 31-60 days 2 (16.7%), less than 30 days of initiation of drug therapy and within 121-150 days 1 (8.3%) patients for each. (Table 6).

Table 5: Distribution of adverse drug reactions as per causative drug.

List of drugs causing ADRs	No. of patients	Percentage (%)
Pyrazinamide	5	27.8
Kanamycin	3	16.7
Ethionamide	3	16.7
Ethambutol	2	11.1
Capreomycin	2	11.1
Amikacin	1	5.5
Levofloxacin	1	5.5
Cycloserine	1	5.5
Total	18	100

Table 6: Distribution of adverse drugs reactions based on onset.

Onset of ADRs (days)	No. of patients	Percentage (%)
<30	1	8.3
31-60	2	16.7
61-90	8	66.7
91-120	0	0
121-150	1	8.3
>150	0	0
Total	12	100

Table 7: Causality assessment as per WHO UMC scale for adverse drug reactions.

Grading	Frequency	Percentage (%)
Possible	8	53.3
Probable	7	46.7
Certain	0	0
Total	15	100

Table 8: Severity assessment using Modified Hartwig and Siegel scale.

Grading	Frequency	Percentage (%)
Mild	3	20
Moderate	11	73.3
Severe	1	6.7
Total	15	100

The WHO UMC scale assessments revealed that out of 15 ADRs, 8 (53.3%) were possible and 7 (46.7%) were probable type of ADRs. None of the ADR reported under certain, unlikely, unclassified or unassessable category. (Table 7).

As per severity assessment using Modified Hartwig and Siegel scale, out of 15 ADRs majority 11 (73.3%) were moderate grading, 3 ADRs (20%) were mild grading and 1 ADR (6.7%) was in severe grading. (Table 8).

DISCUSSION

Drug resistant tuberculosis is hazardous problem globally. In the present study, PMDT therapy as per RNTCP guidelines was given in patients. The occurrence of ADRs was 12 (50%) among patients. This result is comparable to other studies 46.9% reported by Rajendra et al and 57.3% in a meta-analysis by Shansan et al.[11,12]

In the present study the proportion of ADRs were more among females (60%) as compared to males (42.8%). Generally, females are considered to be more at risk of ADRs due to ignorance for the health and diet.

Maximum number of patients with ADRs belonged to the age group below 40 years in present study. i.e. 8 (66.7%). This result is similar to one study that is Ganiyu et al.[13,14] This age group is highly vulnerable to ADRs, due to their high exposure to public places and substandard working environment.

In present study, the most commonly affected system by ADRs was auditory system. i.e. 5 (33.3%). This result is similar to one study that is Ganiyu et al i.e. (35.3%).[13] The early audiometric examination and follow up lead to better detection and management of the adverse events. Timely detection and prompt action of ADRs and their management is essential for effective treatment.

In present study, majority of the ADRs occurs between 61-90 days of drug administration. i.e. 8 (66.7%). Similar to present study Kumari et al suggested that majority of ADRs' onset within 2 - 3 months of initiation of treatment.[15] Better counselling and surveillance could be the reason behind early detection of ADRs. Therefore it is responsibility of health care professional to counsel and guide the patient regarding the early signs of ADRs.

According to WHO - UMC causality scale majority of reactions in present study were 'possible' 8 (53.3%). None of the ADR reported under certain. There are few studies which report equivalent results.[14]

Modified Hartwig and Siegel scale revealed that majority of ADRs 11 (73.3%) were of moderate grading. This result is similar to one study Baig et al i.e. (50.82%).[14]

Limitation of the study

The potential weakness of this study is the small sample size as only hospitalized patients were included for one year study period.

CONCLUSION

Drug resistance tuberculosis treatment is for longer duration and has greater toxicity effects. ADRs due to second line antitubercular drugs contribute to noncompliance and non-adherence to therapy. Thus early detection, reporting and management are required to decrease defaulter rate.

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