Severity Assessment Of Adverse Drug Reactions Among Mdr-Tb And Xdr-Tb Patients With Different Anti Tubercular Regimens

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ABSTRACT

Aim & Objective: Drug-susceptible tuberculosis (DS-TB) requires treatment with first-line drugs (FLDs) Whereas drug-resistant TB (DR-TB) are treated with combination of second-line drugs (SLDs) and fewer FLDs. Adverse drug reactions (ADRs) to these drugs are quite evident as they are being used for longer duration. **Methods:** Patients who were diagnosed with MDR and XDR-TB of either gender. The causality assessment of the ADRs was done by using the WHO and Naranjo's scales. Most ADRs are observed in the continuation phase as compared to intensive phase. Major concerns exist regarding treatment of DR-TB patients, especially with SLDs having lower efficacy more toxicity and high cost as compared to FLDs. **Results:** Most ADRs are observed in the continuation phase as compared to intensive phase.. Major concerns exist regarding treatment of DR-TB patients, especially with SLDs having lower efficacy more toxicity and high cost as compared to FLDs. A variety of ADRs may be produced by anti-TB drugs ranging from mild or minor to severe or major like gastrointestinal toxicity (nausea/vomiting, diarrhoea, and hepatotoxicity), ototoxicity, neurotoxicity (peripheral neuropathy and seizures), nephrotoxicity and cardiotoxicity. Most of ADRs are minor and can be managed without discontinuation of treatment. Few ADRs' can be major causing life-threatening experience leading to either modification or discontinuation of regimen and even mortality. **Conclusion:** A careful monitoring of ADRs during the treatment with anti-TB drugs and early recognition and appropriate management of these ADRs might improve adherence leading to favorable outcome.

Key Words: Tuberculosis, Adverse drug reactions, multidrug resistance, extensively drug resistance.

Introduction

Tuberculosis (TB) is a disease caused by the bacteria called Mycobacterium tuberculosis. In case of tuberculosis and drug resistant tuberculosis, India is one of the high burden countries and as per the global tuberculosis report of 2015, an incidence of 4,80,000 cases were observed to be with MDR-TB (Multi Drug Resistant Tuberculosis) in India [1].

Providing the treatment for MDR-TB is quiet difficult and complex. Unacceptable adverse drug reactions can be observed frequently with the reserve drugs which may result in the frequent change of the regimen [2]. Patients with non-compliance towards the treatment and the prescribing errors during the treatment were the major reasons for drug resistance. The major source of new drug resistant cases can be ongoing transmission of established drug resistance strains in the clinical scenario [3]. When introducing the new anti-TB drugs and regimens, the national TB programmes that systematically monitor the adverse effects associated with the anti-TB drugs are better placed to safe guard the safety of the patient. In the aspect of addressing the safety of current and anti-TB drugs, pharmacovigilance will play a significant part of global and national policy [4,5]. Hence, we made an attempt to monitor the adverse drug reactions among the patients with MDR-TB and XDR-TB (Extensively Drug Resistant Tuberculosis).

AIM AND OBJECTIVES

Aim:

The main aim of the present study is to estimate the prevalence of ADRs among MDR and XDR TB patients treated with different regimens at Damien TB centre.

Objectives:

- 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.
- To categorize the patients based on their demographic parameters.

METHODOLOGY

Study Design: It is a prospective observational cross sectional study

Study site: The present study was carried out at Damien Foundation Urban Leprosy & TB Centre, Nellore with prior approval of institutional Ethics Committee.

Study Duration: The study was conducted for a period of months (July 2021 to 2022)

Research Tool: Naranjo scale was used for causality assessment of the ADRs. ADRs were categorized into four types based on the scores as Definite ADRs (≥9), probable ADRs (5-8), possible ADRs (1-4) and doubtful ADRs (0).

Inclusion criteria

- Patient of either sex of age more than 18 years – 50 years with tuberculosis.
- Diagnosed cases of MDR- TB, enrolled under RNTCP (NTEP) program.
- Agreed to adhere tuberculosis treatment regimen 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.
- Pregnancy patients.
- Patients those were transferred to diagnosis were changed.
- Not ready to give informed consent.
- Not ready to give follow up.

Method of data collection

Patients for this study were included from Damien Foundation Urban Leprosy & TB Centre, Nellore who were diagnosed to have MDR-TB (Isoniazid and Rifampicin resistance

individually or both) admitted in Drug Resistance Tuberculosis Centre. All study subjects were evaluated after written informed consent was obtained. Thorough detailed history was taken regarding the demographic profile, present complaints, past history of tuberculosis, history of any addiction, family history of Tuberculosis was collected using a structured patient data collection form. Detailed general and systemic examination was done to find out any abnormalities. Pre-treatment investigations done included informed consent, urine for albumin, sugar and pregnancy test for female patients (if 18 to 50 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), Moxifloxacin (Mfx) ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and Clofazimine (Cfz) given daily. This was followed by a continuation phase (CP) of 18 months of 4 drugs, namely Lfx (levofloxacin), Eto, E and cycloserine (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, at the end of the study, these adverse event records will be analyzed and statistically interpreted.

All the data analysis was done by using Microsoft excel spreadsheet, version-2009, we used only descriptive statistics like, mean and simple percentage.

All the demographics parameters, graphs, tables were generated, the tool used assess the severity of ADR was analyzed by using Naranjo's scale.

RESULTS

The prevalence of ADRs was 31.69% among the MDR and XDR TB patients treated with different regimens.

All the study subjects were categorized based on gender and represented in table 1, among the total sample of 508 males were 362(**71.25**%) and females were (146) **28.74**%.

Table 1: Categorization of subjects based on Gender

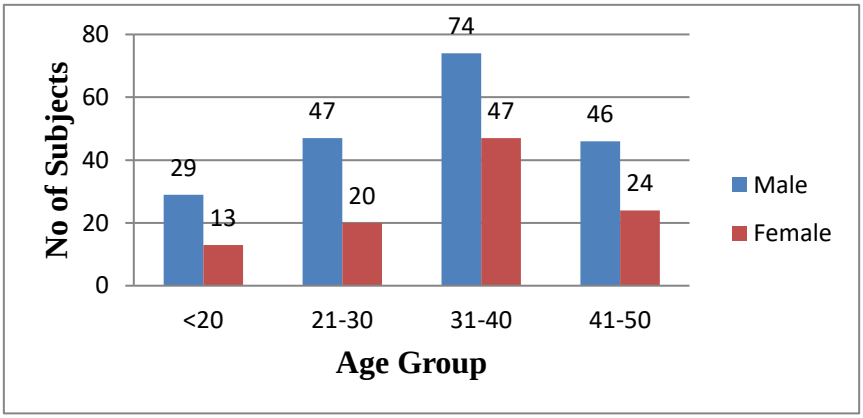
S. No	Gender	No. of subjects	Percentage (%)
1.	MALE	362	71.25
2.	FEMALE	146	28.74
3.	TOTAL	508	100

All the study subjects were categorized based on their age groups as represented in table 2, among them majority of the subjects were in the age group of 31-40 years with 35.23% followed by 41-50 years with 24.21%.

Table 2: Distribution of subjects based on age groups

S. No	Age group	Male	Female	Percentage (%)
1.	<20	69	23	18.11
2.	21-30	83	31	22.44
3.	31-40	121	58	35.23
4.	41-50	89	34	24.21
5.	TOTAL	362	146	100

Fig:1 Graphical Representation of Subjects based on age groups

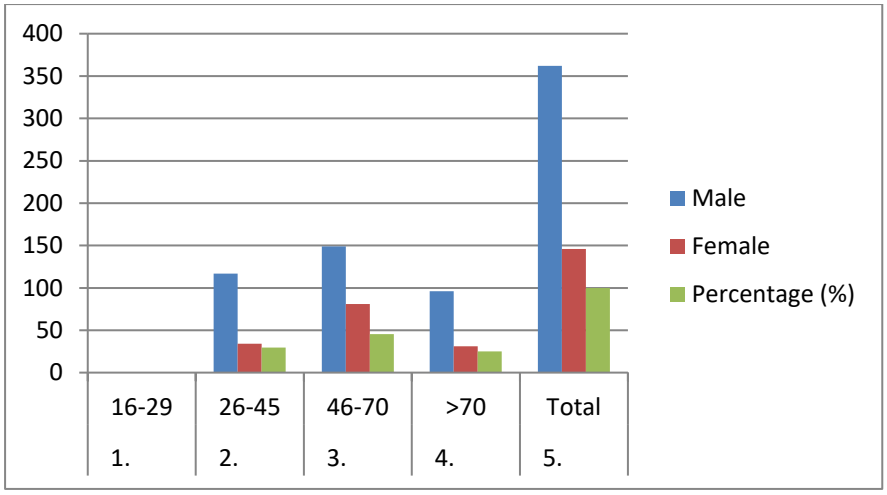


All the subjects were divided based on weight band into four categories as shown in the table 3 as the main stay in the treatment of tuberculosis is weight of the patient.

Table 3: Distribution of Subjects based on weight band

S. No	Weight (In Kg)	Male	Female	Percentage (%)
1.	16-29	00	00	00
2.	26-45	117	34	29.72
3.	46-70	149	81	45.27
4.	>70	96	31	25.00
5.	Total	362	146	100

Fig:2 Graphical Representation of Subjects based on weight band



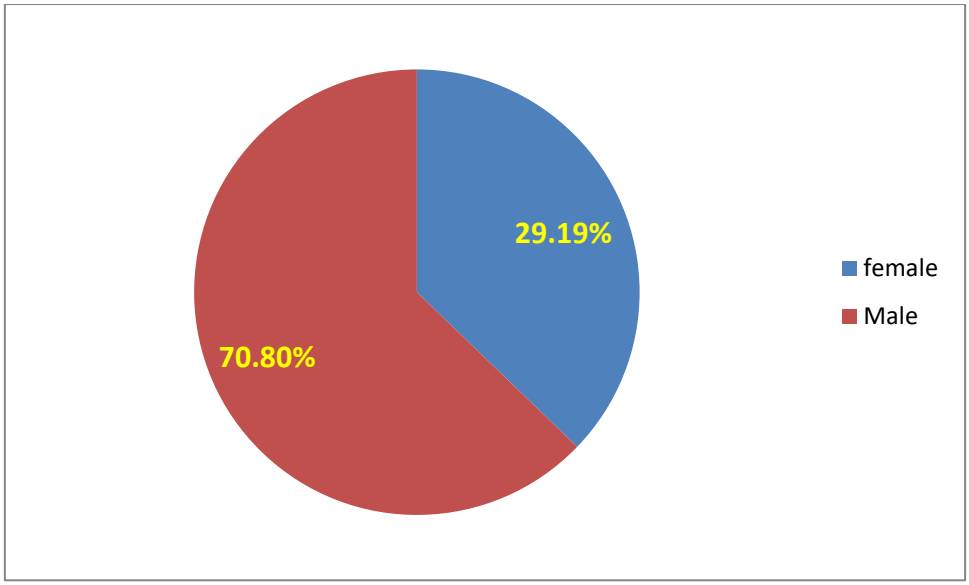
In the present study different subjects were categorized based on the educational status shown in the table 4.

A total of 161 members got 254 Adverse drug Reactions were observed during the study period, were 114(70.80%) of males and 48 (29.19%) females experienced ADRs.

Table 4: Distribution of adverse drug reactions based on gender

Gender	**Number of Subjects**	**Percentage (%)**
Male	114	70.80
Female	47	29.19
Total	161	100

Fig 3: Graphical Representation of Adverse drug reactions based on gender



In the present study ADRs experienced by different subjects were categorized based on the anatomical site affected as shown in the table 5. The most predominant system affected was gastro intestinal tract with 34.86%.

Table: 5 Drug Regimen

AGE	HRZE	M,K,Eto, L,H^h, Z,E	Bdq, L,Lzd, Cf,Cs, PAS, Dlm	TOTAL
<20	1	6	00	7
21-30	6	32	3	41
31-40	13	38	11	62
41-50	8	36	7	51
TOTAL	28	112	21	161

Table 6: Incidence of ADRs in patients of MDR and XDR-TB with different anti-tubercular regimen

S. NO	Age	Male		Female		MDR	XDR	Regimen and phases			ADR Number
		Exposure	NonExposure	Exposure	Non Exposure			IP	CP	All Oral	
1.	<20	6	62	01	22	91	00	11	27	0	07
2.	21-30	32	49	09	22	107	02	18	86	03	41
3.	31-40	41	78	21	37	172	08	34	153	11	62
4.	41-50	35	51	16	18	115	05	29	121	07	51
Total		**114**	**240**	**47**	**99**	**485**	**15**	**92**	**387**	**21**	**161**

Table 7: Frequency of individual ADRs noted during treatment of MDR and XDR-TB patient.

Type of ADR	No. of patients	Percentage (%)
GIT		
Gastrointestinal	74	29.13
Nausea, vomiting	51	20.07
Diarrhea	13	5.11
Hepatitis	07	2.75
Psychological Disorders		
Tinnitus +Vertigo	07	2.75
Insomina+Suicidal Tendencies	09	3.54
Depression	12	4.72
Altered behavior	15	5.90
Peripheral neuropathy	11	4.33

ENT		
Ototoxicity	11	4.33
Vision defect Impaired visual acuity	03	1.18
Skin		
Pruritus with rash	07	2.75
Pruritus without rash	08	3.14
Injection site pain and swelling	09	3.54
Renal		
Renal dysfunction Deranged RFT	02	0.78
Others		
Musculoskeletal Arthralgia	09	3.54
QT prolongation	06	2.36
Total	254	100

All the observed adverse drug reactions observed were assessed for causality assessment using Naranjo scale as shown in the table 6. As per the Naranjo scale in the present study only probable and possible ADRs were observed with possible ADR predominance of 57%.

Table:8 ADRs by different scale

Analysis of ADRs	No.of patients	Percentage
Causality assessment (WHO Scale)		

Certine	11	6.83
Propable	52	38.50
Possible	85	65.21
Unlikely	10	6.21
Unclassifed	2	1.24
Unclassifiable	1	0.62
Naranjo's Scale		
Definite	9	5.59
Probable	66	40.99
Possible	79	49.06
Doubtful	07	4.34
Severity assessment (Hartwig Scale and siegel Scale)		
Mild		
LEVEL 1	19	11.80
LEVEL 2	21	13.04
Moderate		
LEVEL 3	51	31.67
LEVEL 4	47	29.19
Severe		
LEVEL 5	15	9.31
LEVEL 6	04	2.48
LEVEL 7	04	2.48
Preventability Assessment (Schumock and Thomton Scale)		
Definitely Preventable	25	15.52
Probably Preventable	121	75.15
Not Preventable	15	9.31

DISCUSSION

The present observational study has evaluated a DOTS- Plus program, with special reference to Adverse Drug effects in which standard treatment of drug resistant tuberculosis

cases as per RNTCP (NTEP) guidelines has been started in this DR-TB Centre. In the present study of 508 patients, the age group ranged from 18 to 50 years. Maximum number of cases was in the age group 31-40 yrs (35.33%) followed by 41-50yrs (24.00%). The median age of the patients in present study was 31.83 years, as compared to the results published by the study conducted by (Edward *et al.*, 2000),[6] was 28 years and as per the study done in Russia by (Arora VK *et al.*, 2007) was reported as 26 years .[7]

In the present study, majority of the patients were males 362 (71.25%) and Females 146 (28.74%). similar findings with higher frequency were reported in this studies (males 65.33%and females 34.66%)(WHO, 2016)[2]. and proportion of males to females was 65.33% and 34.66% respectively(Arora VK *et al.*, 2007).[7]

In this study ADRs were observed in 31.69% patients, a finding comparable to present study reports notified in different studies. The ADR reported in present study were, Gastrointestinal, Ototoxicity, Injection site swelling/pain, Psychiatric manifestations, Arthralgia, Skin, Renal Involvement, Vision defect, peripheral neuropathy.

Gastro intestinal symptoms were most common adverse reaction observed in this study that is 74(29.13%) similar to other studies(Rohan *et al.*, 2014),[9] (KapadiaVishakha, K *et al.*, 2013),[11]. on the contrary other studies have found observed gastrointestinal ADRs in 42%, 60% and 100% patients respectively(Arora VK *et al.*, 2007) [7] R. Singla(R.Singla *et al.*, 2009),[8] (Abhijeet Singa *et al.*, 2019)[12] (JJ Furin et al, 2001),[13]. Hepatotoxicity was noted in 7(2.75%) patients only. Similarly findings were reported other studies (KapadiaVishakha, K *et al.*, 2013),[11] (JJ Furin et al, 2001),[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 11 (4.33%) was second most common ADR observed in this study of which decreased hearing 4 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 (WHO 1975)[2], (Kapadia Vishakha K *et al.*, 2013)[11] (Kalpesh Jain et al 2013)[14]. Singh R *et al* in 2007 reported ototoxicity in 5.92% patients (Abhijeet Singa *et al.*, 2019),[12]. Kanamycin was withdrawn in 80% of these patients and substituted with PAS (p- amino salicylic acid).

Psychiatric 43 (16.92%) 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 %.(Arora VK *et al.*, 2007)[7] and 15% (Bloss E st al2010).[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 9 (3.54%) 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 9 (3.54%) was fifth common ADR observed in this study. Similar observation was seen in 4.5% and 7.94% respectively. (Rohan *et al.,* 2014),[9,] (Kapadia Vishakha K *et al.,* 2013)[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 7 (2.75%) of which pruritus without rash in and pruritus with rash in 8 (3.14%) patient. Frequency of skin reaction found in this study is similar 4%, 1.58% and 4.5%.(Arora VK *et al.,* 2007)[7](Kapadia Vishakha K *et al.,* 2013)[11] (Torun T et al 2005)[16] On the one of the study reported cutaneous reactions in 43.3% patients (JJ Furin et al, 2001)[13].

Renal involvement was seen 2(0.78%) patients in this study which is our findings are consistent with the studies reporting other studies 1.58%, 2.7% and 2% respectively. (Rohan *et al.,* 2014),[9] (Kapadia Vishakha K *et al.,* 2013),[11] (Abhijeet Singa *et al.,* 2019)[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 3 (1.18%), Peripheral Neuropathy 11(4.33%). our findings seen in a study with frequency of visual disturbance 1(0.9%) and peripheral neuropathy 11 (3.87%) (Rohan *et al.,* 2014),[9].

In present study Causality assessment of 161 members got 254 ADRs was done by Naranjo's Causality Scale, According to the Naranjo's scale, the causality assessment was done and it was observed that among the 161 cases, 9(5.59) were observed to be definite, 79 (53.55) were observed to be possible ADRs 85 (46.44%) were observed to be probable ADRs and where as the remaining 7(4.34) were observed to be doubtful ADRs.. The distribution of 254 ADRs as Mild 24.84%, moderate 60.86% and sever 14.05%, as the study population the patients was hospitalized for ADRs, higher number of ADRs belonged to "Moderate "grade.

Conclusion

ADRs were extremely common in the current study, however the majority of them were handled with little success using pharmacological, nonpharmacological, and psychological techniques mediated by clinical pharmacist changes to the treatment strategy was done. Our study showed that the prevalence of GI adverse effects, psychosis were more

common and could be controlled symptomatically. The majority of ADRs was mild, avoidable, and may have been related to the implicated medicines. Although ADRs were commonly reported, the majority of patients continued their therapy by either stopping the offending medication or receiving supportive care, as we were able to see in our study.

In order to resolve the problem and assist in improving patient compliance, which enables them to tolerate adverse effects, resulting in a decrease in the default rate, routinely monitoring the predictability of ADRs with pertinent clinical parameters and close attention to patient complaints are both necessary.

It emphasizes the significance of tailored and ongoing monitoring during the course of therapy among MDR and XDR tuberculosis patients.

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