

Adverse drug reaction profile of daily regimen antituberculosis treatment

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Abstract

Objectives: The objective was to estimate the proportion of adverse drug reactions (ADRs) to daily regimen antituberculosis treatment (ATT) among the ADRs received in the ADR monitoring center (AMC) of the institution and to describe its pattern.

Materials and Methods: This was a descriptive study conducted in the Department of Pharmacology of a Government Medical College in Central Kerala and the period under study was October 2017–June 2020. The data on ADR were entered into a structured pro forma and data were analyzed using SPSS for Windows Version 16.0 (SPSS Inc., Chicago, USA).

Results: Of the 643 ADRs, 98 (15.24%) were suspected to be due to the daily regimen of ATT. The most common organ system affected was hepatobiliary 46 (46.9%) namely hepatitis in 35 and asymptomatic elevated liver enzymes in 11 followed by eye with 26 reports of decreased vision. In 96 (97.95%), the suspected ADR had probable causality and in 2 (2.04%) it was possible. Seventy-seven (78.6%) ADR reports were serious as well as moderate-level 4b in severity and 57 (58.16%) were probably preventable. The mean days of onset of ADR after starting the ATT regimen were 56.40 ± 58.29 days (range 1–180). Decrease in vision with a mean duration of 125.23 ± 55.46 days had the longest latency in onset among all the ADRs.

Conclusions: Of all the ADRs reported to AMC 15.24% were due to the daily regimen of ATT. Hepatitis was the most common ADR encountered followed by decrease in vision. The majority of the ADRs were probable in causality, serious, moderate-level 4b in severity, and probably preventable.

Keywords: Adverse drug reaction, antituberculosis treatment, daily regimen

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INTRODUCTION

Worldwide TB is one of the top 10 causes of death and a total of 1.5 million people died of TB in 2018. Among the 8 countries that account for two-thirds of the total cases worldwide India leads the count.^[1] Apart from the fatality due to the disease, the morbidity, and mortality of this disease

is partly linked to the adverse drug reactions (ADRs) to the antituberculosis treatment (ATT).^[2] To reduce resistance, decrease the dose required and adverse effects, combination chemotherapy with the first-line ATT recommended by the WHO namely Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), and Streptomycin (S)

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are the mainstay of TB treatment.^[3] The National Strategic Plan of India 2017–2025 builds on the accomplishment and erudition of the previous plans and is expected to transcend the steps required to eliminate TB in India by the year 2025 with robust active surveillance.^[4] The technical and operational guidelines for tuberculosis (TB) control in 2016 have switched on daily fixed drug combination regimen for all TB patients from October 30, 2017 throughout India instead of thrice-weekly intermittent regimen.^[5] In December 2018, the Technical Expert Group decided that all TB patients will be initiated on standard first line anti TB regimen (2HRZE/4HRE), thus lowering the category of streptomycin to a supplemental drug.^[6]

Adverse events due to drug-sensitive as well as resistant TB treatment are one of the most important reasons for treatment interruption and nonadherence. To attain the 2025 goal of complete elimination, we have to ensure prompt referral and management of ADRs. The importance of the study lies in the sparse data available on ADRs with daily regimen of ATT compared to the thrice-weekly regimen in the Indian population. This study was done to estimate the proportion of ADRs due to the daily regimen of ATT among the ADRs reported to the ADR monitoring center (AMC) of the institution as well as to describe the characteristics of the ADR.

MATERIALS AND METHODS

This was a descriptive study done from July 2019 to June 2020 at the Department of Pharmacology, Government Medical College, Kottayam. The period under study was October 2017 to June 2020. The institution was approved as an AMC under the Pharmacovigilance Programme of India (PvPI) in 2012 with access to viginflow. The AMC collects, communicate, and disseminates ADR data by linking with hospitals as well as practitioners and also provides expertise for assessing causality and severity of ADRs using standard algorithms and rating scales. The ADRs are reported in Suspected ADR (sADR) reporting forms. All ADRs reported to the AMC formed the sample population. The data which were received as a part of the PvPI from the inpatient departments of the institution, various hospitals, and the National Tuberculosis Eradication Programme (NTEP) unit of the institution during the period under study were scrutinized for ADRs following daily ATT regimen and were included in the study. The study was initiated after getting clearance from the Institutional Review Board of GMC, Kottayam (IRB No 106/2018 dated December 7, 2018). The data were entered into a structured pro forma. The drugs and organ systems affected were classified based on the therapeutic

classification and the WHO-Adverse Reaction Terminology, respectively. Causality was assessed by WHO-UMC scale as well as Naranjo's algorithm.^[7] Severity and preventability of the ADRs were assessed by modified Hartwig and Siegel scale and Schumock Thornton scale, respectively.^[8] Seriousness of the reaction was categorized according to the Food and Drug Administration criteria.^[9] Predictability was determined by classifying the ADRs as Type A (Augmented) and Type B (Bizarre).^[10] Data were analyzed using SPSS for Windows Version 16.0 (SPSS Inc., Chicago, USA). The continuous variables such as age and number of systems involved were expressed as mean \pm standard deviation. Categorical variables such as gender, suspected drug, systems involved, a temporal relation of ADR, type of ADR, predictability, preventability, severity, causality, and seriousness were expressed as frequencies and percentages.

RESULTS

Out of the 643 ADRs reported to the AMC of the institution during the period under study, 98 (15.24%) were suspected to be due to the daily regimen of ATT. Of the 98 ADRs, 12 (12.2%) were reported in 2017, 32 (32.7%) in 2018, 33 (33.7%) in 2019, and 21 (21.4%) in 2020. The age range was 16–84 years. The mean age of persons who developed ADR to ATT was 51.64 ± 16.07 years and the male:female ratio was 1.33:1. Table 1 summarizes the clinical profile of patients who developed ADR to ATT.

As shown in Table 2, the most common organ system affected was hepatobiliary 46 (46.9%) namely hepatitis in 35 and asymptomatic elevated liver enzymes in 11. The mean total bilirubin was 4.10 ± 4.87 mg/dl, direct bilirubin was 2.27 ± 2.80 mg/dl, serum glutamic-oxaloacetic

Table 1: Clinical profile of patients with adverse drug reaction to antituberculosis treatment

Clinical profile	n=98, n (%)
Gender	
Male	56 (57.1)
Female	42 (42.9)
Age group (years)	
15-45	30 (30.6)
46-75	65 (66.3)
>75	3 (3.1)
TB	
Pulmonary	90 (91.8)
Extrapulmonary-abdominal	2 (2)
Extrapulmonary-lymph node	5 (5.1)
Extrapulmonary-spine	1 (1)
Comorbidity	
Diabetes mellitus	1 (1)
Chronic kidney disease	5 (5.1)
Nil	92 (93.9)
Treatment	
Daily regimen-FDC	98 (100)

TB=Tuberculosis, FDC=Fixed-dose combination

Table 2: Organ systems affected, adverse drug reactions, and suspected drugs in fixed-dose combination

Organ system	n=98, n (%)	ADR	n=98, n (%)	Suspected drugs in the FDC
Electrolyte	1 (1)	Hyponatremia	1 (1)	All ATT
Eye disorders	26 (26.5)	Decreased vision	26 (26.5)	Ethambutol
Gastrointestinal	5 (5.1)	Epigastric pain	1 (1)	All ATT
		Vomiting	3 (3.1)	
		Gastritis	1 (1)	
Hematological	2 (2)	Thrombocytopenia	2 (2)	Rifampicin, INH
Hepatobiliary	46 (46.9)	Hepatitis	35 (25.7)	INH, rifampicin, pyrazinamide
		Asymptomatic elevated liver enzymes	11 (11.2)	
Kidney	1 (1)	Acute kidney injury	1 (1)	Streptomycin
Respiratory	1 (1)	Pneumothorax	1 (1)	All ATT
Skin and appendages	16 (16.3)	Rash	2 (2)	All ATT
		Itching	13 (13.3)	
		Exfoliative dermatitis	1 (1)	

FDC=Fixed-dose combination, ADR=Adverse drug reaction, ATT=Antituberculosis treatment

transaminase 356.92 ± 497.73 IU/L, serum glutamic pyruvic transaminase 253.85 ± 267.28 IU/L from the data available from the ADRs with hepatobiliary dysfunction ($n = 35$). The second-most common affected organ system was eye and the ADR was the decreased vision (26.5%).

As shown in Figure 1, majority of the patients were managed with supportive therapy. There was no mortality reported due to ATT during the period under study and all patients were recovering at the time of reporting of ADR. The WHO-Causality assessment showed that out of the 98 cases, in 96 (97.95%) the suspected ADR was probable, and in 2 (2.04%), it was possible. Of the 98 ADRs, 77 (78.6%) were serious and resulted in hospitalization or caused prolonged hospitalization, 21 (21.4%) were not serious. Twenty (20.4%) ADRs were mild-level 2, 1 was moderate-level 4a, and 77 (78.6%) were moderate-level 4b in severity according to Hartwig and Siegel scale. Fifteen (15.30%) were definitely preventable, 26 (26.5%) were not preventable and 57 (58.16%) were probably preventable ADRs according to modified Schumock and Thornton scale. All the ADRs were type B(Bizzare). The mean days of onset of ADR after starting the ATT regimen were 56.40 ± 58.29 days (range 1–180). Figure 2 summarizes the temporal relation of ADR. Decrease in vision with a mean duration of 125.23 ± 55.46 days had the longest latency in onset among all the ADRs.

DISCUSSION

The WHO defined ADR in 1972 as “A response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.”^[11] Iftikhar and Sarwar in a review article stated that fixed drug combinations are cost-effective, reduce the pill burden, and have logistical advantages, however, it

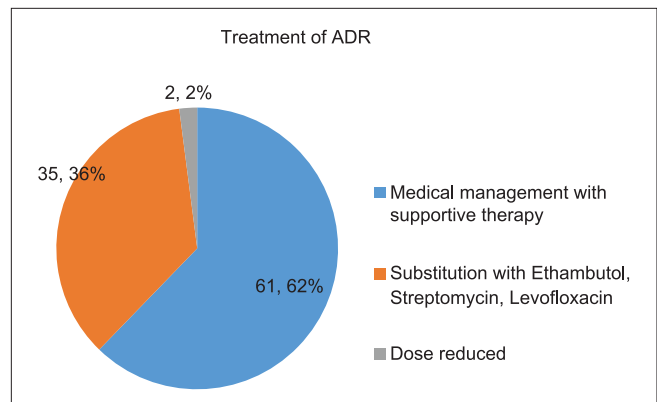


Figure 1: Treatment of adverse drug reaction

also has several disadvantages such as poor bioavailability, enzyme level elevation, difficulty in dose adjustments, and ADRs.^[12] A meta-analysis of five randomized controlled trials found that, four drug fixed-combination therapy did not have a significant overall incidence of adverse effects.^[13] Resende and Santos-Neto state that the major determinants of adverse reactions to ATT are the doses, the time of the day at which the drugs are administered, age above 40 years, nutritional status in terms of loss of body weight >15%, alcohol consumption >101 ml, N-acetyltransferase status, hyponatremia, hypoalbuminemia, and co-infection with HIV.^[14]

Previous studies have shown that the overall incidence of ADRs caused by anti-TB therapy ranges from 5.1% to 83.5%.^[15] In this study, the proportion of ADRs due to ATT was 15.25%. Age-group most affected was 46–75 years (66.3%). Previous studies state that the frequency of adverse reactions increases in a progressive and direct form in relation to age.^[16,17] The male:female ratio of patients reported to have ADR was 1.33:1 in this study. Studies elsewhere in contrast to our study found that the incidence of ADR to ATT was more in females as compared to males.^[18,19] Piparva *et al.*, reported a higher

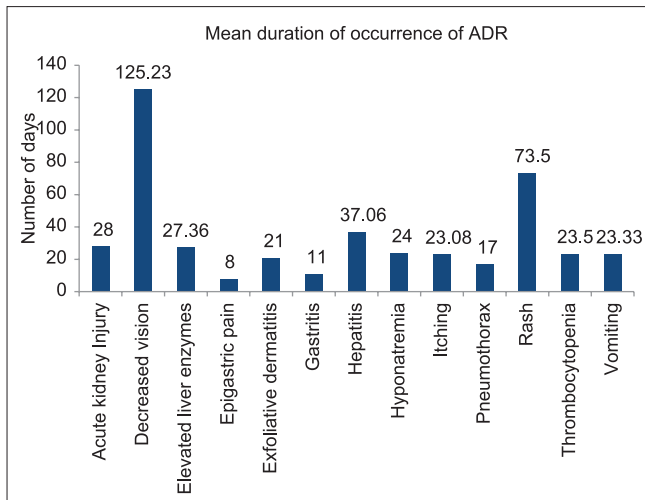


Figure 2: Temporal relation of adverse drug reaction

incidence of ADR to multidrug-resistant TB regimen in males and attributed it to increased awareness of health and care seeking tendency of males.^[20]

The most common organ system affected was the hepatobiliary system (46.9%) with 35 ADRs of hepatitis and 11 of asymptomatic elevated liver enzymes. Studies show that the risk of hepatotoxicity in patients from India is higher than those reported in the West (11.5% versus 4.3%).^[21] The common drugs causing hepatotoxicity are isoniazid, pyrazinamide, and rifampicin. The risk of toxicity of ATT becomes higher when aspartate transferase (AST) >3 times the upper level of normal in the presence of symptoms or >5 times the upper limit of normal in the absence of symptoms. Toxicity of mild level occurs if AST and alanine transferase is <5 times the upper limit of normal, moderate if rise by 5–10 times and if >10 times it is severe. The drugs have to be stopped and reintroduced in such a manner that the least likely causative agent should be reintroduced first.^[12] In patients with hepatitis FDC was replaced with ethambutol, streptomycin, and levofloxacin at the time of reporting of the ADR. Literature shows that high alcohol intake, female gender, older age, intake of other hepatotoxic drugs, poor nutritional status, preexisting liver disease, advanced disease, and acetylator status are risk factors for hepatitis.^[19] The mean duration of onset of asymptomatic elevated liver enzymes was 27.36 ± 34.87 (range 3–125) days and that of hepatitis was 37.06 ± 36.76 (range 1–145) days. In studies done elsewhere, hepatobiliary system was the most common organ system affected with mean duration of onset of liver dysfunction 17 (range 12–68) in one and 53 (range 28–60) days in other.^[19,22]

The proportion of visual impairment in this study is very high (26.5%) compared to those in previous studies with Directly Observed Treatment Strategy which have reported a very low incidence ranging from 0.2% to 1%.^[17,19,23] Ethambutol optic neuritis is dose related and is characterized with painless loss of central vision and cecentral scotomas. This causes reduction in visual field, visual acuity and loss of red green discrimination.^[23,24] Though reversible after stoppage of drug there are several reports of permanent damage.^[23] The mean duration of onset of visual impairment in this study was 125.23 ± 55.46 (range 4–180) days as compared to 46 (range 34–72) days in another.^[19] ADRs related to skin and appendages (16.3%) such as itching, exfoliative dermatitis, and rash accounted for the third most common system in this study. In a Brazilian study, it was noted that in patients receiving RHEZ-FDC ADRs related to skin and appendages was the most common.^[25]

The possible ADRs were Pneumothorax and Hyponatremia reported to our AMC by the NTEP unit of the institution. The causality assessment committee assigned it as possible because there was temporal relation of ATT with the event and it could also be explained by the disease. Khan *et al.*, stated that Pneumothorax, especially in miliary TB, can usually develop during the treatment with ATT.^[26] Choudhary *et al.*, have reported the occurrence of pneumothorax after 5 days of start of ATT.^[27] In this study, pneumothorax occurred 17 days after the initiation of ATT and hyponatremia occurred after 24 days. Jafari *et al.* found that there was no significant correlation between anti-TB medications and hyponatremia.^[28] Lv *et al.* found that the majority of the ADRs (53.1%) were probable in their study which is in line with this study.^[22]

Of the 98 ADRs, 77 (78.6%) were serious and were moderate-level 4b in severity (Hartwig and Siegel Scale), 57 (58.16%) were probably preventable (Schumock Thornton scale). All the ADRs were type B-Bizzare ADRs. In the study by Lv *et al.*, 92.3% ADRs were non-serious.^[22] Yee *et al.* stated that serious ADRs to ATT was common, and resulted in substantial health-care services utilization, as well as prolongation of therapy.^[17] In the study by Sinha *et al.*, most of the ADRs were mild (73.24%) and only 15.59% were severe reactions.^[18] Krishnamurthy *et al.* states that the most important determinants of a treatment outcome of drug-resistant TB are incidence and characteristics of ADR during the treatment which may be applicable to drug sensitive TB as well.^[29]

Limitations of this study are that only data reported to the AMC of the institution were included. There could have been a delay in reporting ADRs so the days of onset of ADR may actually reflect the time the ADRs were found and not the exact time it had happened.

CONCLUSIONS

Of all the ADRs reported to AMC 15.24% were due to the daily regimen of ATT. Hepatitis was the most common ADR encountered followed by decrease in vision. The majority of the ADRs were probable in causality, serious, moderate-level 4b in severity and probably preventable.

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Conflicts of interest

There are no conflicts of interest.

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