A study on incidence of adverse drug reactions of current multidrug resistant pulmonary tuberculosis treatment regimen at a tertiary care centre in kumaon region of Uttarakhand

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Abstract
Background: Treatment of multidrug resistant pulmonary tuberculosis (MDR-PTB) is challenging because of multiple anti-TB drugs, long treatment duration and various adverse drug reactions (ADRs). The aim of this study was to find the incidence of ADRs related to various anti-TB drugs. **Methods:** This was a prospective observational study done from 1st January 2019 to 30th June 2020, in the Department of Respiratory Medicine at Government Medical College, Haldwani, Uttarakhand. **Results:** A total of 163 MDR-PTB patients were reviewed, of which 136 (83.44%) patients experienced >1 ADRs, during intensive phase of treatment. Total 398 ADR episodes were observed, maximum ADRs (134, 33.7%) were related to Gastrointestinal system. Incidence of ADRs was more (96.97%) in 46-60 yrs. of age group, in patients living in rural area (82 of 92, 89%), in married patients (88.07%), in smokers (91.4%), in alcoholics (90.6%), in patients having co-morbidities and in patients who had anemia (88.24%). The most common ADR was joint pain in 36 (26.5%) of 136 patients. **Conclusion:** Strict follow-up with laboratory investigations, providing assurance and exercise plan to the patients is crucial. Healthcare providers should be trained regarding identification and management of ADRs.
Keywords: Incidence, Adverse drug reactions (ADRs), Multidrug resistant pulmonary tuberculosis (MDR-PTB)

Introduction

Drug resistant tuberculosis (DR-TB) has become a problem in high TB countries including India. The most common cause of drug-resistant tuberculosis is undoubtedly the lack of a properly organized system to ensure effective treatment, and particularly the lack of effectively implemented directly observed treatment. The estimated incidence of Multidrug resistant tuberculosis (MDR-TB) / Rifampicin resistant tuberculosis (RR-TB) in India in 2018 was around 1,30,000 highest in the world [1].

MDR-TB is defined as a TB case whose biological specimen is resistant to both isoniazid and rifampicin with or without resistance to other first line drugs based on result from quality assured laboratory [2]. For treatment of RR-/MDR-TB, there are various treatment regimens. Conventional MDR-TB treatment regimen [3] includes six anti-tubercular drugs (Lfx Km Eto Cs Z E) in intensive phase of 6-9 months duration and four anti-tubercular drugs (Lfx Eto Cs E) in

continuation phase of 18 months duration with total duration of 24-27 months. Adherence to therapy in the first six months of treatment is crucial in the management of MDR-TB, as many anti-TB drugs are potentially toxic and have several ADRs, treatment may be terminated prematurely, resulting in a high proportion of failure and in some cases death of the patient.

This study will therefore be undertaken to assess the incidence of ADRs of conventional MDR- PTB regimen drugs during the crucial first six months of treatment.

Materials and methods

Study design
Hospital Based prospective observational study.

Study setting
Department of Respiratory Medicine, Government Medical College, Haldwani, Uttarakhand.

Study duration
From 1st January 2019 to 30th September 2020

Sample size
All newly registered 163 MDR-PTB patients enrolled at PMDT centre of Department of Respiratory Medicine of Dr. Susheela Tiwari Government Hospital, Haldwani between 1st January 2019 to 31st December 2019.

Inclusion criteria
1. All CBNAAT/ LPA confirmed newly registered MDR-PTB patients.
2. 18 years of age or older.

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3.   All MDR PTB-HIV co-infected patients.

Exclusion criteria
1.   Age less than 18 yrs.
2.   Patients receiving CAT I and CAT II anti tubercular treatment, extensively drug-resistant (XDR) cases.
3.   Patients who did out give consent for the interview.
4.   Pregnant women.

Prior to data collection, ethical clearance was sought from the Ethical Committee, Government Medical College, Haldwani.

A written consent was taken from all potentially eligible subjects and subjects were excluded from the study if they were not matched with Package for Social Sciences) version 16.0 statistical software was used for data analysis. P- value of < 0.05 was considered statistically significant.

inclusion criteria of the study. There were three patients who were HIV reactive and they did not give consent, thus excluded from the study. Information from the participants was collected by in-depth interview using pre-designed, pre- tested semi-structured questionnaire. Patients recruited in the study were admitted in MDR-TB wards and conventional MDR-PTB treatment regimen was started according to weight band of each patient. Patients were monitored clinically and biochemically for any ADR.

Patients who express their inability to come for monthly follow up was interviewed telephonically for any ADR and their responses were documented. All filled questionnaires were entered as data into the computer using Microsoft Excel 2007 and SPSS (Statistical

Results
Out of total MDR-PTB 163 patients, 136 (83.44%) patients experienced one or more ADRs during intensive phase of treatment. Total 398 ADR episodes were observed. Of these 136 patients, maximum 51 (31.3%) patients had 4 ADRs, as shown in Table 2.

Table 1: Number of ADRs among total patients

Number of ADRs	tal number of patients (n =163)	Percentage (%)
0	27	16.56 %
1	15	9.20 %
2	31	19.02 %
3	39	23.93 %
4	51	31.3 %

Out of total 398 ADR episodes in 136 patients, maximum number of ADR episodes 209 (52%) were observed in 131 (96.3%) MDR-PTB patients within first 30 days of initiation of intensive phase of treatment, as shown in Table 3.

Table 2 : Duration of onset of ADRs from initiation of intensive phase of treatment

Duration of onset of ADRs	ber of ADR episodes (n=398)	mber of patients* (n=136)
0 – 7 days	83 (20.85%)	73 (53.7%)
8 – 30 days	126 (31.66%)	96 (70.6%)
31 – 60 days	75 (18.84%)	63 (46.3%)
61 – 90 days	66 (16.58%)	51 (37.5%)
91 – 120 days	43 (10.80%)	34 (25%)
121 – 150 days	5 (1.26%)	4 (2.9%)

***multiple response**

Incidence of ADRs with respect to different variables
Incidence of ADRs with respect to different variables is shown in Table 4.
Incidence of ADRs was almost equal in females (41 of 48, 85.4%) and males (95 of 115, 82.6%). Incidence of ADRs was maximum (96.97%) in 46-60 years of age group (32 of 33 patients), which was statistically significant (p-value = 0.005).
Incidence of ADRs was more in MDR-PTB patients living in rural area, i.e. 89.1% which was statistically significant (p-value = 0.026). Maximum incidence of ADRs (88.07%) was seen in married patients, which was statistically significant (p-value = 0.024).
Incidence of ADRs was more in those patients who had any of the

addiction factors like smoking, alcohol, tobacco or drug abuse (92 of 103, 89.3%). Among 103, incidence of ADRs was 91.4% in smokers (p-value = 0.002) and 90.6% in alcoholics (p-value = 0.047), which was statistically significant.
Incidence of ADRs was more (95.3%) in patients having one or more co-morbidities, which was statistically significant (p-value = 0.001). All of our diabetic patients (14, 100%), hypertensive patients (18, 100%) and 54 of 57 patients who had COPD developed ADRs, which was statistically significant with p-value = 0.021, 0.045 and 0.004, respectively.
Incidence of ADRs was more (88.24%) in anemic patients, which was statistically significant (p-value = 0.007).

Table 3: Incidence of ADRs with respect to different variables

Variables	Number of patients (n=163)		p-value
	Developed ADRs (n=136)	**t developed ADRs (n=27)**	
Sex			
Male (n=115)	95 (82.6%)	20 (17.4%)	
Female (n=48)	41 (85.4%)	7 (14.6%)	0.66
Age group (in years)			
18-30 (n=72)	52 (72.22%)	20 (27.78%)	
31-45 (n=44)	40 (90.9%)	4 (9.1%)	
46-60 (n=33)	32 (96.97%)	1 (3.03%)	0.005
>60 (n=14)	12 (85.71%)	2 (14.29%)	
BMI (kg/m²)			
<18.5 (n=118)	95 (80.51%)	23 (19.49%)	
18.5-24.9 (n=42)	38 (90.5%)	4 (9.5%)	
25.0-29.9 (n=3)	3 (100%)	0	0.242

Residence			
Rural (n=92)	82 (89.1%)	10 (10.9%)	
Urban (n=71)	54 (76.1%)	17 (23.9%)	0.026
Marital status			
Married (n=109)	96 (88.07%)	13 (11.93%)	
Unmarried (n=54)	40 (74.07%)	14 (25.93%)	0.024
Education status			
Illiterate (n=28)	25 (89.3%)	3 (10.7%)	
Primary (n=10)	7 (70%)	3 (30%)	
Secondary (n=29)	26 (89.7%)	3 (10.3%)	
High School (n=41)	37 (90.24%)	4 (9.76%)	
Intermediate (n=41)	29 (70.7%)	12 (29.3%)	
Graduate and above (n=14)	12 (85.7%)	2 (14.3%)	0.074
Occupation			
Unemployed (n=33)	28 (84.85%)	5 (15.15%)	
Unskilled worker (n=38)	33 (86.8%)	5 (13.2%)	
Semi-skilled worker (n=31)	27 (87%)	4 (12.9%)	0.732

Skilled (n=38)	32 (84.2%)	6 (15.8%)	
Professional (n=21)	15 (71.43%)	6 28.57%)	
Retired (n=2)	1 (50%)	1 (50%)	
Addiction (103)[*]			
Smoking (n=93)	85 (91.4%)	8 (8.6%)	0.002
Alcohol (n=64)	58 (90.6%)	6 (9.4%)	0.047
Tobacco (n=51)	46 (90.2%)	5 (9.8%)	0.117
Drug abuse (n=2)	1 (50%)	1 (50%)	0.526
Resistance			
Primary (n=43)	38 (88.4%)	5 (11.6%)	
Secondary (n=120)	98 (81.7%)	22 (18.3%)	0.310
Co-morbidity[*]			
Co-morbidity present (n=64)	61 (95.3%)	3 (4.7%)	0.001
Diabetes mellitus (n=14)	14 (100%)	0	0.021
Hypertension (n=18)	18 (100%)	0	0.045
COPD (n=57)	54 (94.74%)	3 (5.26%)	0.004
Hepatitis (n=1)	1 (100%)	0	0.655
Seizure disorder (n=2)	2 (100%)	0	0.526
Hypothyroidism (n=2)	2 (100%)	0	0.526

*multiple responses

Table 4: Laboratory parameter

Laboratory parameter	Number of patients		p-value
	Developed ADRs (n=136)	**Not developed ADRs (n=27)**	
Haemoglobin level Anemic (n=119) Non-anemic (n=44)	105 (88.24%) 31 (70.5%)	14 (11.76%) 13 (29.5%)	0.007

Distribution of ADRs according to Body Systems, number of patients affected and total number of ADR episodes
In our study, total number of body systems involved by 398 ADR episodes were 12, of which maximum number of ADR episodes (134, 33.7%) were related to Gastrointestinal system observed in maximum 75% (102) patients, as shown in Table 5.

Table 5 : Distribution of ADRs according to Body Systems, number of patients affected and total number of ADR episodes

Distribution of ADRs according to Body Systems (n=39)[*]	Number of patients affected (n=136) (%)	Total number of ADR episodes (n=398) (%)
Gastrointestinal (n=11)	102 (75%)	134 (33.7%)
Central nervous system (n=10)	58 (42.65%)	69 (17.34%)
Vestibulocochlear (n=4)	47 (34.56%)	57 (14.32%)
Musculoskeletal (n=2)	43 (31.62%)	49 (12.31%)
Whole Body as general (n=3)	28 (20.59%)	32 (8.04%)
Peripheral nervous system (n=1)	16 (11.76%)	16 (4.02%)
Ophthalmological (n=1)	10 (7.35%)	10 (2.51%)
Dermatological (n=2)	9 (6.62%)	9 (2.26%)
Hepatobiliary (n=1)	9 (6.62%)	9 (2.26%)
Respiratory (n=2)	9 (6.62%)	9 (2.26%)
Endocrine (n=1)	2 (1.5%)	2 (0.50%)
Genitourinary (n=1)	2 (1.5%)	2 (0.50%)

multiple responses

The most common ADR was joint pain seen in 36 of 136 (26.5%) patients. Mean duration of onset of various ADRs from initiation of intensive phase of treatment was 41.65 days. Nausea has minimum mean duration of onset (4.26 days) whereas blurring of vision had the longest mean duration of onset (110 days), as shown in Table 6.

Table 6 : ADRs, patients affected, suspected drugs and duration of onset from initiation of treatment in days

ADRs (n=39)*	Patients affected (n=136)	Suspected drugs	Duration of onset from initiation of treatment (in days)	
			Mean	Range
Joint pain	36 (26.5%)	Z Lfx	72.22	15-125
Nausea	34 (25%)	Eto Z E	4.26	2-20
Loss of appetite	28 (20.6%)	Any drug	17.68	7-50
Decrease hearing	24 (17.65%)	Km	102.92	70-130
Weakness	21 (15.44%)	Any drug	32.71	12-70
Vertigo	17 (12.5%)	Km Cs Lfx Eto	24.12	3-70
Vomiting	17 (12.5%)	Eto Z E	12.94	7-20
Tingling and numbness in foot and palms	16 (11.8%)	Km Lfx Eto E	13.25	5-25
Anxiety	14 (10.3%)	Any drug	18.19	4-40
Drowsiness	14 (10.3%)	Any drug	68.2	40-110
Giddiness	13 (9.6%)	Km Eto Lfx Z	19.62	3-50
Pain at injection site	13 (9.6%)	Km	77.69	20-110
Heartburn sensation	12 (8.82%)	Any drug	7.67	2-20
Depression	11 (8.1%)	Cs Lfx Eto	72.73	40-110
Headache	11 (8.1%)	Cs	19	5-40
Abdominal pain	10 (7.4%)	Eto Lfx E Z	5.6	2-15
Blurring of vision	10 (7.4%)	E Eto	110	80-110
Insomnia	9 (6.62%)	Any drug	65.56	40-100
Jaundice	9 (6.62%)	Z Eto Lfx	54.44	35-80
Aphthous ulcers	7 (5.15%)	Any drug	18.57	10-35
Flatulence	7 (5.15%)	Any drug	5.71	2-20
Gastritis	7 (5.15%)	Eto Lfx E Z	9	3-20
Weight loss	7 (5.15%)	Any drug	52.14	40-70
Rashes	6 (4.4%)	Any drug	15	8-25
Dyspepsia	5 (3.7%)	Any drug	6.6	2-15
Dyspnoea	5 (3.7%)	Any drug	58	20-110
Constipation	4 (2.9%)	Any drug	9.25	3-20
Facial swelling	4 (2.9%)	Any drug	52.5	40-70
Haemoptysis	4 (2.9%)	Any drug	58.75	35-80
Diarrhoea	3 (2.21%)	Eto	6.67	3-12
Forgetfulness	3 (2.2%)	Any drug	66.67	50-80
Itching	3 (2.21%)	Any drug	35	15-50
Psychosis	3 (2.2%)	Cs Lfx	70	70
Tinnitus	3 (2.21%)	Km Cs Lfx Eto	41.67	35-50
Hypothyroidism	2 (1.5%)	Eto	30	20-40
Nephrotoxicity	2 (1.5%)	Km	105	80-130
Seizures	2 (1.5%)	Cs Lfx	95	70-120
Hypersomnia	1 (0.74%)	Any drug	10	10
Suicidal thoughts	1 (0.74%)	Cs Eto	80	80

*multiple responses

Discussion

In our study, out of total MDR-PTB 163 patients, 136 (83.44%) experienced one or more ADRs during intensive phase of treatment. Kamendra Singh Pawar et al (2017) [4] had reported that out of their total 120 patients, 117(97.5%) experienced one or more ADR during intensive phase with majority (52.1%) experienced ≥ 4 ADRs. Anita Velingker et al (2020) [5] found that 99 (49.3%) cases had 167 ADRs. The reasons for the heterogeneity in the incidence of ADRs might be related to differences in definitions of ADR terminologies, whether the ADRs were subjective or objective and/or variations in the anti-With respect to BMI of patients, our study observed highest incidence of ADRs (100%) in MDR-PTB patients with BMI between 25.0-29.9 kg/m^2 (p-value = 0.242). It has been reported that the effects of obesity on drug metabolism to increase the risk of ADRs have resulted in occurrence of ADRs [9, 10].In our study, incidence of ADRs was more in patients living in rural area (82 of 92, 89% rural vs

TB drug regimens [6].We observed that incidence of ADRs was almost equal in female and male patients (85.4% female vs. 82.6% males, p-value = 0.66). Occurrence of ADRs was maximum (96.97%) in 46- 60 years of age group (32 of 33 patients) which was statistically significant (p-value = 0.005). Studies conducted in Nepal and Ethiopia have also reported that incidence of developing ADRs were more in elderly as elder patients have too exhausted organs to metabolize toxic substances from the body, putting patients at increased risk for developing ADRs [7, 8].

54 of 71, 76% urban) which was statistically significant (p-value = 0.026). Maximum incidence of ADRs (88.07%) was seen in married patients which is statistically significant (p- value = 0.024). Similar results had been shown by Tembeka Sineke et al (2019) [11].
In our study, incidence of ADRs was 91.4% in smokers (p-value = 0.002) and 90.6% in alcoholics (p-value = 0.047), which was

statistically significant. Similar results were shown in study conducted by Nafees Ahmad et al (2016) [12].We observed that incidence of ADRs in patients with primary drug resistance pattern was 88.4% (38 of 43), while incidence of ADRs in patients with secondary drug resistance was 81.7% (p-value = 0.310), which was statistically insignificant. Rohan Hire et al (2014) [13] and Nafees Ahmad et al (2016) [12], however, had reported that incidence of ADRs was more in their patients with acquired drug resistance.

In our study, incidence of ADRs was more (95.3%) in patients having one or more comorbidities, which was statistically significant (p-value = 0.001). Rohan Hire et al (2014)[13] had also observed that 80% of their diabetic patients developed ADRs. Thus, our study highlights that the risk of experiencing ADRs in patients with co-morbidities was higher which could be due to the fact that the pill burden and drug-drug interactions put these patients at increased risk for developing different ADRs [14, 15].

In our study, incidence of ADRs was more (88.24%) in patients who had anemia, which was statistically significant (p-value = 0.007). Mehari Woldemariam Merid et al (2019) [16] and Tembeka Sineke et al (2019) [11] had also reported similar results. This may be due to

chronicity of TB, predisposing patients to delayed gastro-intestinal absorption of nutrients and poor tolerance to drugs and development of ADRs [17].

In our study, total number of body systems involved by 398 ADRs episodes we observed were 12, of which maximum number of ADRs (134, 33.7%) were related to Gastrointestinal system. Similar results were observed by Keerthivasan Sivanmani et al (2017) [18], Anita Velingker et al (2020) [5]. However, in contrast to our study, Shivaji V Patil et al (2017) [19] reported that central nervous system was the most common system affected, contributed 41.28% of total ADRs.

In our study, the most common ADR was joint pain which was present in (36 of 136, 26.5%) patients followed by nausea in (34, 25%) patients. Anita Kumari et al (2018) [20], Madan Sigdel et al (2016) [7], Tembeka Sinekel et al (2019) [11] had also reported that joint pain was the most common ADR in their patients.

In our study, mean duration of onset of various ADRs from initiation of intensive phase of treatment was 41.65 days. Arif I Dela et al (2017) [21] reported similar results with respect to duration of onset of psychiatric symptoms, nausea, vomiting and blurring of vision.

Conclusion
It is recommended that strict follow-up along with laboratory investigations during the intensive phase and the first 30 days of intensive phase in particular is important. The role of providing proper assurance, a proper diet and exercise plan to reduce the weight should be provided. Co-morbidities should be managed optimally to minimize chances of ADRs while managing MDR-PTB. In view of high incidence of ADRs, there is a need of future research to develop new anti- MDR-TB drugs which have less tendancy to produce ADRs and which have the potential to shortens the duration of treatment.

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