Original Article

Ambispective study of adverse drug reactions in multi-drug resistant tuberculosis patients in Warangal, Telangana

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) has become a global threat concerning to a risk of high mortality with the potential to cause adverse drug reactions (ADRs) which if not managed properly may affect patient compliance, resulting in below par treatment outcome. **Aim:** The aim of the study was to study, assess, and report the ADRs of patients diagnosed with MDR-TB. **Subjects and Methods:** An ambispective, observational study was conducted among confirmed cases of MDR-TB patients without any comorbidities during the period of January 2015–December 2018 in patients of age 15 years and above. **Statistical Analysis:** Data were analyzed descriptively using MS-Excel sheet 2013 and Chi-square test in GraphPad Prism 8.2.1. Results were expressed as either frequency, percentage, or mean ± standard deviation. ADRs were evaluated for causality, severity, and preventability attributes. **Results:** In the sample size of 400 patients, 236 (ADRs) were reported among 136 patients. The proportion of ADRs was higher in males ($P = 0.0001$) and in the age group of 36–75 years ($P = 0.0211$). Most commonly encountered ADRs include nausea and vomiting (35.31%) and arthralgia (14.04%), followed by peripheral neuropathy (8.93%) and giddiness (8.93%). Overall, 53% were of possible category and 60% of moderate level severity and 85% were unpreventable ADRs. **Conclusion:** Our study included 13 types of ADRs, of which most commonly reported were nausea and vomiting, arthralgia, and peripheral neuropathy and least common were psychosis, nephrotoxicity, and gynecomastia with a higher incidence in males. Majority of ADRs were moderate, unpreventable ADRs and had a possible relationship with the suspected drugs.

KEY WORDS: Adverse drug reaction, Causality, multidrug resistant tuberculosis, preventability assessment, severity

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INTRODUCTION

Antimicrobial resistance has become a topical health and security concern for countries worldwide. In the course of previous years, it has become increasingly clear that global efforts to end tuberculosis (TB) will continue to face a major challenge with the widespread dissemination of TB strains that are resistant to the medicines used in its treatment.[1] India (24%) is responsible for almost half of the world's cases of multidrug-resistant TB (MDR-TB).[2] Drug-resistant TB has been known from the time anti-TB drugs were first introduced for the treatment of TB. Currently, the World Health Organization estimated the incidence of MDR TB

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in India is estimated to be around 147,000. This translates to around 11 patients/100,000 population annually as per the global TB report 2017.[3] Treatment of MDR TB requires the use of second-line antitubercular drugs which are given for a longer duration.[4] In this study, we tend to report the occurrence of adverse drug reactions (ADRs) encountered throughout MDR-TB treatment. A standardized category four (CAT IV) regimen implemented by the Revised National TB Control Programme (RNTCP) is followed. ADRs usually associated with the second-line anti-TB drugs have a severe impact on adherence to treatment. As it is the key to the successful outcome, identification and early management of ADRs play a major role in MDR-TB management.[5] The study aims to (i) obtain patients' demographic details; (ii) measure frequency, type, and reporting of ADRs; (iii) evaluate programmatic management of adverse reactions using programmatic management of drug-resistant TB guidelines, and (iv) to assess causality, severity, and preventability of adverse reactions during treatment.

SUBJECTS AND METHODS

Study design

A prospective, observational study was conducted among patients admitted during the period of January 2015–December 2018 in the nodal drug-resistant TB Centre. MDR TB diagnosed patients of age 15 years and above, without any other comorbidities and having all pretreatment investigations as normal were included in the study. Patients under 15 years of age, pregnant women, or presenting with any other comorbidities and HIV-positive patients were excluded from the study. The study was approved by the institutional ethics committee.

Data collection

The required patient-specific data were collected from patient's case sheets including sociodemographic data (age, gender, and weight), MDR-TB details (new cases and defaulter), diagnostic details, detailed treatment information and duration of therapy, investigations such as complete blood count, liver function tests, thyroid profile, renal function tests, etc.

The required data for ADRs were collected from the patient case sheets as well as from the patients and their caretakers and were entered in the designed ADR reporting form, which includes various details such as demographic details, disease characteristics, date and type of reaction, medication history, and other relevant information.

As per RNTCP guidelines, intensive phase of CAT IV regimen includes six drugs kanamycin (Km), levofloxacin (Lfx), ethionamide (Eto), ethambutol (E), pyrazinamide (Z), and cycloserine (Cs) and continued for a duration of 6–8 months. These drugs are to be taken daily except kilometer which is to be taken 6 days/week. Whereas, continuation phase includes four drugs (Lfx, Eto, E, and Cs) taken for 18 months. Para-aminosalicylic acid (PAS) is a reserved drug which replaces the offending drug in patients who develops ADR. The patients of MDR-TB are treated according to their weight bands.[2,5]

Collected data were analyzed using MS-Excel sheet 2013 and Chi-square test in GraphPad Prism 8.2.1, GraphPad Software Inc., San Diego, California, United States Of America.

RESULTS

In this study, out of 400 patients, 182 were in the age group of 18–35 years; 218 were in the age group of 36–75 years. Thus, most patients were in the age group of 36–75 years. Nearly 76% (304) were males and females were (96) 24%; with a mean age of 40.32 ± 14.17 years and mean weight of 40.05 ± 7.66 kg at starting of the study. We can conclude that patients of age group of 6–75 years had higher proportion of ADRs than other age group (62.50% vs. 37.50%, $P = 0.0211$) and proportion of ADRs among males was higher than females (77.94% vs. 22.06%, $P = 0.0001$).

As mentioned in Table 1, in a total of 400 patients, 76% (304) were males and females were (96) 24%. Gender-wise distribution of MDR-TB patients is illustrated in Figure 1.

Out of 400 patients, 45% (182) belonged to the age group of 18–35 years and 55% (218) belonged to the age group of 36–75 years with a mean age of 40.32 ± 14.17 years at starting of the study as illustrated in Figure 2.

Among 400 patients, 2.75% (11) belonged to the weight band 16–25 kg, 78% (312) patients belonged to the weight band 26–45 kg, and 19% (77) belonged to the weight band 46–70 kg as illustrated in Figure 3.

Prevalence of ADRs among gender, age, and weight bands is illustrated in Figure 4.

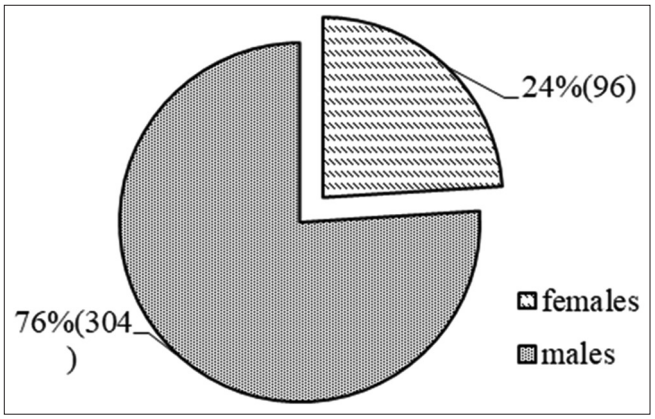

Figure 1: Gender wise distribution of multi-drug resistant tuberculosis patients

Table 1: Year-wise distribution of demographic details of patients with multidrug resistant tuberculosis

	Age group (years)		Sex		Weight band (kg)		
	18-35	36-75	Male	Female	16-25	26-45	46-70
With ADRs							
2015	18	34	41	11	-	43	9
2016	7	17	19	5	2	18	4
2017	20	31	41	10	1	39	11
2018*	6	3	5	4	1	8	-
Total (*n*=136), *n* (%)	51 (37.5)	85 (62.5)	106 (77.94)	30 (22.05)	4 (2.65)	108 (77.27)	24 (17.64)
Without ADRs							
2015	39	40	20	59	2	58	19
2016	59	50	30	79	4	85	20
2017	15	20	8	27	-	25	10
2018*	18	23	8	33	1	36	4
Total (*n*=264), *n* (%)	131 (49.62)	133 (50.37)	66 (25)	198 (75)	7 (2.75)	204 (78)	53 (20.07)

*Weight bands were changed in the PMDT guidelines 2017 hence from 2018 (16-29 kg) and (30-45 kg) is followed. ADRs: Adverse drug reaction, PMDT: Programmatic management of drug-resistant tuberculosis

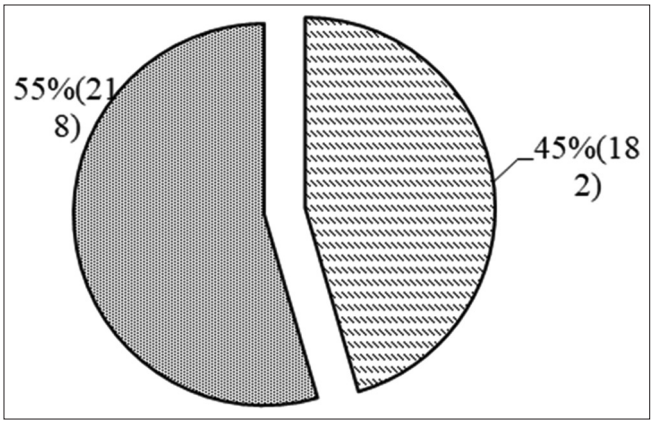

Figure 2: Age wise distribution of multi-drug resistant tuberculosis patients

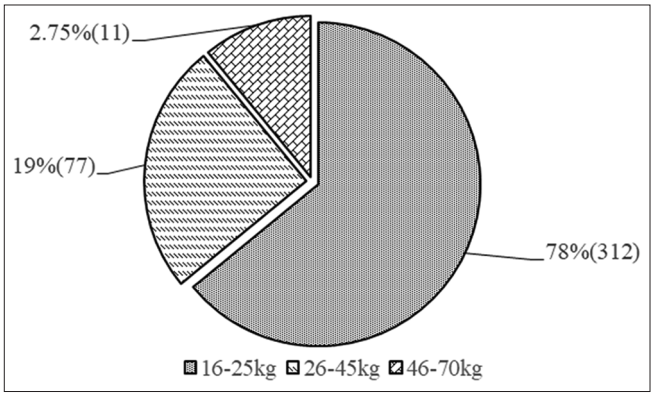

Figure 3: Weight band distribution of multi-drug resistant tuberculosis patients

The most frequently occurring ADRs were seen among males (183) as shown below in Table 2.

As mentioned below in Table 3, the most frequently occurring ADRs were seen in the age group of 36–75 years. The most frequently occurring ADRs were seen in the weight band 26–45 kg as shown below in Table 4.

ADRs encountered in patients were managed symptomatically, and in severe cases, the offending drug was replaced. In patients suffering from gastrointestinal symptoms such as nausea, vomiting, and severe gastritis, proton pump inhibitors were administered as symptomatic treatment.

Arthralgia, a musculoskeletal system-related ADR, was mostly encountered with the drugs pyrazinamide and Lfx and was symptomatically treated with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

In few patients suffering from dermatological ADRs such as acne vulgaris and dermatitis, the offending drug Eto and Lfx were replaced with PAS, respectively, and others were treated with antihistamines.

Eto being the offending drug in patients suffering from peripheral neuropathy; tablet pyridoxine 100 mg was given 6 days/week.

Cs, the offending drug causing psychosis was stopped in two patients and was replaced with T. PAS granules in two patients.

Patients suffering from hypothyroidism were symptomatically treated with T. Eltroxin 50 mcg/PO/OD, and thyroid profiles were checked at regular intervals.

In patients suffering from gynecomastia, the suspected drug Eto was replaced with PAS granules.

Nephrotoxicity was not frequently reported; however, the suspected drug Km was replaced with PAS in one patient, and the same treatment was continued with symptomatic treatment in others.

Vestibular toxicities were treated by administering tablet vertin 8 mg/PO/TID in case of Tinnitus and mild hearing loss and in cases of ototoxicity dose of the offending drug Km was decreased.

Table 2: Gender wise prevalence of various adverse drug reactions

ADRs	Gender	
	Male, *n* (%)	Female, *n* (%)
Gastrointestinal symptoms		
Nausea and vomiting	20 (37.73)	63 (34.42)
Severe gastritis	9 (16.98)	10 (5.46)
Musculoskeletal disorders		
Arthralgia	5 (9.43)	28 (15.30)
Skin and subcutaneous tissue disorders		
Acne vulgaris	4 (7.54)	9 (4.91)
Dermatitis	2 (3.77)	5 (2.73)
Central nervous systems disorders		
Peripheral neuropathy	2 (3.77)	19 (10.38)
Giddiness	6 (11.32)	15 (8.19)
Endocrine disorders		
Hypothyroidism	1 (1.88)	6 (3.27)
Gynaecomastia	0	3 (1.63)
Psychiatric disorders		
Psychosis	0	4 (2.18)
Renal toxicity		
Nephrotoxicity	0	3 (1.63)
Vestibular toxicities		
Ototoxicity	1 (1.88)	5 (2.73)
Tinnitus and mild hearing loss	3 (5.66)	13 (7.10)
Total (*n*)	53	183

n=236. ADRs: Adverse drug reaction

Table 3: Age-wise prevalence of adverse drug reactions

ADRs	Age groups (years)	
	18-35	18-35
Gastrointestinal symptoms		
Nausea and vomiting	35 (39.32)	48 (32.65)
Severe gastritis	12 (13.48)	7 (4.76)
Musculoskeletal disorders		
Arthralgia	1 (1.12)	32 (21.76)
Skin and subcutaneous tissue disorders		
Acne vulgaris	12 (13.48)	1 (0.68)
Dermatitis	1 (1.12)	6 (4.08)
Central nervous systems disorders		
Peripheral neuropathy	0	21 (14.28)
Giddiness	14 (15.73)	7 (4.76)
Endocrine disorders		
Hypothyroidism	5 (5.61)	2 (1.36)
Gynecomastia	1 (1.12)	2 (1.36)
Psychiatric disorders		
Psychosis	4 (4.49)	0
Renal toxicity		
Nephrotoxicity	1 (1.12)	2 (1.36)
Vestibular toxicities		
Ototoxicity	0	6 (4.08)
Tinnitus and mild hearing loss	3 (3.37)	13 (8.84)
Total (*n*)	89	147

n=236. ADRs: Adverse drug reaction

As stated below in Table 5, the frequency of occurrence of at least 1 ADR was higher in all the groups of age, sex, and weight band.

Table 6 shows the distribution of ADRs during treatment. The most common side effect reported by the end of the 6th month was nausea and vomiting, followed by other common side effects including severe gastritis, giddiness and tinnitus, and mild hearing loss. The higher incidence

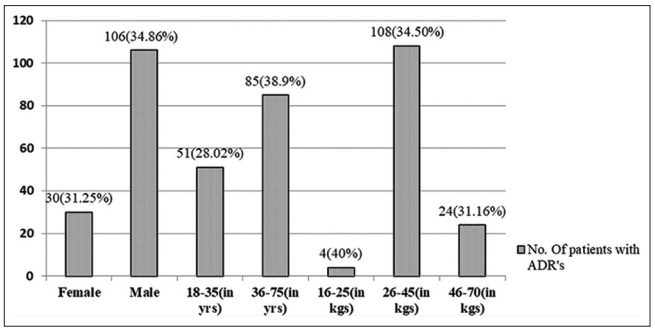

Figure 4: Prevalence of adverse drug reactions

of ADRs at the end of the 6th month of therapy was seen in males. The most common side effect reported by the end of the 12th month was nausea and vomiting, followed by other common side effects including arthralgia and peripheral neuropathy. The higher incidence of ADRs at the end of the 12th month of therapy was seen in males. The most common side effect reported by the end of the 24th month was nausea and vomiting followed by severe gastritis in females and arthralgia, tinnitus, and mild hearing loss in males.

Causality Assessment of each ADR (n = 236) according to Naranjo's Scale[6] was identified as 29 ADRs (12.28%) as "definite" ADRs, 82 ADRs (34.74%) as "Probable" ADRs, and 125 ADRs (52.96%) as "Possible" ADRs as mentioned in Table 7.

According to Modified Hartwig and Seigel severity scale,[7] Out of 236 ADRs, four were classified as mild level 1 ADRs, 58 were classified as mild level 2 ADRs; 36 were classified as moderate level 3 ADRs, 56 were classified as moderate level 4a ADRs, fifty were classified as moderate level 4b ADRs; 22 were classified as severe level 5 ADRs, and 10 were classified as severe level 6 ADRs.

According to Schumock and Thornton preventability scale,[8] 36 ADRs (15.25%) were classified as "Preventable" ADRs and 200 ADRs (84.74%) were classified as "Unpreventable" ADRs as mentioned in Table 8.

DISCUSSION

MDR-TB is an increasing worldwide concern, with most cases arising from a combination of physician error and patient noncompliance throughout the treatment of susceptible TB.

In total, 400 MDR-TB cases with no comorbidities were included from the registered cases at district TB center from the year January 2015 to December 2018. The mean age of patients was 40.32 years among which 76% (304) were males and females were (96) 24%.

In our study, 136 (34%) patients developed at least one treatment-related ADR and were hospitalized for the same

Table 4: Weight-band wise prevalence of various adverse drug reactions

ADRs	Weight bands (kg)		
	16-25, *n* (%)	26-45, *n* (%)	46-70, *n* (%)
Gastrointestinal symptoms			
Nausea and vomiting	1 (20)	63 (33.87)	19 (42.22)
Severe gastritis	1 (20)	15 (8.06)	3 (6.66)
Musculoskeletal disorders			
Arthralgia	0	29 (15.59)	4 (8.88)
Skin and subcutaneous tissue disorders			
Acne vulgaris	1 (20)	9 (4.83)	3 (6.66)
Dermatitis	1 (20)	6 (3.22)	0
Central nervous systems disorders			
Peripheral neuropathy	0	19 (10.21)	2 (4.44)
Giddiness	0	13 (6.98)	8 (17.77)
Endocrine disorders			
Hypothyroidism	0	4 (2.15)	3 (6.66)
Gynecomastia	0	3 (1.61)	0
Psychiatric disorders			
Psychosis	0	2 (1.07)	2 (4.44)
Renal toxicity			
Nephrotoxicity	0	3 (1.61)	0
Vestibular toxicities			
Ototoxicity	1 (20)	5 (2.68)	0
Tinnitus and mild hearing loss	0	15 (8.06)	1 (2.22)
Total (*n*)	5	186	45

n=236. ADRs: Adverse drug reaction

Table 5: Frequency of the occurrence of adverse drug reactions in multi-drug resistant tuberculosis patients during the course of therapy

	18-35 (years)	36-75 (years)	Female	Male	16-25 (kg)	26-45 (kg)	46-70 (kg)
At least 1 ADR, *n* (%)	23 (45.09)	43 (50.58)	15 (50)	51 (48.11)	3 (75)	53 (49.07)	10 (41.66)
At least 2 ADR's, *n* (%)	19 (37.25)	25 (29.41)	8 (26.66)	36 (33.96)	1 (25)	36 (33.33)	7 (29.16)
At least ≥3 ADR's, *n* (%)	9 (17.64)	17 (20)	7 (23.33)	19 (17.92)	0	19 (17.59)	7 (29.26)
Total (*n*)	51	85	30	106	4	108	24

n=136. ADRs: Adverse drug reaction

Table 6: Distribution of adverse drug reactions experienced after the start of therapy

	Frequency, *n* (%)		
	After 6 months of therapy	After 12 months of therapy	After 24 months of therapy
Gastrointestinal symptoms			
Nausea and vomiting	20 (30.76)	57 (39.86)	6 (21.42)
Severe gastritis	8 (12.30)	6 (4.19)	5 (17.85)
Musculoskeletal disorders			
Arthralgia	3 (4.61)	25 (17.48)	5 (17.85)
Skin and subcutaneous tissue disorders			
Acne vulgaris	4 (6.15)	7 (4.89)	2 (7.14)
Dermatitis	3 (4.61)	4 (2.79)	0
Central nervous systems disorders			
Peripheral neuropathy	5 (7.69)	13 (9.09)	3 (10.71)
Giddiness	7 (10.76)	14 (9.79)	0
Endocrine disorders			
Hypothyroidism	4 (6.15)	3 (2.09)	0
Gynaecomastia	2 (3.07)	1 (0.69)	0
Psychiatric disorders			
Psychosis	2 (3.07)	2 (1.39)	0
Renal toxicity			
Nephrotoxicity	0	3 (2.09)	0
Vestibular toxicities			
Ototoxicity	0	3 (2.09)	3 (10.71)
Tinnitus and mild hearing loss	7 (10.76)	5 (3.49)	4 (14.28)
Total (*n*)	65	143	28

ADRs: Adverse drug reaction

which was similar to the study conducted by Rathod *et al*.,[9] as compared to Hire *et al*. (50%) and Törün *et al*. (69.2%).[10,11] Whereas 264 (66%) cases were not associated with ADR. The demographic characteristics of patients receiving treatment

Table 7: Causality assessment and severity assessment of adverse drug reactions

ADR (*n*=236)	Naranjo Scale[7]			Modified Hartwig and Siegel Scale[8]		
	Definite	Probable	Possible	Mild	Moderate	Severe
Acne vulgaris	8	3	2	0	13	0
Arthralgia	0	18	15	7	23	3
Dermatitis	3	4	0	0	7	0
Giddiness	0	9	12	3	16	2
Gynecomastia	3	0	0	0	3	0
Hypothyroidism	7	0	0	0	7	0
Nausea and vomiting	0	27	56	38	36	9
Nephrotoxicity	0	0	3	0	0	3
Ototoxicity	3	3	0	3	2	1
Peripheral neuropathy	0	8	13	3	13	5
Psychosis	4	0	0	0	0	4
Severe gastritis	0	5	14	6	10	3
Tinnitus and mild hearing loss	1	5	10	2	12	2
Total, *n* (%)	29 (12.28)	82 (34.74)	125 (52.96)	62 (26.27)	142 (60.16)	32 (13.55)

ADRs: Adverse drug reaction

Table 8: Schumock and thornton preventability assessment (*n*=236)[9]

Preventability	*n* (%)
Preventable ADR	36 (15.25)
Unpreventable ADR	200 (84.74)

ADRs: Adverse drug reaction

for MDR-TB [Table 1] in the present study were comparable to the previous study conducted by Dela *et al*.[4]

In this study, the majority of patients were within the age group of 36–75 years with a mean age of 40.32 ± 14.17 years which was in assistance to the study by Dela *et al*.,[4] who reported similar results.

The individualized regimen was used as per RNTCP which included pyrazinamide (Z), ethambutol (E), parenteral aminoglycosides (Km), fluoroquinolones (Lfx), Eto, and Cs. Most frequently reported ADRs were GI side effects, joint pain, and weakness. Same sets of ADRs were also reported in a study done by Kapadia *et al*., Hoa *et al*., Akshata *et al*., and Shinde *et al*.[12-15]

This study shows that side effects of drugs used in the treatment of MDR TB reported by patients were nausea and vomiting (35.16%), arthralgia (13.98%), giddiness (8.89%), peripheral neuropathy (8.89%), gastritis (8.05%), tinnitus and mild hearing loss (6.77%), and acne vulgaris (5.50%). This finding is consistent with the findings of Törün *et al*. and Bhatt *et al*.[11,16]

In our study, the first most common ADR reported was nausea and vomiting 83 (35.16%) similar to the study by Bloss *et al*.,[17] and the suspected oral drugs which may cause gastrointestinal upset include fluoroquinolones, pyrazinamide, Eto, and PAS. For the management of this ADR, proton pump inhibitors were administered symptomatically.[18-21]

Arthralgia 33 (13.98%) was the second most common ADR reported according to our study. This is mostly encountered with the drugs pyrazinamide and Lfx and is symptomatically treated with the administration of NSAIDs.[18-21]

Giddiness 21 (8.89%) was the thirst most common reported ADR affecting the Otovestibular system. Km is the offending drug causing this ADR which was symptomatically treated.[18-21]

For the patients with complaints of peripheral neuropathy 21 (8.89%), Eto being the offending drug; T. Pyridoxine 100 mg was given 6 days/week.[18-21]

Severe gastritis 19 (8.05%) was the fifth most common ADR reported in our study which was caused due to drugs Lfx and Eto treated by administering proton pump inhibitors and antacids.[18-21]

In contrast to the study of Patel *et al*.,[22] Km is the suspected drug to cause tinnitus and mild hearing loss 16 (6.77%), for which tablet vertin 8 mg/PO/OD was given for $n = 16$ patients and the dose of Km was reduced in one patient[18-21] which is in contrast to the study of Patel *et al*.[22] and Arora *et al*.[23] where the offending drug was either stopped or replaced with PAS.

Dermatological ADRs such as acne vulgaris 13 (5.50%) and dermatitis 7 (2.96%) were also reported with the use of drugs Eto and Lfx, respectively. The offending drug Eto was replaced with PAS granules ($n = 4$) and Lfx was replaced with PAS ($n = 1$).[18-21] Dermatological ADRs rank first which required the withdrawal of the offending drug.

Hypothyroidism 7 (2.96%) was reported less frequently similar to the study conducted by Akshata *et al*.[14] which may be because of under diagnosis since thyroid profiles are checked at baseline and only on clinical suspicion. Symptomatically, T. Eltroxin 50 mcg/PO/OD was prescribed, and thyroid profiles were checked at regular intervals.[18-21]

Ototoxicity 6 (2.54%) is one of the irreversible ADRs reported with MDR therapy which requires discontinuation of the offending drug Km. However, in our study, Km dose was decreased in $n = 1$ patient, and the same regimen was continued in others ($n = 5$).[18-21]

Gynecomastia 3 (1.27%) was another ADR reported not so frequently and the suspected drug Eto was replaced with PAS granules.[18-21]

Nephrotoxicity 3 (1.27%) was not frequently reported compared to ototoxicity, similar to the study conducted by Törün *et al*.,[11] and the suspected drug Km was replaced with PAS in $n = 1$ patient and the same treatment was continued with symptomatic treatment in others ($n = 5$).[18-21]

Psychosis (1.69%) was reported in four patients, among which capsule Cs was stopped in two (50%) patients and was capsule Cs was replaced with T. PAS granules in 2 (50%) patients.[18-21]

The total number of ADRs shown by 400 patients was 236, at least one ADR was reported in 67 (49.26%) patients, at least two ADRs were reported in 44 (32.35%) patients, and more than two ADRs were reported in 26 (19.11%) patients. A similar comparison was done in his study by Hire *et al*.[10]

In addition, ADRs were reported through real-time spontaneous reporting system by a physician in a study conducted by Shinde *et al*.[15] Whereas, in the present study, data of only patients hospitalized for a complaint of ADRs were gathered which could have resulted in underreporting of minor ADRs in some patients.

The most common side effect reported by the end of the 6th month was nausea and vomiting, followed by severe gastritis, giddiness and tinnitus, and mild hearing loss. The higher incidence of ADRs at the end of the 6th month of therapy was seen in Males. The most common side effect reported by the end of the 12th month was nausea and vomiting, followed by arthralgia and peripheral neuropathy. The higher incidence of ADRs at the end of the 12th month of therapy was seen in males. The most common side effect reported by the end of the 24th month was nausea and vomiting followed by severe gastritis in females and arthralgia, tinnitus, and mild hearing loss in males. These studies were in assistance with the findings of Törün *et al*.[11] and Patel *et al*.[22]

Causality assessment of all ADRs was done using Naranjo's causality assessment scale, 29 ADRs (12.28%) as "definite" ADRs. Definite ADRs were 32 in total including ototoxicity (3), psychosis (4), tinnitus (1/16), dermatitis (3), hypothyroidism (7), acne (8), gynecomastia (3), and nephrotoxicity (3). Rest of the ADRs were classified as 82 ADRs (34.74%) as "Probable" ADRs and 125 ADRs (52.96%) as "Possible" ADRs which was conflicting to the study conducted by Shinde *et al*.[15] and Hire *et al*.[10]

Modified Hartwig's and Seigel scale was used for understanding the severity of the ADRs where ADRs are classified as 62 (26.27%) were classified as "Mild" ADRs, 142 (60.16%) were classified as "moderate" ADRs, 32 (13.55%) were classified as "severe" ADRs which were comparable with the studies of Dela *et al*.,[4] Hao *et al*.,[13] and Hire *et al*.[10]. Severe ADRs include nausea and vomiting (9/83), severe gastritis (3/19), nephrotoxicity (3), psychosis (4), arthralgia (3/33), ototoxicity (1), tinnitus (2), giddiness (2), and peripheral neuropathy (5/21).

On doing Schumock and Thornton Preventability assessment, 36 ADRs (15.25%) were "Preventable" ADRs and 200 ADRs (84.74%) were "Unpreventable" ADRs.

Our study highlights the importance of careful monitoring and timely management of adverse events in a large population for a period of 4 years which helps to evaluate the incidence of ADRs associated with MDR-TB regimen efficiently since long-term follow-up of the patients was possible.

Limitations

Since it's both retrospective and prospective study, this may lead to documentation errors and reporting bias since the physician is responsible for documenting ADRs. Under diagnosis of some ADRs is possible since clinical data were obtained only on physician suspicion and laboratory tests were not frequently repeated unless suspected.

CONCLUSION

Our study showed that the prevalence of mild ADRs such as GI adverse effects could be managed symptomatically and major adverse effects such as ototoxicity, psychosis, and nephrotoxicity in few cases required a slight change in therapy. Majority of ADRs were moderate, unpreventable ADRs and had a possible relationship with the suspected drugs. As we could observe in our study, although ADRs were reported routinely, the majority continued the treatment with either supportive treatment or discontinuation of the offending medication. Hence, routinely monitoring the predictability of ADRs with relevant clinical parameters and close watch on patient complaints can cease the issue and help improving patient's compliance which enables them to tolerate adverse effects, resulting in a drop of the default rate.

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Conflicts of interest

There are no conflicts of interest.

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