ORIGINAL RESEARCH ARTICLE

Incidence of Adverse Drug Reactions (ADRs) and their Determinants among Sputum-Positive Pulmonary TB Patients in A Metropolitan Area, Bengaluru: A Prospective Study

Manasa Divakar[1], Ananth Ram[2], Lalitha K[3]*

[1]Siddaganga Medical College and Research Institute, Tumakuru, Karnataka, India
[2,3]M S Ramaiah Medical College, Bengaluru, India

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ABSTRACT

Background: India accounts for 2.42 million new Tuberculosis cases in 2022. Treatment adherence is major challenge, ADRs being one of the main causes of poor adherence. Early identification and addressing of ADRs can improve adherence, reducing associated morbidity and drug resistance. With introduction of daily FDC regimen in India, we intend to study incidence of ADRs and their determinants among Pulmonary TB patients who are on FDC daily regimen.

Methodology: Newly diagnosed drug-sensitive PTB patients aged 18 years and above were recruited. A pre-tested questionnaire was administered and patients were followed up to document ADRs. Causality and severity were assessed using the WHO-UMC scale and Hartwig's severity assessment scale respectively.

Results: Among the study participants', 95 (78.5%) developed any ADRs. Incidence rate was 13.2 (6.98–19.22) per 100-person month follow-up with GI symptoms being most common. Increasing age [OR=4.7(1.6–14.8)] and weight [OR=5.1(1.3–16.2)] were found to be significantly associated with ADRs. All ADRs were classified as 'probable' and 'mild' in nature according to WHO scale and Hartwig's severity assessment scale respectively.

Conclusion: Occurrence of ADRs is common, most of them are mild, and occurring in intensive phase. Hence, early identification and appropriate counselling during intensive phase is critical.

Key words: Tuberculosis, ADRs, FDC daily regimen, WHO-UMC scale, Hartwig's severity assessment scale

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***Correspondence:** Dr. Lalita K (Email: lalithakgs7@gmail.com)

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INTRODUCTION

Tuberculosis (TB) is a communicable disease and a major cause of ill health, ranking among top 10 causes of death worldwide. The disease is a global pandemic, resulting in an estimated 6.4 million new cases in 2021.[1] India has highest TB burden, accounting for more than two-thirds of the global cases with 2.42 million new cases in 2022.[1,2]

In 1994, use of Fixed drug combinations (FDCs) in anti-TB therapy was recommended by World health organization (WHO) and International Union against Tuberculosis and Lung Disease (IUATLD).[3] Also, non-adherence to intermittent regimens and inappropriate prescriptions were believed to be major contributing factors to this public health problem in India.[4,5] Therefore, daily regimen for all TB patients was initiated since October 2017.[3] Advantages of FDCs are; simplified treatment and drug management, lower default rates, decreased probability of monotherapy, pill burden and drug resistance, thereby improving adherence in various settings. Despite these advantages, there is uncertainty about their effectiveness because of higher doses and associated Adverse drug reactions (ADRs).[4]

TB is still a major health problem because of poor patient compliance and ADRs. Further, these factors contribute to the development of resistant strains, which is a great concern. Also, ADRs can contribute to excessive healthcare costs through increased patient morbidity and mortality.[6,7] So there is a need to identify ADRs at the earliest possible time and take precautions to alleviate side effects. Monitoring and reporting of ADRs is essential to identify the culprit drug, tailoring appropriate doses and therapeutic regimens for patient, as they are also an important factor in deciding treatment outcomes.[8]

With the adaptation of new FDC regimen in India, it is important to assess incidence of ADRs, identify the factors affecting them, and study their impact on treatment outcomes. Therefore, we intend to assess the incidence of ADRs and their determinants at the end of six months of treatment.

METHODOLOGY

A Descriptive Longitudinal Study was conducted in Tuberculosis units (TUs) and Peripheral health institutes (PHIs) in the Bruhat Bengaluru Mahanagara Palike (BBMP) area to study the incidence of adverse drug reactions among newly diagnosed drug-sensitive sputum-positive pulmonary TB patients on the FDC regimen; to study the determinants of the incidence of the ADRs among the study participants on a daily regimen; and also, to assess the causality and severity of ADRs.

For logistics purposes, among the three zones in BBMP, the west zone was selected by probability sampling, out of which five TUs, namely Nandini Layout, Geleyarabalaga, Yeshwantpur, Palace Guttahalli, and Sultanpalya, were selected randomly. Newly diagnosed smear-positive drug-sensitive pulmonary TB cases aged 18 years and above, who were on a daily regimen taking the anti-tuberculosis treatment (ATT) FDCs as prescribed according to the weight of the patient were enrolled.

Inclusion Criteria: Adults aged 18 years and above newly diagnosed smear-positive drug-sensitive pulmonary TB were included in the study. However, HIV-positive patients, MDR-TB case, critically ill morbid bedridden, or unconscious patients, or patient with Pre-existing liver and kidney disease were excluded from the study.

Ethical clearance was obtained on 27th October, 2018, from the institutional ethical committee of the M S Ramaiah Medical College, Bengaluru, with the number EC/PG-17/2018 and prior permission was taken from the concerned authority, the District TB Officer of BBMP, Bengaluru, to conduct the study in the selected TUs.

The patients were recruited from August 2019 to June 2020 with last case being followed up until the end of November 2020. A total of 121 patients who were enrolled were followed up on a weekly basis during the intensive phase and on monthly basis during continuous phase, either telephonically or in person. A pretested, semi-structured questionnaire was used to collect data pertaining to adverse drug reactions and their determinants. During follow up, occurrence of any adverse drug reactions or any missed doses during the treatment course were documented. If any ADR was reported, causality and severity were assessed using the WHO-UMC scale and Hartwig's severity assessment scale, respectively. WHO-UMC system for standardized case causality assessment of ADRs is a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the ADRs. Based on the different assessment criteria, they are classified into 'certain', 'probable/likely', 'possible', 'unlikely', 'conditional' and 'unclassifiable'.[9] In Hartwig and Siegel severity assessment scale, the ADRs are classified into 'mild', 'moderate' and 'severe' based on criteria under seven levels of ADRs. Those reported under levels 1 and 2 are classified as mild, levels 3 and 4 are classified as moderate and levels 5, 6 and 7 are classified as severe.[10]

Further, if the patients agreed to a visit to their house, a visit was made along with TBHV to document the housing conditions, such as the presence of a smoke outlet in the kitchen, ventilation, lighting, overcrowding, etc. In the event that the patients did not permit us to visit their house, details were obtained through an oral interview.

Those with minor ADRs were counselled not to discontinue the ATT and were referred to the MO-TC (Medical Officer-TB Control) for further management to alleviate their symptoms. In case of major ADRs, it was envisaged to refer such cases to MOTC or higher

centres for further management. However, in our study, there were no major ADRs reported. All efforts were made to counsel all the patients to adhere to the treatment and complete it until cure.

Data was entered into an MS Excel sheet and then exported into IBM SPSS Statistics version 18. All the quantitative parameters were expressed as mean and standard deviation, median and interquartile range, frequency, and percentage. The incidence of ADRs was calculated among the TB cases in terms of events occurring per man-month at the end of the intensive phase and at the end of treatment. The Chi-square test was used to find the association of ADRs with socio-demographic factors and other clinical determinants. The strength of association, bivariate odds ratio with a 95% confidence interval, and forward multiple logistic regression analysis were applied. A p value of 0.05 was considered statistically significant.

RESULTS

In the present prospective study, 121 study participants were recruited and followed up for the whole treatment course six months. Among 121 subjects, 70 (57.9%) were males. The median age of the study participants was 37 (49.5-26.5) years, and the mean weight and height were 55.72 ± 8.9 kg and 159.5 ±7.2 cm, respectively. About 42 (34.7%) of participants were in the age group of 18–29 years, out of which 16 (39.1%) were males and 26 (60.9%) were females.

Majority of the study participants belonged to the Hindu religion, were married, belonged to a nuclear family, and resided in slum areas. More than 50% of the study population had a literacy level lower than high school, and the majority belonged to either homemakers or students in employment status. Almost 50% of the study population belonged to the lower middle class according to the modified Kuppuswamy scale, and the majority had separate kitchens, but almost one-third of households had kitchen with no smoke outlets. More than fifty percent of households had overcrowding and inadequate ventilation. Any form of tobacco use was present in 40 (33.1%) of the study participants, with a similar proportion consuming alcohol. (Table 1)

Among the study participants, the most common symptoms reported at the time of diagnosis were cough and fever in 102 (84.8%) and 91 (75.4%) studies, respectively. Study participants reported multiple symptoms. The median duration taken from the onset of symptoms to the initiation of treatment for TB was 27 (17–36) days. This duration was > 30 days in 49 (40.6%) of the study participants. The direct benefit transfers of Rs. 500 for each month was low at the time of recruitment due to either the unavailability of a bank account under the subject's name or an Aadhar card. The proportion availing of this benefit as well as its utilization for nutrition increased at the end of the intensive phase and the continuation phase. The utilization of the money provided was ascertained by asking the subjects regarding what was purchased. If it was for eggs, meat or any grocery items, it was classified under the utilization for nutrition. The others were classified accordingly as per the answers given by the subjects like pooling into family income or using it for transportation or medicine. (Table 2)

Table 1: Distribution of study participants according to socio-demographic profile (N=121)

Variables	Cases (%)
Religion	
Hindu	102 (84.3)
Others (Christian and Muslim)	19 (15.7)
Marital Status	
Single	28 (23.1)
Married	80 (66.1)
Widowed/ Separated/Divorced	13 (10.8)
Type of Family	
Nuclear Family	71 (58.7)
Joint/ Three generation Family	50 (41.3)
Area of residence	
Slum	80 (66.2)
Non-slum	41 (33.8)
Education	
Post-graduation/ Graduation	25 (20.6)
Intermediate/diploma	32 (26.4)
≤High School	64 (52.9)
Employment status	
Profession/Semi-profession	11 (9.0)
Skilled	36 (29.7)
Semi-skilled/ Unskilled	18 (14.9)
Not gainfully employed	56 (46.2)
Socio-economic status (Kuppuswamy classification)	
Upper middle (II)	9 (7.4)
Lower middle (III)	58 (47.9)
Upper lower (IV)/ lower (V)	54 (44.7)
Separate kitchen	
Present	108 (89.3)
Absent	13 (10.7)
Smoke outlet in kitchen	
Present	78 (64.5)
Absent	43 (35.5)
Any household member smoking inside house	
Yes	47 (38.8)
No	74 (61.2)
Overcrowding (floor space area)	
Present	65 (53.7)
Absent	56 (46.3)
Ventilation	
Adequate	42 (34.7)
Inadequate	79 (65.3)
Any form of tobacco use	
Yes	40 (33.1)
No	77 (63.6)
Smoking status	
Current smoker	11 (9.2)
Former smoker	21 (17.4)
Never smoker	89 (73.6)
Alcohol consumption	
Yes	44 (36.4)
No	81 (66.9)

Table 2: Utilization of Nikshay Poshan Yojana money among the study participants at the different stages (N= 121)

Characteristics	At the recruitment	At the end of intensive phase	At the end of continuous phase
Monthly Nikshay Poshan Yojana deposit [n (%)]	84 (69.4)	109 (90.1)	107 (88.4)
Utilization of deposit for food [n (%)]	24 (28.5)	36 (33.0)	41 (38.3)

Table 3: Description of occurrence and incidence of ADRs among study participants (N=121)

ADRs	Cases/Rate
Proportion of TB cases who developed any ADRs (%)	95 (78.5)
Incidence rate (95% CI) of ADRs during intensive phase of treatment	39.1 (30.8-47.4) episodes/100 person months
Incidence rate (95% CI) of ADRs at the end of follow up	13.2 (6.98-19.22) episodes/100 person months

Table 4: Bivariate and multivariate analysis of the determinants associated with ADRs (N=121)

Variables	ADR present (n=95) (%)	ADR absent (n=26) (%)	OR (95% CI)	*P value*	aOR (95% CI)	*P value*
Age						
>40	49 (92.5)	4 (7.5)	5.9 (1.9 -18.2)	0.006	4.7 (1.6 – 14.8)	0.007
≤40	46 (67.6)	22 (33.4)	Ref			
Type of family						
Nuclear family	50 (70.4)	21 (29.5)	Ref	0.010		
others	45 (90)	5 (10)	3.8 (1.3-10.5)			
Socio economic status						
Upper lower/ lower class	47 (87)	7 (13)	2.7 (1.1-6.9)	0.037	-	
Upper/ lower middle class	48 (71.6)	19 (28.4)	Ref			
Weight						
≥50	62 (72.9)	23 (27.1)	3.2 (1.6-10.1)	0.028	5.1 (1.3 - 16.2)	0.014
≤50	33 (91.7)	26 (8.3)	Ref			
BMI (kg/m2)						
≥23	76 (74.5)	26 (25.5)	1.3 (1.1-1.5)	0.039	-	
<22.9	19 (100)	0 (0)				
Diabetes mellitus						
Present	33 (91.7)	3 (8.3)	4.1 (1.2-14.6)	0.018	-	
Absent	62 (72.9)	23 (27.1)	Ref			
Pallor						
Present	50 (87.7)	7 (12.3)	3.0 (1.2 -7.8)	0.026	-	
Absent	45 (70.3)	19 (29.7)	Ref			

OR - Unadjusted Odds ratio derived from bivariate analysis; aOR – Adjusted Odds Ratio derived from multivariate analysis

Diabetes mellitus (29.6%), hypertension, and cardiovascular diseases were the most commonly reported co-morbidities by the study participants. Almost half of the study population had pallor. Though the majority of the subjects had a normal BMI, fifteen percent had a BMI less than 18.5 kg/m^2 at the time of diagnosis. They were counselled on proper dietary intake and nutritional supplements.

In this study, 121 study participants were followed up for six months, accounting for 726 months of follow-up. A total of 108 (78.2%) study participants developed any ADRs. Accordingly, the incidence rate of ADR was found to be 13.2 (95% CI: 6.98–19.22) per 100 person-months during the whole follow-up period. Since all the ADRs were reported in the intensive phase, the incidence rate of ADRs during the intensive phase of treatment, which is 242 person months of follow-up, is 39.1 (95% CI: 30.8–47.4) per 100 person months. (Table 3)

Socio-demographic profiles and clinical and personal history variables like age, gender, type of family, area of residence, Socio economic status (SES) classification, weight, BMI, comorbidities, personal habits, findings of a general physical examination, and treatment outcomes were associated with the presence of any ADRs. Among them, socio-demographic characteristics like subjects aged above 40 years, weight above 50kg, Nuclear family, and lower class of SES, as well as presence of co-morbidities like diabetes mellitus, weight, BMI, and the presence of pallor in the general physical examination, are significantly associated with the presence of any ADRs with a *p value <0.05.* In multivariate analysis, subjects aged above 40 years [OR = 4.7 (95% CI: 4.7 (1.6–14.8)] and weighing more than 50kg [OR = 5.1 (95% CI: 1.3–16.2)] were found to be significantly associated with the presence of ADRs. (Table 4)

The most common system involved was gastrointestinal (59, or 63.8%), followed by dermatological (18, or 19.4%). The most common symptom was nausea, followed by epigastric pain, loss of appetite, body pain, vomiting, etc. Dermatological symptoms like rashes and itching were also seen (Figure 1).

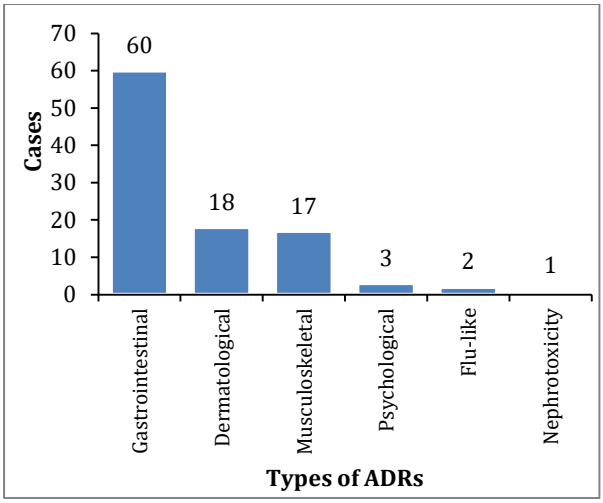

Figure 1: Distribution of type of ADR among study participants (N=95)

Causality assessment[9]: Using the WHO causality assessment scale, all the ADRs in the present study were classified as "probable." None of them were classified as "possible," "certain, "conditional," or 'unclassifiable' as per the criteria.

Severity assessment[10]: The severity of ADRs was assessed using Hartwig's severity assessment scale. All the ADRs reported were **mild** in nature, and none of them had moderate or severe reactions. Among the mild reactions, all of them were of **level 1,** i.e., an ADR occurred but required no change in treatment with the suspected drug. No other treatment, like an antidote, was required. No increase in the length of hospital stays or ICU requirements due to ADR was observed. No permanent harm or death to the patient due to ADR occurred.

Those with minor ADRs were counselled not to discontinue the ATT and were referred to the MO-TC (Medical Officer-TB Control) for further management to alleviate their symptoms. In the case of major ADRs, it was envisaged to refer such cases to MOTC or higher centres for further management. However, in our study, there were no major ADRs reported. All efforts were made to counsel all the patients to adhere to the treatment and complete it until cure.

Discussion

With the introduction of FDCs in India, there are only a few studies assessing the incidence of adverse drug reactions and their determinants, including their effects on treatment outcomes. Some studies suggest that the ADRs are increased[7], while others suggest that they remain the same when compared to the intermittent regimen.[11] This study, being prospective in nature, assessed the incidence of ADRs and their determinants, their causality, and their severity.

In the present study, the median age in males was 39.6 (IQR: 48.25–29.75) years, and the median age in females was 29.5 (51.5–23.25) years. Similarly, in a study conducted by Anwith HS et al.[12], the mean age was 40 ± 16.1 years. In the present study, the educational status of study participants less than or equal to high school was 43.5%. In a study conducted by Duru C. B. et al.[13], those who had less than or equal to a secondary educational level were 61.4%. Awareness of the cause of the disease and their attitude towards receiving and adhering to the treatment might indirectly be related to the educational status of the patients. Hence, it's essential to give proper counselling and create awareness.

In this study, about 78.2% of the study population developed any ADR (symptoms) during the course of the treatment. All the ADRs were reported in the intensive phase only. Similarly, a study conducted in Brazil by Sant' Anna et.al, 78.8% of the participants presented with at least one ADR in this prospective cohort study where frequent follow-ups every 15 days was done.[14] In a study conducted in Chitradurga district, Karnataka, by Bhangari K et al.[15] the ADRs were found to be 54.5% in the daily regimen. This proportion was lower when compared to our study. Another study by Mandal P. K. et al.[16] found a 35% incidence of ADRs in the daily regimen at the end of the intensive phase, which is an even lower incidence than compared to our study. Similarly, in a study conducted by Kapil Mate et.al., in Nagpur, the ADRs were present in 36.4 % of 750 patients.[17] The probable reason for the higher incidence of ADRs in our study could be weekly follow-up in the intensive phase, when the probability of occurrence of ADRs is higher and none of the ADRs were missed on the record with minimal recall bias.

In the current study, the most common ADRs reported were gastrointestinal (63.8%). Similarly, in another study by Ramakrishnan et al.[6] conducted in Tirunelveli, the most common ADRs reported were also gastrointestinal symptoms like nausea (20%), hepatitis (19%), gastritis (15%), vomiting (13%), diarrhoea (9%), abdominal cramps (9%), etc. Singh A et al.[7] conducted a study in Uttar Pradesh where gastrointestinal symptoms were the most common ADRs reported among 100 subjects. In another study by Ahmed N et.al[18] in Pakisthan, Gastrointestinal disturbance was the most commonly observed adverse event (42%), followed by psychiatric disturbance (29.3%), arthralgia (24.3%), and ototoxicity (21%). A review article by Prasad R et.al.[19] from Uttar Pradesh also reported that the most common ADRs reported were Gastro-intestinal system related. Cutaneous symptoms like maculopapular rashes were reported common in a study by Sharma RK et.al.[20]. The increased incidence of GI side effects could be attributed to multiple drug therapy as a major predisposing factor for ADRs. All the four drugs Isoniazid, pyrazinamide, ethambutol and also rifampicin to some extents are known to cause GI related ADRs like loss of appetite, nausea, vomiting and diarrhea.

In this study, sociodemographic characteristics like age of the patients, type of family and SES, co-

morbidities like diabetes mellitus, weight and BMI of the subjects, and presence of pallor in the general physical examination were found to be significantly associated with the presence of any ADRs with a *p value 0.05*. In multivariate analysis, increasing age [OR = 4.7 (95% CI: 4.7 (1.6–14.8)] and weight [OR = 5.1 (95% CI: 1.3–16.2)] were found to be statistically significant. In a study conducted by Siribaddana A et al.[21], patients who had ADR were slightly older compared to patients who didn't have ADR. A significant proportion of patients (44%) above the age of 60 had adverse reactions. Another study by Maqbool M et.al.[22] in Jammu and Kashmir showed that the subjects aged more than 60 years was significantly associated with ADRs. A study done in Peru by Chung-Delgado et.al.[23] ages, especially those over 40 years, overweight or obesity, anemia and smoking was significantly associated with the presence of ADRs. This can be attributed to the changes in the body due to aging process which can in turn affect the metabolism of the concerned drugs taken. Also, with the increasing weight, the dosage of the drugs taken will increase according to the classified weight bands given under the program. Hence, increasing the probability of occurrence of ADRs, especially if the weight falls near the upper band in the category.

In this study, the subjects who had any ADR had higher odds of having poor outcomes than the patients who didn't experience any ADR during the course of the treatment, but this was not statistically significant. In a study conducted by Singh et al.[8], patients without ADRs had a significantly better outcome as compared to patients with ADRs in FDC daily regimen patients (p = 0.05). ADRs affect the course of treatment, adherence, and outcomes. It is essential to monitor, identify in time, and treat accordingly to prevent drug resistance and poor outcomes.

The WHO causality assessment scale used in this study showed that all the ADRs reported were 'probable'. The Hartwig-Siegal scale showed that all the ADRs were mild in nature. In a study on the assessment of ADRs in anti-TB drugs conducted by Kuriachan S et al.[9], as per causality assessment, 80% of ADRs were assigned "possible", 11% "probable" and 9% "certain". As per the severity scale, 27.7% of ADRs were severe, and 36.9% were moderate. Kiran M et.al.[24] conducted a study in Mandya, Karnataka, which showed that most of the ADRs belonged to mild category as per Modified Hartwig and Siegel scale. In another study by Gunjan U et. al.[25], the WHO causality scale showed 54.54% ADRs as 'probable' and 43.8% ADRs as 'possible'. Most of the reactions were mild on the severity scale. Though the same scales were taken to assess the causality and severity, the ADRs, like hepatitis, neurotoxicity and nephrotoxicity, were assessed with various investigations in the above study. But in the current study, we did not conduct any further investigations to ascertain the drug – adverse effect relationship, and ADR was assessed and classified only based on the symptoms reported by the patients. Further evaluations were not done, which is one of the limitations of this study.

These are few limitations of this study. a) The ADRs were assessed through telephonic interview. This could have led to information bias and recall bias. Assessment of psychological symptoms telephonically was difficult which could be underreported. b) The severity and causality of ADRs were classified based only on the symptoms described by the patients. Further studies with supportive invasive investigations based on the symptoms is necessary to assess the association of the ADRs with the anti-TB drugs and determine the nature of their severity. c)Due to the social stigma, about 12.5 % of the study participants did not consent to visit their respective houses for assessing the housing environment. Hence the housing conditions reported would not be completely accurate.

Conclusion

The occurrence of ADRs was common, most of them occurred in the intensive phase and were mild in nature. In this study, subjects with increasing age, belonging to lower socio-economic strata, living in nuclear families, weighing more than fifty kilograms, presence of co-morbidities and pallor, were associated with presence of ADRs. ADRs are also known to be associated with poor adherence, drug resistance, increased morbidity, and poor treatment outcomes. Most of these adverse effects are GIT related adverse effects which can be overcome by symptomatic therapy and counselling. Hence, it is very vital to counsel the patients before starting treatment regarding the expected ADRs, to identify the ADRs early, and to report them promptly to the health workers for improved patient compliance and treatment outcomes under the program. Hence, pharmacovigilance of antitubercular drugs is very much essential for successful treatment of TB and its elimination.

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