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Original Research Article

Adverse drug reactions and treatment outcome analysis in multidrug resistant tuberculosis patients at a DOTS plus site

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ABSTRACT

Background: Multidrug resistant tuberculosis (MDR TB) requires treatment with expensive, toxic, anti-tubercular drugs over a longer duration. Adverse drug reaction (ADR) to second line anti tubercular drugs affect compliance and hence treatment outcome. The primary objective of this study was to analyse ADRs and if these resulted in change or permanent suspension of drug. We also analysed treatment outcome, treatment adherence and co morbidities associated with MDR patients.

Methods: A retrospective study was carried out at DOTS plus site in department of Pulmonary Medicine, Goa Medical College on registered MDR cases from November 2011 to October 2016. Socio demographic profile, diagnosis, treatment and ADRs were evaluated, ADRs were evaluated for frequency, causative drugs, management aspect and impact on treatment outcome.

Results: Out of 201 MDR cases, 99 cases had 167 ADRs. Majority of patients having ADRs were in age group of 30-50 years with mean±standard deviation 36.82±14.47, 59 (59.59%) males and 40 (40.40%) females, 92 (92.92%) retreatment cases and 7 (7.07%) newly diagnosed. Majority of ADRs were vomiting 31(18.56%), joint pain 31 (18.56%), gastritis 21 (12.57%), hearing impairment 16 (9.58%), numbness in leg 14 (8.38%), depression 12 (7.18%). Treatment outcome of cases with ADR was cured 45 (45.45%), treatment completed 16 (16.16%), progressed to XDR 6 (6.06%), transferred out 5 (5.05%), defaulter 14 (14.14%), death 13 (13.13%).

Conclusions: It is very important to recognise at the earliest and treat the ADRs with least modification of the treatment regimen to have a good treatment outcome.

Keywords: Adverse drug reaction, ADR management, DOTS plus, MDR TB, RNTCP

INTRODUCTION

Multidrug resistant tuberculosis (MDR TB) possesses a threat to global tuberculosis control programme. Incidence of MDR in new cases is 3.3% and in previously treated cases is 20% globally.^{1,2} India has second highest MDR TB burden in the world after China.^{3,4} China and India together contribute to 50% of MDR TB cases.^{1,5}

Revised National Tuberculosis Control Programme (RNTCP) in India follows the internationally recommended DOTS plus guidelines for treatment of MDR TB known as Category 4 regimen. Completing MDR TB treatment is quite challenging due to toxic second line drugs used in treatment over a longer duration which usually cause adverse drug reactions.^{1,6,7} Besides this the drugs are also expensive

Limited data on adverse drug reactions in MDR TB patients is available in India Hence more knowledge is

required on characteristics and management of ADRs in MDR TB patients.

Hence this study was undertaken to assess the various adverse drug reactions and also to see if this adverse drug reactions resulted in change in treatment or permanent suspension of drug. Treatment outcome, treatment adherence and various co morbidities associated with MDR TB patients were also analysed.

The aim of this study was to analyse ADRs and if these ADRs resulted in change in treatment or permanent suspension of drug. The treatment outcome, treatment adherence of the patient, co morbidities associated with MDR TB patients were also assessed.

METHODS

It was a Retrospective descriptive observational study. This study was conducted in DOTS plus site at the department of pulmonary medicine, Goa Medical College. Study population consisted of registered MDR TB patients. Study took place from November 2011 to October 2016. Information about the patients was collected from hospital records of DOTS plus site in the department of pulmonary medicine, Goa Medicine College.

Inclusion criteria

All registered MDR TB cases were included.

Exclusion criteria

TB cases other than MDR were excluded from the study.

All registered MDR cases at the DOTS plus site in the department of pulmonary medicine, GMC during November 2011 to October 2016 were included in the study. Sociodemographic profile (age, gender, weight, past history of diseases), MDR TB details (causes of MDR TB, diagnostic details), treatment details and ADRs were recorded and evaluated.

ADRs were further evaluated for frequency, causative drug, management aspect and impact of treatment outcome. It was also analysed if these ADRs resulted in change in treatment or permanent suspension of drug. The treatment outcome, treatment adherence of the patient, co morbidities associated with MDR TB patients were also assessed.

Patients were diagnosed to have MDR TB if they were found resistant to isoniazid and rifampicin with or without resistance to other first line drugs on drug sensitive testing (DST) results.^{3,8}

MDR TB patients are provided treatment under category 4 regimen under RNTCP kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol

and cycloserine during 6-9 months of intensive phase and 4 drugs ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine for 18 months of continuation phase.^{3,9} Drug dosages of MDR TB cases were decided according to weight bands.^{3,9} P-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (kanamycin, ofloxacin, PZA, ethionamide) or 2 bacteriostatic (ethambutol, cycloserine) drugs were not tolerated.

Statistical analysis

Data was entered in MS excel spreadsheet. Data was analysed using SPSS software version 21.0.

RESULTS

A total of 201 drug susceptibility testing (DST) confirmed MDR TB cases were registered from November 2011 to October 2016. Among them, 99 cases (49.25%) had ADR while 102 cases (50.74%) had no adverse drug reaction (Table 1).

Table1: Socio demographic details of MDR cases with ADRs (n=99).

Socio demographic profile	No. of cases (%)
Age (in years)	
<30	36 (36.36)
30-50	46 (46.46)
50-80	17 (17.17)
Sex	
Male	59 (59.59)
Female	40 (40.40)
Initial weight (in Kg)	
<45	48 (48.48)
≥45	51 (51.51)
History	
New cases	7 (7.07)
Retreatment cases	92 (92.92)
Co morbidity	
HIV	1 (1.01)
DM	8 (8.08)
HIV and DM	0 (0)
Treatment adherence	
Yes	90 (90.90)
No	9 (9.09)
Treatment outcome	
Cure	45 (45.45)
Rx completed	16 (16.16)
Progress to XDR	6 (6.06)
Transfer out	5 (5.05)
Defaulter	14 (14.14)
Death	13 (13.13)

Out of 99 cases, 167 ADRs were noted. Majority of the patients in this 99 cases were in the age group of 30- 50 years with mean±standard deviation was 36.82±14.47, while 59 cases (59.59%) were males, 40 cases (40.40%)

were females, 92 cases (92.92%) were retreatment cases, 7 cases (7.07%) were newly diagnosed MDR TB cases, 9 cases (9.09%) had co morbidities (HIV- 1.01%, DM-8.08%) while 90 cases (90.90%) had good treatment adherence as shown in Table 1.

Table 2: Incidence of adverse drug reactions and suspected drug (n=167).

ADR	No. of cases (%)	Suspected drug	No. of cases
Gastrointestinal			
Vomiting	31 (18.56)	Ethionamide	17
		Not mentioned	14
Loose motion	2 (1.19)	Not mentioned	2
Gastritis	21 (12.57)	Ethionamide	18
		Not mentioned	3
Hepatitis	4 (2.39)	Not mentioned	4
Psychological			
Depression	12 (7.18)	Cycloserine	10
		Not mentioned	2
Suicidal tendency	4 (2.39)	Cycloserine	4
Joint pain	31 (18.56)	PZA	30
		Not mentioned	1
Ringing in ears	2 (1.19)	Kanamycin	2
Numbness in legs	14 (8.38)	INH	7
		Ethionamide	5
		Not mentioned	2
Hearing impairment	16 (9.58)	Kanamycin	16
Hypothyroidism	3 (1.79)	Ethionamide	3
Nephrotoxicity	8 (4.79)	Kanamycin	8
Giddiness	11 (6.58)	Kanamycin	10
		Not mentioned	1
Gynaecomastia	3 (1.79)	Ethionamide	3
Skin rash	4 (2.39)	Not mentioned	4
Apthus ulcers	1 (0.59)	Not mentioned	1
Total ADRs	167		

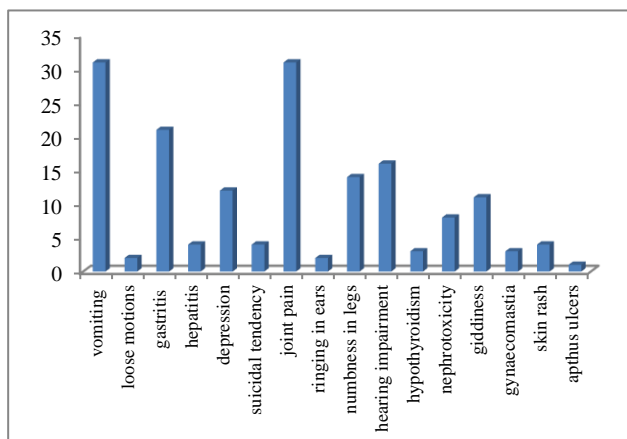


Figure 1: Incidence of ADRs.

Majority of ADRs were Vomiting 31 cases (18.56%), joint pain 31 cases (18.56%), gastritis 21 cases (12.57%), hearing impairment 16 cases (9.58%), numbness in legs

14 cases (8.38%), depression 12 cases (7.18%), while the less frequent ones were suicidal tendency 4 cases (2.39%), skin rash 4 cases (2.39%), hypothyroidism 3 cases (1.79%), gynacomastia 3 cases (1.79%), loose motions 2 cases (1.19%), ringing in ears 2 cases (1.19%) as shown in Table 2 and Figure 1.

111 ADRs (66.46%) required stoppage of one or more drugs. Permanently stopped drugs were cycloserine (psychological ADR) Kanamycin (ototoxicity, nephrotoxicity), ethiomamide (gastrointestinal ADR) while 51 cases (30.53%) were treated symptomatically, 5 cases (2.99%) required reduction in drug dosage, none of the cases required treatment change as shown in Table 3.

Table 3: Type of management of ADRs.

Type of management	No of cases (%)
Symptomatic treatment	51 (30.53)
Stopped 1 or more drugs	111 (66.46)
Treatment change	0
Reduce drug dosage	5 (2.99)

Treatment outcome of these 99 cases was also analysed and it was found that 45 cases (45.45%) were declared cured, 13 cases died (13.13%), 14 cases (14.14%) were defaulters, 16 cases (16.16%) completed treatment, 6 cases (6.06%) were switched over to cat v and 5 cases (5.05%) were transferred out as shown in Table 1 and Figure 2.

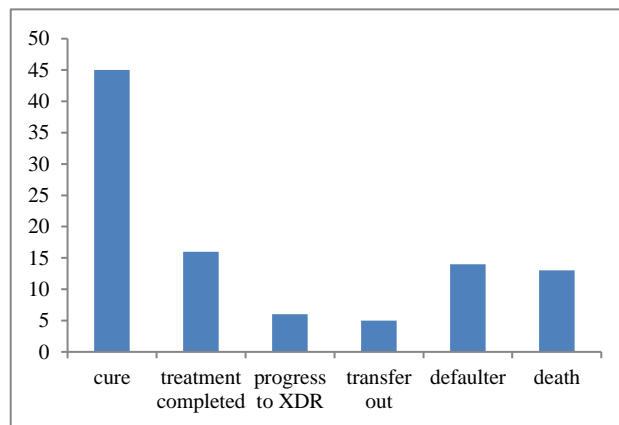


Figure 2: Treatment outcome of cases with ADRs.

DISCUSSION

MDR TB is an increasing global problem. The treatment for MDR TB is more complex as compared to the basic DOTS treatment as it requires prolonged treatment with less efficacious and highly toxic drugs.³ Due to all these factors MDR patients on treatment are more prone to various ADRs resulting in dropouts, insufficient treatment and thereby low success rates.¹ In present study the majority of patients (46.46%) were in the age group of 30-50 years with mean±standard deviation 36.82±14.47. Of the study subjects 59 males (59.59%)

and 40 females (40.40%), showing that there is higher occurrence of MDR cases in males compared to females. This age group particularly males, is the economically productive age group as compared to the older age group and hence increased exposure to the drug resistant cases. Besides they are more prone for addictions such as smoking and alcohol intake as well as psychological stress which weakens their immunity and increases the risk of developing the diseases. Similar results were obtained by other workers like Bhat GS et al, where mean age was 33.64±11.03 years, by Datta et al, where mean age was 39±4.7%years, by Patel SV et al where mean age was 35.01±12.25 years and by Dela AI et al where mean age was 35.69±12.88.^{1,3,10,11} Similar results of male preponderance was seen by Cavanaugh et al 83%, by Chiang et al 71%, by Patel SV et al 71.8% and Arif I Dela AI et al 71.2%.^{1,3,12,13} In present study MDR TB was diagnosed in 92 retreatment cases (92.92%) that is, who had already received the first line anti tubercular drugs in the past and where cases of default, treatment failure or relapsed after treatment. Remaining 7 cases (7.07%) of MDR TB were newly diagnosed TB cases that is, who were never exposed to anti TB drugs. Present findings confirm with those of Dela et al where 96% of total MDR cases were in the retreatment group as compared to 4% new cases.¹

In present study 9 cases (9.09%) had co morbidities like HIV and DM which was similar to the study by Dela et al in which 7.2% had these co morbidities.¹ In present study 90 cases (90.90%) had treatment adherence as compared to only 9 cases (9.09%) who had no good treatment adherence, thus showing a very efficiently functioning DOTs programme follow up, monitoring and supervision. In the study by Dela et al 63.2%, had good treatment adherence.¹ In present study the commonly encountered ADR were vomiting (most common) 31 cases (18.56%), joint pains 31 cases (18.56%), gastritis 21 cases (12.57%), hearing impairment 16 cases (9.58%), numbness in legs 14 cases (8.38%), depression 12 cases (7.18%), giddiness 11 cases (6.58%) which is almost similar to the study conducted by Nathanson E et al in 5 DOTS plus site and the 5 most common adverse reactions observed were nausea/vomiting, diarrhoea, arthralgia, dizziness vertigo and hearing disturbances.¹⁴ It was also similar to the study conducted in Tamil Nadu, Pauline et al where it was found that the main side effects were GI disturbances, giddiness, arthralgia, depression, jaundice and impaired hearing.¹⁵

In present study 111 (66.46%) adverse drug reactions were managed by stopping one or more drugs while 51 reactions (30.53%) were managed symptomatically whereas 5 reactions (2.99%) required reduction in drug dosage, none of the drug reactions required change in the regimen which was similar to the study done by Joseph et al which reported that 58% required termination of offending drug whereas Chaing et al reported that 21.4% patients required medications to be stopped.^{13,15} The differences noted in the different studies may be due to

differences in training, their experiences and capacity to detect ADRs and their management. In present study patients who complained of decreased hearing 16 cases (9.58%) were put on PAS and injection Kanamycin was stopped, Arora VK et al also observed that injection Kanamycin was stopped in 5% patients due to hearing loss.¹⁶ In present study patients who complained of joint pain 31 cases (18.56%) were managed symptomatically PZA has been known to increase uric acid levels. Often it is asymptomatic but severe hyperuricemia can lead to renal failure.¹ Nathanson E et al reported 11% with minor joint pain managed symptomatically.¹⁴ In present study vomiting was seen in 31 cases (18.56%) which was managed symptomatically. In the study by Dela et al ADR of vomiting was 24.5%.¹ In present study depression was reported in 12 cases (7.18%) and suicidal tendency 4 cases (2.39%), Cycloserine was the suspected drug and hence was discontinued. Severe psychiatric manifestations including hallucination, anxiety, depression, euphoria, behavioural disorder and suicidal ideation or attempts have been reported to occur in 9.7-50% of individuals receiving cycloserine.^{1,17} Cycloserine associated neurotoxicity is likely due to diminished CNS production of gamma aminobutyric acid caused by inhibition of glutamic decarboxylase In addition to drug toxicity psychosocial factors contribute to psychiatric complications.^{1,17,18}

In present study 14 cases (8.38%) complained of peripheral neuropathy (numbness in legs). They improved by increasing dose of pyridoxine to 200mg daily. In present study the treatment outcome profile of MDR patients with ADR showed cure in 45 cases (45.45%), treatment completed in 16 cases (16.16%), progression to XDR TB in 6 cases (6.06%), transfer out in 5 cases (5.05%), defaulter in 14 cases (14.14%) and death in 13 cases (13.13%) which is almost similar to the study by Dela et al where treatment outcome amongst these cases was cure (59.72%), progression to XDR TB (13.88%), transferred out (0.8%), defaulter (4.8%) and death (14.94%).¹

Limitations

As it is a retrospective study we were able to analyse the data that was available within the treatment cards hence under reporting, reporting bias of ADRs is possible.

CONCLUSION

It is very important to timely recognise and treat the ADRs during the management of MDR TB cases with minimum modification of the regimen and thus to improve the compliance of the patient and the treatment outcome.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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