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Research Article

ASSESSMENT OF ADVERSE DRUG REACTIONS IN TUBERCULOSIS PATIENTS OF SOUTH INDIA

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ABSTRACT

Back ground: Tuberculosis (TB) has become one of the biggest public health challenges in India currently. India is one of the six countries accounted for 60% of the new cases in 2015. Objective: To monitor ADRs and report the occurrence of ADRs, their extent and severity with first line drugs. Materials and methods: The study was a prospective observational, hospital based case control study conducted in Govt. Infectious disease hospital, Guntur, India. The incidence of adverse drug reactions were identified and causality, severity were also analyzed. Results: The record of 308 ADRs was reported among 182(45.5%) patients with ADR occurrence of 1.69 per patient. Of the participants, 264(66%) were male. Maximum number of ADRs were seen in retreatment cases which was proved statistically (P=0.0027). There was a strong significant difference between HIV infected (OR= 3.69, 95% CI= 1.31-2.91; P < 0.0001) and HIV uninfected in occurrence of ADRs. Significant difference was found in total number of ADRs in Cat-I and Cat-II patients. Among 308 reported ADRs, tingling and numbness 34(11.04%) and anorexia 34(11.04%) were the most common ADRs reported. Maximum ADR events were mild 143(46.4%) followed by moderate 131(42.5%) and severe 34(11.0%). The most offending drug for causing ADRs is Isoniazid (32.47%), followed by Pyrazinamide (27.59), Rifampicin (24.36), Ethambutol (11.36) and Streptomycin (11.36%). Conclusion: This research creates the importance of close monitoring of patients who were at higher risk of getting ADRs by health care team and necessary steps should be taken in selecting the right drug regimen.

Key words: Adverse drug reactions, Directly Observed Treatment Short-Course (DOTS), Tuberculosis

INTRODUCTION

Tuberculosis remains one of the serious infectious diseases affecting people in the developing countries and the most important risk factor is human immunodeficiency virus (HIV).[1] Tuberculosis (TB) is a highly contagious infection caused by an acid-fast bacterium, Mycobacterium tuberculosis.[2] Early days physicians referred Tuberculosis as Phthisis, derived from a Greek term for wasting, because weight loss, cough, fever and hemoptysis were its main clinical presentations.[3] Tuberculosis (TB) has become one of the biggest public health challenges in India currently.[4] India is one of the six countries (India, Indonesia, China, Nigeria, Pakistan and South Africa) accounted for 60% of the new cases in 2015.[5] As per the Global TB report 2017 the estimated incidence of TB in India was approximately 28,00,000 accounting for about a quarter of the world's TB cases.[6]

Directly Observed Treatment Short-Course (DOTS) was introduced in India in 1993 as part of Revised National Tuberculosis Control Program (RNTCP) which has shown to be effective in TB patients.[7,8] Furthermore, World Health Organization (WHO) has recommended the use of standard short course therapy for active TB in HIV positive patients.[9] DOTS program involves the drug combinations of Isoniazid (INH), Rifampicin (RFP), Pyrazinamide (PZA), Ethambutol (EMB), and/or Streptomycin (SM) every other day for 6-9 months for complete treatment of TB.[10] Even though there are more benefits, some unwanted adverse drug reactions such as arthralgia, hepatotoxicity, gastrointestinal disorders, neurological disorders, visual disturbance, headache and skin rashes may be caused by DOTS therapy.[11,12] A higher incidence of Adverse Drug Reactions (ADRs) was noticed to occur in the first three months of therapy.[13] ADR is defined by the WHO as an unintended and noxious response to a drug that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function.[14] No anti-TB drug is without adverse reaction which is life threatening and lead to non-adherence.[15] ADRs are major limiting factor for completion of drug therapy under RNTCP which requires attention of all health care professionals.[16]

However, ADRs to the TB drugs have become a major area of concern for the medical professionals and health authorities. Therefore this study aims at occurrence of ADRs, their extent and severity with first line drugs.

MATERIALS AND METHODS

Study design and settings

The study was a prospective observational, hospital based case control study conducted in Govt. Infectious disease hospital,

Guntur, India from January, 2015 to December 2016. It was based only on those patients who experience an adverse reaction to medicine use, either during their stay in hospital or visiting the DOTS centre.

Ethics committee approval

The study protocol was prepared and submitted to the Govt. infectious disease hospital on human subject research for ethical clearance. The study was approved and issued ethical clearance certificate for the same (GOVT/ETH.COM/1180/2017).

Inclusion criteria

All patients suffering from pulmonary TB with or without HIV, both new cases and retreatment cases, patients who were visiting the DOTS centre, patients who were hospitalized while taking anti-TB drug regimen included in the study.

Exclusion criteria

All other forms of TB (extra pulmonary), like military TB, TB pleurisy, hilar and/or mediastinal lymphadenopathy, spinal, intestinal and genitourinary TB were excluded. Some patient's records were excluded due to incomplete information and transferred out to other health care clinics after the declination of the prescribed treatment.

Study procedure

Data on the reported ADRs were evaluated to understand the pattern of the ADR with respect to patient demographics, nature of the reactions, characteristics of the drugs involved, and outcome of the reactions. The adverse drug reaction occurring had to be identified, causality, severity was also to be analyzed. ADRs were identified by patient chart review method, spontaneous reporting by health care professionals. The degree of association of an adverse effect with a drug was done with the help of WHO scale where it involves certain; Probable; Possible; unlikely; unclassified.[17] After the causality assessment has been done, the severity of the ADR was analyzed using adapted Hart wig severity scale. The scale was classified as mild: a reaction that does not required treatment or prolongation of hospital stay; moderate: a reaction that requires treatment and/or prolongs hospitalization by at least one day; severe: a reaction that was potentially life threatening or contributes to the death of patient was permanently disabling requires intensive medical care or results in a congenital anomaly cancer or unintentional overdose.[18]

Statistical analysis

Data were recorded on a pre-designed proforma and managed on an MS Office Excel spread sheet. The descriptive statistics was represented by mean ± standard deviation and percentages. Graph Pad prism version 5.0 statistical software was used for the data analysis. The Adjusted Odds ratio (AOR) at 95% confidence interval was calculated for certain risk factor of ADRs in tuberculosis patients. For all analyses, *p<0.05, **p<0.01 and ***p<0.001 were regarded as statistically significant.

RESULTS

In total, 400 tuberculosis patients were registered at DOTs centre. The record of 308 ADRs was reported among 182(45.5%) patients with ADR occurrence of 1.69 per patient. The age of patients ranged from 20 to 76 years (mean= 45.79 ± 12.54). The occurrence of ADRs is 3 times more in patients aged above 50 years than that of patients aged below 50 years which was proved significant (OR=3.63; CI=2.37-5.55; *P*< 0.0001). Of the participants, 264(66%) were male, 136(34%) were female. The incidence of ADRs was higher in female (58.82%) when compared to male (52.27%) but it was not significant (*P*= 0.243). Majority of patients belongs to ≤45 category and had more incidence of ADRs which was statistically significant (*P*=0.0074). There were 67.25% (269) new cases and 32.75% (131) were retreatment cases. Maximum number of ADRs were seen in retreatment cases which was proved statistically (*P*=0.0027). 188(47%) patients have at least one co-morbidity and had double the number of ADRs when compared to patients 212(53%) without co-morbidity. There was a strong significant difference between HIV infected (OR= 3.69, 95% CI= 1.31-2.91; P < 0.0001) and HIV uninfected in occurrence of ADRs. It had been estimated that 272 (68%) patients resulted in smear positive whereas 128(32%) resulted in smear negative. ADRs were more common in smear negative patients. Regarding category of treatment, 267(66.75%) undergone cat-I treatment and 133(33.25%) undergone cat-II treatment. Significant difference was found in total number of ADRs in cat-I and cat-II patients. There were 47.25% (189) cases had a history of smoking and 35.25% (141) had a habit of alcohol consumption. ADRs observed in smokers and alcoholics were higher compared to that of non-smokers and non-alcoholics respectively. Polypharmacy was seen in 260(65%) patients whose prevalence was more in ADRs. Table 1 showed that factors associated with occurrence of ADRs in tuberculosis patients.

Among 308 reported ADRs, tingling and numbness 34(11.04%) and anorexia 34(11.04%) were the most common ADRs reported followed by insomnia 29(9.41%), arthralgia 27(8.76%) and vomiting 23(7.47%). The organ systems most affected by ADRs were the nervous system (27.92%), followed by the gastrointestinal disturbances (24.67%), hypersensitivity (9.1%), musculoskeletal system (8.76%), hematological (6.82%), ophthalmic (6.49%), urinary tract (2.92%) and others (13.31%). The most commonly identified adverse drug reactions affecting nervous system were tingling and numbness 34(11.04%) followed by insomnia 29(9.41%), seizures 13(4.22%) and headache 10(3.24%). The drugs responsible for these effects were INH and EMB. Of 308 reported ADRs, 76(24.67%) were related to gastrointestinal tract. Majority of gastrointestinal tract ADRs were anorexia 34(11.04%) followed by vomiting 23(7.47%), hepatotoxicity 7(2.27%), abdominal pain 6(1.95%) and diarrhea 6(1.95%). INH, PZA and RFP were responsible for these ADRs. 28(15.38%) patients were affected with hypersensitivity reactions among which 13 cases (4.22%) were erythema, 9 (2.92%) Urticaria and 6 (1.95%) skin allergies. Drugs responsible for these ADRs were INH, RFP, PZA and EMB. 27(8.76%) cases of arthralgia were seen in 14.84% of patients. Thrombocytopenia 15(4.87%) topped the list in hematological reactions, followed by anemia 6(1.95%). Drugs causing thrombocytopenia were RFP and PZA where as drug causing anemia was INH. 10.99% of patients reported ophthalmic manifestations like blurred vision 12(3.89%) and color blindness 8(2.59%) which were caused by EMB. Dysuria 7(2.27%) and hyperuricemia 2(0.65%) were noticed among the patients with 4.94% of them. The other ADRs like edema 15(4.87%), ototoxicity 10(3.25%), glossitis 9(2.92%) and photosensitivity 7(2.27%) accounted for 13.31%. Distribution of adverse drug reactions in all tuberculosis patients was shown in Table 2.

Based on severity of ADRs in patients, ADRs were classified into mild ADRs, moderate ADRs and severe ADRs. Maximum ADR events were mild 143(46.4%) followed by moderate 131(42.5%) and severe 34(11.0%). In this study severe ADRs found were seizures (nervous system), diarrhea and hepatotoxicity (gastrointestinal disturbances), thrombocytopenia (hematological) and ototoxicity (others). As per WHO scale, probability of ADR is classified into 3 categories. Most of the ADRs 215(69.8%) were having probable relationship with the

suspected drugs followed by possible 93(30.19%) as shown in the Table 3.

The most offending drug for causing ADRs was Isoniazid (32.47%), followed by Pyrazinamide (27.59%), Rifampicin (24.36%), Ethambutol (11.36%) and Streptomycin(11.36%). Table 4 had shown drugs most frequently implicated for ADRs.

DISCUSSION

Tuberculosis is the most pandemic infectious disease in developing countries like India. Revised National Tuberculosis Control Program (RNTCP) was introduced in India in 1993 as part of tuberculosis control programs. The main hurdle for non-adherence to the anti-TB drug regimen is occurrence of ADRs. So the present study focused on monitoring and evaluating the ADRs causality and severity and finding drugs which is responsible for more ADRs.

In our study ADR occurrence rate was 1.69 per patient. Incidence of ADR was higher in females compared to males. In contrast to this, a study conducted by Dedun AR et al[19] showed that incidence of ADRs was more common in males. The reason for more occurrences of ADRs in females might be due to female's different life stages like pregnancy, menarche which modifies the drug response.[20]

It was apparent from the study that patients aged above 50 years had triple the number of ADRs compared to the patients below 50 years which can be comparable to other study showed that the elderly showed a higher frequency of adverse drug reactions (18.5% vs. 40.7%, $p<0.05$).[21]

Weight loss was more common in all tuberculosis patients. The present study expressed that patients belongs to ≤45 category had more incidence of ADRs which was statistically significant. It is due to decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation.[22]

Most of the cases enrolled in this study were new cases. Only a small group of patients were retreatment cases. Retreatment involves relapse, failure, transferred in and return after default. Treatment failure was the most common group among patients who had failed initial treatment.[23] Smoking, alcohol consumption, drug resistance during treatment period were important risk factors for relapse which leads to more ADRs.[24] From this study we can understand that the chances of getting ADRs in retreatment group were higher compared that of new cases.

Patients with co-morbidities had experienced more ADRs than that of patients without co-morbidities. Co-morbidity can drastically weaken the immune system. Co-presentation of TB with other communicable and non-communicable diseases is considered as an important risk factor for result of more ADRs.[25] Among co-morbidities, diabetes mellitus cases were highest which was similar to other study.[26]

Our study demonstrated that HIV is one of the major risk factors for causing more number of ADRs in tuberculosis patients. Patients co-infected with HIV had 3 times more risk than patients without HIV. Similar results were seen in a study by sadiq s et al[27] and fellay J et al[28] showed that concomitant HAART and ATT results in more ADRs. Most of the ADRs in patients with HIV were occurred within a year.[29]

The result determined that smear negative patients were affected by more ADRs. Smear negative patients may have all symptoms of tuberculosis but many of these patients give positive culture test for mycobacterium later. So there is confusion whether to start chemotherapy or to wait for some more time. This time lag may lead to more complications like late response for certain drug regimen and also more ADRs.[30]

Patients receiving CAT II drugs were prone to develop more ADRs (59.39%) than patients with CAT I drugs (38.57%). This was in accordance with the study done by dhanalakshmi d et al where ADRs percentage was 48.8% and 21.1% in CAT II and CAT I drugs respectively.[31]

Our study depicted that 47.25% patients were smokers and 35.25% had habit of alcohol. Incidence of ADRs was more in smokers and alcohol intake patients which results in weakened immunity.[32,33]

Prevalence of ADRs was more in patients with polypharmacy which might be major concern in medication errors and drug interactions which further lead to adverse drug reactions.[34,35]

Nervous system was the first most organ system affected in our study. It was noticed that tingling and numbness 34(11.04%) was found to be major ADR followed by insomnia 29(9.41%), seizures 13(4.22%) and headache 10(3.24%). But this is disagreed with the other studies [36,37] where GIT system was affected more. But current study showed GIT is the second most organ affected. Among GIT ADRs, the major ADR was anorexia 34(11.04%) followed by vomiting 23(7.47%), hepatotoxicity 7(2.27%), abdominal pain 6(1.95%) and diarrhea 6(1.95%). This is in similar to the study conducted by Rashmi pusunoori et al.[38]

Majority of ADR events were mild 143(46.4%) followed by moderate 131(42.5%) and severe 34(11.0%). In this study severe ADRs found were seizures, diarrhea, hepatotoxicity, thrombocytopenia and ototoxicity. Other study[39] depicted that severe ADRs were decreased hearing, psychosis, dizziness, tinnitus, nausea, vomiting, joint pain, depression and rash.

Most of the ADRs 215(69.8%) were having probable relationship with the suspected drugs followed by possible 93(30.19%) which is dissimilar with the studies where most of the ADRs were having possible relationship with suspected drugs.[27,40]

Isoniazid was topped the list of anti-tubercular drugs causing ADRs (32.47%) followed by pyrazinamide (27.59%), rifampicin (24.36%), ethambutol (11.36%) and streptomycin (44.22%).[41] INH was mainly responsible for causing Tingling and numbness (11.03%). The exact mechanism of INH induced peripheral neuropathy is not well understood. It interferes with the metabolism of vitamin B6 leading to inactiveness of B6. It necessitates the supplementation of pyridoxine.[42] The severe ADRs caused by PZA were thrombocytopenia (3.25%) and hepatotoxicity (1.3%). Thrombocytopenia is unusual and is characterized by expeditious destruction of platelets and is secondary to pyrazinamide.[43] It is difficult to diagnose but easy to prevent just by stopping the exposure to the same drug again.[44] The reported anti tubercular drug-induced hepatotoxicity lies between 2% and 28%.[45] Hepatotoxicity caused by PZA is due to the toxic metabolite 5-hydroxypyrazinoic acid (5-OH-PA).[46] Even though RFP caused more number of arthralgia, all were mild in severity. All primary anti-tubercular drugs may cause thrombocytopenia. In Rifampicin induced thrombocytopenia, rifampicin should not be re-administered as it causes subsequent immune reaction even at small doses.[47] Blurred vision is a well-known problem arising from ethambutol used for about 8 months but it is reversible on discontinuation of offending drug and is dose dependent.[48] The risk factors considered for this ethambutol induced blurred vision were age, hypertension and renal diseases.[49]

Table 1: Factors associated with occurrence of ADRs in tuberculosis patients

Variables	Cases with ADR (n=182)	Cases without ADR (n=218)	AOR (95% CI)	*P*-Value
Age(years)				
≤50	84(37.73)	165(66.26)	1.00	
>50	98(64.9)	53(35.09)	3.63(2.37-5.55) ***	<0.0001
Gender				
Female	56(41.17)	80(58.82)	1.00	
Male	126(47.7)	138(52.27)	1.30(0.85-1.98)	0.243
Initial Weight				
>45	58(36.94)	99(63.05)	1.00	
≤45	124(51.02)	119(48.97)	1.78(1.18-2.68) **	0.0074
History				
New cases	108(40.14)	161(59.85)	1.00	
Retreatment	74(56.48)	57(43.51)	1.93(1.27-2.95) **	0.0027
Co-morbidity				
No	80(37.73)	132(62.26)	1.00	
Yes	102(54.25)	86(45.74)	1.96(1.31-2.91) **	0.0013
HIV status				
Negative	143(41.32)	203(58.67)	1.00	
Positive	39(72.22)	15(27.77)	3.69(1.96-6.95) ***	<0.0001
Smear test				
Positive	112(41.17)	160(58.82)	1.00	
Negative	70(54.68)	58(45.31)	1.72(1.12-2.63) *	0.0133
Treatment type				
Cat-I	103(38.57)	164(61.42)	1.00	
Cat-II	79(59.39)	54(40.6)	2.33(1.52-3.56) ***	0.0001
Smoking				
No	84(39.81)	127(60.18)	1.00	
Yes	98(51.85)	91(48.14)	1.63(1.09-2.42) *	0.0162
Alcohol				
No	109(42.08)	150(57.91)	1.00	
Yes	73(51.77)	68(48.22)	1.48(0.98-2.23)	0.074
No of drugs				
≤5	59(42.14)	81(57.85)	1.00	
>5	123(47.36)	137(52.69)	1.23(0.81-1.87)	0.344

Statistical Significance: *p<0.05, **p<0.01 and ***p<0.001

Table 2: Distribution of adverse drug reactions in all tuberculosis patients

Sl. No	Description of ADR	No. of ADRs n= 308(%)	No. of patients n= 182(%)	Suspected product
1	**Nervous system**	**86(27.92)**	**86(47.25)**	
	Tingling and numbness	34(11.04)	34(18.68)	Isoniazid
	Insomnia	29(9.41)	29(15.93)	Isoniazid
	Seizures	13(4.22)	13(7.14)	Isoniazid
	Headache	10(3.24)	10(5.49)	Ethambutol
2	**Gastrointestinal disturbances**	**76(24.67)**	**76(41.75)**	
	Anorexia	34(11.04)	34(18.68)	Pyrazinamide
	Vomiting	23(7.47)	23(12.64)	Rifampicin/Pyrazinamide
	Hepatotoxicity	7(2.27)	7(3.85)	Isoniazid/Pyrazinamide
	Abdominal pain	6(1.95)	6(3.30)	Rifampicin
	Diarrhea	6(1.95)	6(3.30)	Pyrazinamide
3	**Hypersensitivity**	**28(9.1)**	**28(15.38)**	
	Erythema	13(4.22)	13(7.14)	Isoniazid/Pyrazinamide
	Urticaria	9(2.92)	9(4.95)	Rifampicin
	Skin allergy	6(1.95)	6(3.30)	Ethambutol/Pyrazinamide
4	**Musculoskeletal system**	**27(8.76)**	**27(14.83)**	
	Arthralgia	27(8.76)	27(14.84)	Rifampicin
5	**Hematological**	**21(6.82)**	**21(11.53)**	
	Thrombocytopenia	15(4.87)	15(8.24)	Pyrazinamide/Rifampicin
	Anemia	6(1.95)	6(3.30)	Isoniazid
6	**Ophthalmic**	**20(6.49)**	**20(10.99)**	
	Blurred vision	12(3.89)	12(6.59)	Ethambutol
	Color blindness	8(2.59)	8(4.40)	Ethambutol
7	**Urinary tract**	**9(2.92)**	**9(4.94)**	
	Dysuria	7(2.27)	7(3.85)	Pyrazinamide
	Hyperuricemia	2(0.65)	2(1.10)	Pyrazinamide/Ethambutol
8	**Others**	**41(13.31)**	**41(22.53)**	
	Edema	15(4.87)	15(8.24)	Rifampicin
	Ototoxicity	10(3.25)	10(5.49)	Streptomycin
	Glossitis	9(2.92)	9(4.95)	Isoniazid
	Photosensitivity	7(2.27)	7(3.85)	Pyrazinamide/streptomycin

Table 3: Causality and severity assessment of ADRs

S.NO	Description of ADR	Frequency(%)	Severity			Probability	
			Mild	Moderate	Severe	Possible	Probable
1	**Nervous system**	**86(27.92)**	**39(27.27)**	**34(25.95)**	**13(38.23)**	**10(4.65)**	**76(81.72)**
	Insomnia	29(9.41)	29(20.27)				29(31.18)
	Seizures	13(4.22)			13(38.23)		13(13.97)
	Peripheral neuropathy	34(11)		34(25.95)			34(36.55)
	Headache	10(3.24)	10(6.99)			10(4.65)	
2	**Gastrointestinal disturbances**	**76(24.67)**	**61(42.6)**	**6(4.58)**	**9(26.47)**	**12(5.58)**	**64(68.81)**
	Anorexia	34(11.04)	34(23.77)				34(36.55)
	Abdominal pain	6(1.95)	6(4.19)			6(2.79)	
	Vomiting	23(7.47)	17(11.88)	6(4.58)			23(24.73)
	Diarrhea	6(1.95)	4(2.79)		2(5.88)	6(2.79)	
	Hepatotoxicity	7(2.27)			7(20.58)		7(7.52)
3	**Hypersensitivity**	**28(9.1)**		**28(21.37)**		**13(6.04)**	**15(16.12)**
	Erythema	13(4.22)		13(9.92)		13(6.04)	
	Urticaria	9(2.92)		9(6.87)			9(9.67)
	Skin allergy	6(1.95)		6(4.58)			6(6.45)
4	**Musculoskeletal system**	**27(8.76)**	**27(18.9)**			**27(12.55)**	
	Arthralgia	27(8.76)	27(18.88)			27(12.55)	
	Hematological	**21(6.82)**		**15(11.45)**	**6(17.64)**		**21(22.58)**
	Thrombocytopenia	15(4.87)		9(6.87)	6(17.64)		15(16.12)
5	Anemia	6(1.95)		6			6(6.45)
	Ophthalmic	**20(6.49)**		**20(15.26)**			**20(21.5)**
	Blurred vision	12(3.89)		12(9.16)			12(12.9)
6	Color blindness	8(2.59)		8(6.1)			8(8.6)
	Urinary tract	**9(2.92)**	**9(6.29)**			**7(3.25)**	**2(2.15)**
7	Dysuria	7(2.27)	7(4.89)			7(3.25)	
	Hyperuricemia	2(0.65)	2(1.39)				2(2.15)
	Others	**41(13.31)**	**7(4.89)**	**28(21.4)**	**6(17.64)**	**24(11.16)**	**17(18.27)**
8	Edema	15(4.87)		15(11.45)		15(6.97)	
	Ototoxicity	10(3.25)		4(3.05)	6(17.64)		10(10.75)
	Glossitis	9(2.92)		9(6.87)		9(4.18)	
	Photosensitivity	7(2.27)	7(4.89)				7(7.52)
	Total	**308(100)**	**143(46.4)**	**131(42.5)**	**34(11.0)**	**93(30.19)**	**215(69.8)**

Table 4: Drugs most frequently implicated for ADRs

DRUGS	No. of ADRs (%)	Frequency of ADR with %
Isoniazid	100(32.47)	Tingling and numbness 34(11.03),Insomnia 29,Seizures 13(4.22), Glossitis 9(2.92), Erythema 6(1.95), Anemia6(1.95), Hepatotoxicity 3(0.97)
Pyrazinamide	85(27.59)	Anorexia 34(11.03), Thrombocytopenia 10(3.25), vomiting 10(3.25), Dysuria7(2.27), Erythema 7(2.27), Diarrhea 6(1.95),Hepatotoxicity 4(1.3),Photosensitivity 4(1.3), Skin allergy 2(0.64),Hyperuricemia 1(0.32)
Rifampicin	75(24.36)	Arthralgia 27(8.76), Edema15(4.87), Vomiting 13(4.22), Urticaria 9(2.92), Abdominal pain 6(1.95),Thrombocytopenia 5(1.62)
Ethambutol	35(11.36)	Blurred vision 12(3.9),Headache 10(3.25), Color blindness 8(2.6), Skin allergy 4(1.3), Hyperuricemia 1(0.32)
Streptomycin	13(4.22)	Ototoxicity 10(3.25),Photosensitivity 3(0.97)

Streptomycin is an amino glycoside antibiotic included in the category II drug regimen for re-treatment cases. Streptomycin induced ototoxicity is manifested as ataxia and nystagmus due to vestibular impairment followed by damage to vestibular sensory cells.[50] Streptomycin is predominantly vestibulotoxic which is reversible and dose dependent.[51]

CONCLUSION

All anti-tubercular drugs trigger one or more ADRs which may lead to non-adherence and had shown many unpleasant affects in TB patients particularly in patients co-infected with HIV. The effective management of tuberculosis includes initiation and successful completion of treatment with least possible side effects. This creates the importance of close monitoring of patients who were at higher risk of getting ADRs by health care team and necessary steps should be taken in selecting the right drug regimen and creating the awareness of causes and immediate reporting of ADRs among tuberculosis patients. The interventions should be done in patients whose weight is below 45 kg, smokers, alcoholics, elderly, retreatment cases and smear negative and HIV co-infected patients.

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ABBREVIATIONS

ADR: Adverse Drug Reaction,
AOR: Adjusted odds ratio,
ATT: Anti Tubercular Therapy,
DOTS: Directly Observed Treatment Short-Course,
EMB: Ethambutol,
Govt. ID: Government Infectious Disease,
HAART: Highly Active Antiretroviral Therapy,
INH: Isoniazid,
PZA: Pyrazinamide,
RFP: Rifampicin,

RNTCP: Revised National Tuberculosis Control Program,
SM: Streptomycin,
WHO: World Health Organization.

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