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Adverse drug reactions observed with Anti tubercular drugs used in treatment of Drug resistant tuberculosis

Raj Kamal Singh[1] Vinay Kumar[2] Rashmi Singh Kushwaha[3]

ABSTRACT

Background: -Tuberculosis is one of health problem in India. Emergence of MDR-TB had further increased the disease burden owing to its difficult & longer duration of treatment. Treatment of MDR TB Is associated with increased incidence of ADR which adversely affects the outcome and compliance. **Material & Method**:- A retrospective study of MDR TB cases reporting with ADR at Nodal DRTB centre Jhansi are recoded and analysed. **Result**:-Among total of 303 patients reporting, most frequent ADR observed was Gastro intestinal symptoms (53.79%) followed by dermatological (18.81%) and neurological symptoms (18.81%). ADRs were significantly associated with non-compliance to treatment and default. **Conclusion**:-A proper counselling of the patient prior to start of therapy must be done .Probable ADR to treatment must be explained such that early recognition and intervention with minimal or no modification can be done. Early detection and proper management of ADRs will ensure better compliance and treatment outcome.

Key Words: Adverse drug reaction, Multi drug resistant tuberculosis, National Tuberculosis Elimination Programme.

Introduction

Tuberculosis is a communicable chronic infection caused by Mycobacterium *tuberculosis*. The disease is one of the major leading causes of death globally[1]. Multi drug resistant strains of tuberculosis has been recognized and evaluated since 1960s .These multi drug resistant strains are more hardy and are difficult to treat as compared to susceptible ones. The frequency of MDR TB reporting had been continuously rising , posing serious global threat to mankind and efforts to control tuberculosis3 .Incidence of MDR TB is 3.3% of new cases globally and 20% (approx..) in re-infected cases. India is among the top most countries which are worst hit by the disease. In India prevalence of MDR TB is 2.3% among new cases and 12-17% among re-infected cases[2] .Treatment of MDR TB requires use of second line anti tubercular drugs along with first line drugs which is usually more toxic .These drugs (in combination) are being used for a longer duration as compared to treatment of susceptible strains[4, 5]. This leads to increased chance to develop adverse drug reactions during treatment[6] . In this study we had tried to analyse types of adverse drug reactions caused by different drugs and use the result for planning SOP for better adherence to treatment by patients.

1. TB & Chest Diseases, Associate Professor, Department of TB & Chest, Rani Durgawati Medical College, Banda Mob No. 9450247330, **Email-** drrajkamal2602@gmail.com)
2. Pharmacovigilance Associate, Department of Pharmacology,MLBMedical College Jhansi, **E-mail:** vinaykumar070786@gmail.com
3. Lady Medical Officer, District Women's Hospital, Jhansi

Corresponding Author : Dr Raj Kamal Singh, Associate Professor, Department of TB & Chest, Rani Durgawati Medical College, Banda, **Email-** drrajkamal2602@gmail.com ; Moble 9450247330

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Material and Method

This study is a retrospective study to analyse adverse drug reactions observed by use of drugs for treatment of multi drug resistant tuberculosis. Our study includes 303 patients diagnosed with multi drug resistant TB. These patients were taking anti-tuberculosis treatment and reported with adverse drug reactions in their course of treatment. These patients were started treatment at Nodal DRTB centre at Department of TB and Chest MLB medical College Jhansi. Patients receiving treatment from September 2021 to March 2022 are included in the study. Diagnosis of the patient was made by sputum direct microscopy associated with CBNAAT and LPA (for both first-line and second-line ATT) from NTEP accredited Lab. Patients were admitted and treatment was started as per protocol regimen after pre-treatment evaluation. The treatment regimen followed is as per the guidelines of PMDT under NTEP. Patients were followed for atleast one week as an indoor hospitalized, for any adverse events in response to the treatment started. After discharge patients are followed-up fortnightly for the next two months and then monthly afterwards. Patients reporting adverse events are taken care of, immediately (if in the initial first week or after admission), by adding drugs to relieve symptoms of adverse events, stoppage or replacement of the suspected drug (ATT).

Result

Total of 303 patients included in study are analysed for adverse drug reactions to therapy. Out of these 303 patients 221 (72.9 4%) are male and 82 (27.0 6 %) are female. These patients belong to age group of 15-71 years. There are 231 patients in the age group of 18-44 years which constituted about 76.24% of the total study participants. Of these 231 patients, 66 (21.78%) are female and 165 (54.46%) are male. The pattern of adverse drug reaction reporting is uniform in all age groups **[Table-1].** No significant gender or age predilection to adverse drug reactions is observed.

Table -1: Analyzed for adverse drug reactions to therapy (n=303)

Age	Sex				Grand Total	
	Female		Male			
	No.	%	No.	%	No.	%
<18	2	0.66	5	1.65	**7**	**2.31**
18-44	66	21.78	165	54.46	**231**	**76.24**
45-71	14	4.62	51	16.83	**65**	**21.45**
Grand Total	**82**	**27.06**	**221**	**72.94**	**303**	**100.00**

All patients were started treatment regimen for drug resistant TB as per standard guidelines recommended by World Health Organisation and endorsed by Government of India under National Tuberculosis Elimination Programme. The regimen consisted Isoniazid, Pyrazinamide, Ethambutol, Ethionamide, Fluoroquinolones (Levofloxacin & Moxifloxacin), Aminoglycosides (Kanamycin & Capreomycin). These drugs were used on weight basis as per the NTEP guidelines.

Adverse drug reactions most frequently observed are GI symptoms in 163 (53.79%) patients, followed by dermatological reaction in 57 (18.81%) and neurological adverse events in 57 (18.81%). Other adverse drug reactions that were observed are Joint pain (3.96%), QTc prolongation (2.31%) cases **[Table 2].**

Table -2: Adverse drug reactions of the studied cases (N=303)

Reaction		Sex					
		Female		Male		Grand Total	
		No.	%	No.	%	No.	%
Dermatology symptoms	**Acneiform eruption**	5	1.65	9	2.97	**14**	**4.62**
	Itching, rashes	15	4.95	28	9.24	**43**	**14.19**
GI symptoms	**Diarrhoea**	1	0.33	7	0.33	**8**	**2.64**
	Gastric pain	4	1.32	21	1.32	**25**	**8.25**
	Vomiting	7	2.31	14	4.62	**21**	**6.93**
	Nausea	32	10.56	75	24.75	**107**	**35.31**
	Loss of appetite	0	0.0	2	0.66	**2**	**0.66**
Neurological symptoms	**Anxiety**	0	0.0	2	0.66	**2**	**0.66**
	Blurred vision	1	0.33	1	0.33	**2**	**0.66**
	Headache	1	0.33	1	0.33	**2**	**0.66**
	Hearing decreased	3	0.99	24	7.92	**27**	**8.91**
	Vertigo	3	0.99	2	0.66	**5**	**1.65**
	Peripheral neuropathy	5	1.65	9	2.97	**14**	**4.62**
	Ringing sensation	0	0.0	3	0.99	**3**	**0.99**
	Vision loss	0	0.0	2	0.66	**2**	**0.66**
Miscellaneous	**QTC prolongation**	2	0.66	5	1.65	**7**	**2.31**
	Joint pain	2	0.66	10	3.30	**12**	**3.96**
	Others	1	0.33	6	1.98	**7**	**2.31**
Grand Total		**82**	**27.06**	**221**	**72.94**	**303**	**100.00**

Anti-tuberculosis drug which was found to be most frequently associated with Adverse drug reactions were observed to be Ethambutol 96 (31.68%) followed by Isoniazid 69 (22.77%), Ethionamide 49 (16.17%), Aminoglycoside (Kanamycin, Capreomycin) 41 (13.53%), Pyrazinamide 30 (9.9%) **[Table 3].**

Table- 3: Adverse drug reaction in different drugs.

Reaction	Drugs																Grand Total	
	Bedaquiline		Kanamycin		Capreomycin		Pyrazinamide		Ethionamide		Ethambutol		Isoniazid		Others			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Dermatology																		
Acneiform eruption	0	0.0	0	0.0	1	0.33	0	0.0	0	0.0	1	0.33	12	3.96	0	0.0	**14**	**4.62**
Itching, rashes	0		2	0.66	1	0.33	18	5.94	0	0.0	1	0.33	18	5.95	1	0.33	**43**	**14.19**
GI symptoms																		
Diarrhoea	0	0.0	0	0.0	0	0.00	5	1.65	5	1.65	2	0.66	1	0.33	0	0.0	**8**	**2.64**
Gastric pain	0	0.0	0	0.0	01	3.33	0	0.0	0	0.0	17	5.61	3	0.99	0	0.0	**25**	**8.25**
Vomiting	0	0.0	1	0.33	0	0.00	1	0.33	2	0.66	10	3.30	6	1.98	1	0.33	**21**	**6.93**
Nausea	0	0.0	1	0.33	0	0.00	1	0.33	2	0.66	10	3.30	6	1.98	1	0.33	**21**	**6.93**
Loss of appetite	0	0.0	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.66	0	0.00	**2**	**0.66**
Neurological symptoms																		
Anxiety	0	0.0	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.66	0	0.00	**2**	**0.66**
Blurred vision	0	0.0	0	0.00	0	0.00	0	0.00	0	0.00	2	0.66	0	0.00	0	0.00	**2**	**0.66**
Headache	0	0.0	0	0.00	0	0.00	0	0.00	0	0.00	1	0.33	1	0.33	0	0.00	**2**	**0.66**
Hearing decreased	0	0.0	25	8.25	0	0.0	0	0.0	0	0.0	1	0.33	0	0.00	0	0.00	**26**	**8.58**
Vertigo	0	0.0	2	0.66	1	0.33	0	0.0	1	0.33	1	0.33	0	0.0	0	0.0	**5**	**1.65**
Peripheral neuropathy	0	0.0	1	0.33	0	0	0.0	0	0.0	0	0	0.00	12	3.96	2	0.66	**15**	**4.95**
Ringing sensation	0	0.0	3	0.99	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	**3**	**0.99**
Vision loss	0	0.0	0	0.0	2	0.66	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	**2**	**0.66**
Miscellaneous																		
Qtc prolong-ation	7	2.31	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	7	**2.31**
Joint pain	0	0.0	0	0.0	0	0.0	5	1.65	1	0.33	4	1.32	0	0.0	2	0.66	12	**3.96**
Others	0	0.0	0	0.0	1	0.33	0	0.0	0	0.0	0	0.0	1	0.33	5	1.65	7	**2.31**
Grand Total	**7**	**2.31**	**35**	**11.55**	**6**	**1.98**	**30**	**9.90**	**49**	**16.17**	**96**	**31.68**	**69**	**22.77**	**11**	**3.63**	**303**	**100.0**

Discussion

Treatment of tuberculosis has been always a difficult task since recognition of disease. India is among very high burden countries of the world for tuberculosis. Emergence of MDR strains of tuberculosis had further complicated the treatment. The drugs used for the treatment of these strains are toxic and used for longer duration than usual. The longer duration of treatment had been associated with increased frequency of adverse drug reactions with these drugs. Increase in frequency of adverse drug reactions results in increased dropout rate and poor compliance to treatment which reflects as poor treatment outcome.[7.]

In this study majority of patients were from age group 18-44 years.This age group is at higher risk of getting infected due their high mobility and exposure to different working environment. This high mobility of this group can be attributed to their economic responsibility. These individual are prone to addiction and psychological stress which may lead to decreased immunity and increased chances of getting infected. Immunity plays a fair role in development of disease .Once the individual gets infected with the tuberculosis bacilli, is mostly likely to develop disease. There was no significant association between age and adverse drug reactions as well as gender and adverse drug reactions.

Treatment regimen used was as per National Tuberculosis Elimination Programme guidelines for treatment of Drug Resistant -Tuberculosis. The regimen included Isoniazid, Pyrazinamide, Ethambutol, Ethionamide, Parenteral Aminoglycoside (kanamycin & capreomycin), Fluoroquinolones (Levofloxacin& Moxifloxacin). Most frequently observed adverse drug reactions were GI symptoms (163, 53.79%) followed by Dermatological symptoms which was observed in (18.81%) and neurological symptoms in (18.81%). These observations are similar to those observed in study by Akshata et al. in Bangluru [3], and by Vishaka and Sanjay, Ahemdabad [8] and Hoa et al in Vietnam [9]. These reported adverse drug reactions were of mild to moderate severity and results are similar to study done by Hoa et al in Vietnam[9]. These adverse drug reactions were managed by adding certain drugs for symptomatic relief and do not require any major change in treatment protocol. Among adverse drug reactions related to GI system were nausea (35.31%), vomiting (6.93%) gastric pain (8.25%) were the most observed one. Possible drugs for these symptoms were Ethambutol (27.3%) and Ethionamide (15.51%). Dermatological symptoms include Acneiform eruptions (4.62%), Itching and Rashes (14.19%). These symptoms were more by Isoniazid (9.9%) and Pyrazinamide (5.94%). Neurological symptoms include Decreased hearing (8.58%), Peripheral neuropathy (4.95%) Vertigo (1.65%), Ringing sensation (0.99%).These symptoms were more by Kanamycin (9.9%), Isoniazid (4.95%).Other adverse drug reactions observed during treatment were Joint pain (3.96%) which were more with Pyrazinamide (1.65%) and Ethambutol (1.32%). Pyrazinamide and Ethambutol are associated with increasing uric acids levels[10]. QTc prolongation (2.31%) was observed few cases which were due to Bedaquiline (2.31%).

Adverse drug reactions observed in the study were mostly of mild to moderate severity. These adverse drug reactions were managed symptomatically. Management included adding few drug for symptomatic relieve and withholding of suspected drug for time being. Drugs were re-introduced in phased manner, once the symptoms improved. Alteration in treatment regimen was no required in most of cases except few (only 2) cases in which extent of severity of adverse drug reaction was serious.

Relevance of study

The study helps develop a systematic operating protocol that is to be followed prior to start of anti-tubercular drug therapy in cases of drug-resistant tuberculosis. This would help in early recognition of adverse drug reactions. Accordingly, appropriate corrective measures could be taken. This would further help in reducing noncompliance to treatment by patients due to fear of adverse events. Better treatment compliance would eventually lead to a better clinical success rate of treatment with a lesser number of failures or defaulters.

Conclusion

Most frequent side effects were GI symptoms followed by Dermatological and Neurological symptoms. Most of these symptoms were of mild to moderate severity and are managed by drug dose adjustment along with addition of few drugs without altering the standard treatment protocol. These adverse drug reactions had fairly negative impact on patient's psychology which forces him for treatment default and non-compliance to treatment. Hence a proper counselling of patients prior to start of therapy is very important for better compliance to treatment by patients and best clinical results of treatment.

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