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Research Article

Safety evaluation of directly observed treatment short course (DOTS) regimen in a tertiary care hospital, Pune

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ABSTRACT

Background: Directly observed treatment short course (DOTS) is a cornerstone of Revised National Tuberculosis Control Program of India. Adverse drug reactions (ADRs) induced by this therapy is common and it causes significant morbidity and mortality. Hence, the present study was undertaken to determine the incidence and pattern of ADRs and to assess causality and severity.
Methods: We conducted prospective, observational study at DOTS center of tertiary care hospital, Pune. 150 pulmonary tuberculosis patients undergoing DOTS therapy were enrolled. They were monitored weekly in an intensive phase and monthly in the continuation phase. The suspected ADRs were recorded and assessed for causality and severity by standard algorithms.
Results: Incidence of ADRs due to DOTS was 19.33% & total 35 ADRs had occurred in our study. Gastrointestinal intolerance, arthralgia & itching with or without rashes were most common ADRs (incidence rates: 12.67%, 2.67% and 2.67%, respectively). On evaluation of causality by Naranjo algorithm, majority of ADRs 91.43% were "possible." As per WHO- Uppsala Monitoring Center scale, majority of ADRs 91.43% were "possible." As per Modified Hartwig and Siegel scale, majority of ADRs were "moderate" (48.57%) but 8.57% were "severe." Female gender was found to be a significant risk factor for developing ADRs (odds ratio: 3.08, 95% confidence interval: 1.33-7.12. 3.33%). ADRs & hepatotoxicity was major reason for defaulting from DOTS (60%).
Conclusion: ADRs induced by DOTS are common and there is need of incorporating pharmacovigilance system for this vital public health program. Counseling of patients for timely prevention, detection, and management of ADRs will help in minimizing the further occurrence of ADRs.

Keywords: DOTS, Adverse drug reactions, Tuberculosis, Pharmacovigilance

INTRODUCTION

Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. India ranked first amongst all TB high-burden countries, having 2.2 million incident cases and 3,00,000 deaths in 2011.[1] In order to intensify the efforts to control TB, Government of India gradually replaced National Tuberculosis Program with the Revised National Tuberculosis Control Program (RNTCP).[2] Directly observed treatment short course (DOTS) is the cornerstone of RNTCP which requires continually taking drug combinations of isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), ethambutol (EMB) and/or streptomycin (SM)every other day for 6-9 months.[3,4]

Though efficacy of DOTS is well-proven, studies have shown that utilization of multidrug regimens can cause undesirable adverse drug reactions (ADRs) of varying degrees of severity, such as hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgia, and neurological disorders.[5-9] In addition, ADRs are regarded as one of the major causes of non-adherence to anti-TB treatment.[10] ADRs may eventually contribute to the extension of treatment duration, final termination, drug resistance and treatment failure.[11] As to the overall incidence of ADRs caused by anti-TB therapy, no consensus has been reached worldwide, with the incidence of ADRs ranging from 5.1% to 83.5%, respectively.[5-8,12-19]

National TB programs are generally well structured to monitor patients and have a long tradition of following up care using standardized indicators, they do not collect information on ADRs directly.[20] There is a dearth of published literature about anti-TB drug-induced mortality,

morbidity and reduced quality of life, particularly in low-resource settings.[20] Majority of studies regarding ADRs of anti-TB drugs are hospital-based retrospective studies. There is paucity of population based prospective studies especially for Indian population. So, present study was undertaken to determine incidence & pattern of ADRs. ADRs were assessed for causality and severity. Influence of various possible risk factors for developing ADRs was also studied.

METHODS

The present study was prospective, observational study conducted at DOTS center of a tertiary care hospital, Pune during the period between October 2011 and May 2013. The study was started after getting approval from Institutional Ethics Committee [BVDU/MC/36]. A total of 150 patients diagnosed pulmonary TB of either sex and at least 18 years of age, undergoing DOTS regimen were enrolled in the study. HIV positive patients & multidrug-resistant TB patients were excluded. A therapeutic profile of all the patients were maintained in data collection form standard RNTCP card in which DOTS category, date of start and completion of DOTS treatment, record of follow-up and outcome of the patient's treatment were recorded. These patients were monitored for ADRs during their entire treatment regime. Follow-up was done weekly in intensive phase & monthly in continuation phase. During the follow-up, patients were questioned specifically regarding the occurrence of any adverse effect of TB drugs. ADRs were recorded in standard CDSCO ADR form. All decisions relating to management of the patients including drugs and investigations were taken by DOTS center personnel. Investigator did not interfere in the management of patient and only observed the proceedings.

ADRs were classified as per the WHO adverse reaction terminology.[21] All the ADRs were evaluated for their causality using Naranjo's Algorithm[22] and the WHO Uppsala Monitoring Centre (UMC) scale.[23] Suspected ADRs with causality status less than "possible" were not considered for further analysis. Severity assessment was done using the Hartwig et al. Scale.[24] For causality and severity assessment, all the suspected ADRs were discussed with the medical officer & treating clinician. Influence of various possible risk factors for developing ADRs was also studied.

Statistical methods

Data analysis was performed using Microsoft Excel and GraphPad Prism (software version 5). Results were expressed as numbers and percentages. Descriptive statistics were used to analyze data regarding incidence, causality, and severity assessment of ADRs. For influence of possible risk factors for developing ADRs, odds ratio (OR) was used. $p<0.05$ was considered as statistically significant.

RESULTS

The present study was carried out in DOTS center of a tertiary care hospital, Pune. A total of 174 patients with pulmonary TB were screened. Among them, 150 patients were enrolled as per study criteria (Table 1).

In our study, maximum number of tubercular patients was in age group of 18-40 years (56.66%). Majority of patients were males (60%). Majority of patients were from Category I (80%). Out of 150 patients, 21.67% were alcoholics. Median weight of patients was 48 kg.

As shown in Figure 1, the most frequently occurred ADRs were gastrointestinal system disorders (12.67%). This was followed by skin and appendages disorders, musculo-skeletal system disorders and central & peripheral nervous system disorders (2.67% each).

Total 35 ADRs occurred in 29 patients. Gastrointestinal (GI) intolerance was most frequently occurred ADR (12.67%). It was followed by arthralgia (2.67%) & hepatotoxicity (2%).

Naranjo algorithm revealed that out of 35 ADRs 32 (91.43%) were "possible" and 3(8.57%) were "probable." "Probable" ADRs included two cases of hepatotoxicity and one case of ototoxicity.

The WHO scale assessment revealed that out of 35 ADRs 32 (91.43%) were "possible" and 1 (2.86%) were "probable" and two ADRs (5.71%) were "certain." "Certain" ADRs included two cases of hepatotoxicity.

The severity assessment showed that majority of ADRs (17, 48.57%) were "moderate," followed by "mild" (15, 42.86%). Only 3 (8.57%) were "severe" ADRs.

Table 2 shows that likelihood of ADRs was significantly higher among female patients (OR: 3.08). Though the risk of

Table 1: Baseline characteristics of study population (n=150).

Parameter	No. (%)
1. Age group (years)	
18-40	85 (56.66)
41-60	59 (39.33)
>60	6 (4)
2. Sex	
Male	90 (60)
Female	60 (40)
3. DOTS category	
Category I	120 (80)
Category II	30 (20)
4. Alcoholics	31 (20.67)
Weight (kg) median-(inter-quartile range)	48 (38-58)

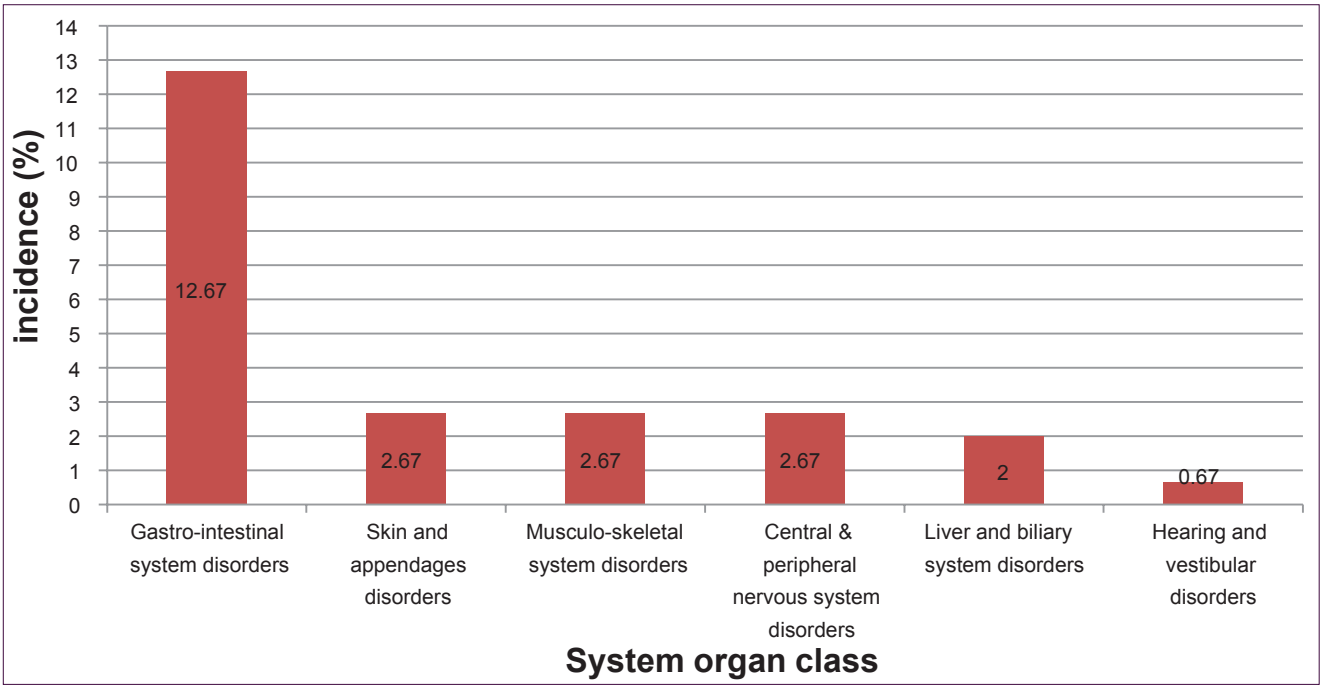

Figure 1: Incidence of ADRs as per system organ class.

Table 2: Influence of possible risk factors for developing ADRs.

Possible risk factors	Total patients	No. of patients with ADR (incidence, %)	Odds ratio	Confidence interval
1. Age				
18-40	85 (56.66)	17 (20)	1	
41-60	59 (39.33)	10 (16.95)	0.81	0.34-1.94
>60	6 (4)	2 (33.33)	2	0.34-11.85
2. Gender				
Male	90 (60)	11 (12.22)	1	1.33-7.12
Female	60 (40)	18 (30)	3.08**	
3. DOTS category				
Category I	120 (80)	22 (18.33)	1	0.52-3.56
Category II	30 (20)	7 (23.33)	1.36	
4. Alcohol habits				
Non-alcoholic	119 (79.33)	20 (16.81)	1	0.81-5.04
Alcoholic	31 (20.67)	9 (29.03)	2.02	

**p<0.001

ADRs was seen higher with aged over 60 years, alcoholics and Category II patients, it was not statistically significant.

DISCUSSION

The use of limited number of medicines in the public health programs that treat large number of patients provide an opportunity to quickly generate real life data on the efficacy, safety, and tolerability of the medicines. The public health programs provide a unique opportunity for improving pharmacovigilance activities in resource-limited settings.[25] The RNTCP of India has implemented a successful DOTS strategy since 1993.[26] However not much data are available to reinforce the safety and tolerability of the medicines or to characterize patient's risk profile. Identification of the ADR profile of drugs can provide valuable information for the prescribers and policy makers in implementing appropriate measures to prevent the occurrence of similar ADRs. With keeping these objectives in mind, we conducted this study.

Incidence of ADRs due to DOTS regimen was 19.33%. Twenty-nine patients developed at least one ADR & six patients developed two ADRs. Thirty-five ADRs in total were detected. Compared with the most hospital-based studies,[7,8,12-17] the incidence of ADRs in our study was lower. The hospitalized participants were likely to have more

complex and serious diseases and were monitored more frequently, thus increasing the chances of discovering ADRs. In a population based study conducted by Marra et al.,[6] incidence of ADRs was 30% which was more compared to our study. This could be due to smaller sample size & exclusion of extra pulmonary TB patients & HIV positive patients in our studies as they have increased chances of ADRs.[5,27] ADRs due to anti-TB drugs depend on multiple factors such as ethnicity, age and nutritional status, together with the presence of preexisting diseases or dysfunctions, such as alcoholism, impaired liver function, impaired kidney function, drug interaction, etc.[8] All ADRs occurred in an intensive phase. Other studies have also shown that majority of ADR occur in intensive phase.[6,7]

In our study, 19 patients (incidence: 12.67%) developed GI intolerance (nausea/vomiting/gastritis)as shown in Table 3. This was most frequently observed ADR. (19 out of 35) (54.25%). All of them occurred in first 2 weeks of the treatment. Most of them (13) were mild & not given any symptomatic treatment. Six of them were given symptomatic treatment like omeprazole or domperidone. One female in our study had persistent gastritis & vomiting. She was given symptomatic treatment in form of omeprazole & domperidone for a week. Liver function tests were carried out & values were within normal range. However, patient was not comfortable with the treatment & eventually defaulted. GI upset could occur with any oral medication. Though many possible risk factors are suggested for various ADRs of anti-TB drugs, no specific risk factor is studied for GI intolerance. Incidence of GI upset is 12.67% in our study is comparable to studies by Shinde et al.[28] (12.65%) & Marra et al.[6] (10%). In general, gastrointestinal effects are mild but may be severe enough in occasional patients requiring modification in the treatment.

Table 3: Types & incidence of adverse drug reactions.

System organ class - type of ADR	No. of patients (incidence, %)
1. Gastro-intestinal system disorders	19 (12.67)
GI intolerance (nausea/vomiting/gastritis)	19 (12.67)
2. Skin and appendages disorders	4 (2.67)
Itching without rash	2 (1.3)
Itching with rash	2 (1.3)
3. Musculo-skeletal system disorders	4 (2.67)
Arthralgia	4 (2.67)
4. Central & peripheral nervous system disorders	4 (2.67)
Peripheral neuropathy	2 (1.3)
Drowsiness	2 (1.3)
5. Liver and biliary system disorders	3 (2)
Hepatotoxicity	3 (2)
6. Hearing and vestibular disorders	1 (0.67)
Ototoxicity	1 (0.67)

Other most frequently occurred ADR was arthralgia which occurred in four patients (incidence: 2.67%) (Table 3). All of them occurred in 1st month except in one patient who developed it in 3rd month. None of the case was severe & they were given symptomatic treatment with aspirin or diclofenac. Two patients were advised for serum uric acid levels, but it turned out to be within normal range. All patients were reassured and advised to increase intake of fluids. Arthralgia is a known ADR of PZA.[29] Incidence of 2.67% in our study is comparable to other studies.[7,8,12-17]

Four patients (incidence: 2.67%) developed itching with or without rash (Table 2). Two patients had only itching & no rash while one had mild rash with itching which was observed in 1st week. Reactions were mild in all of them except one patient. They were given symptomatic treatment with antihistamines & they got subsided. One female had maculopapular rash over inner thighs & medial aspect of upper limbs in the 1st week of treatment. All drugs were stopped immediately & patient was referred to dermatology department. Desensitization was tried out & INH was found as an offending agent. Before she could be put on modified regimen, she defaulted. Itching with or without rash is generally attributable to INH, SM, RFP or PZA.[29] Isoniazid is more commonly involved out of all four drugs. In the present study, one case of rash was attributed to INH while the other case of rash could not be attributed to one specific drug as it was mild & no dechallenge or desensitization was carried out. Incidence of 2.67% in our study is less compared to study of Marra et al.[6] where incidence was 7.5%. This might be because of inclusion of HIV patients (5.5%) as patient with HIV has increased chances of skin reactions.[30]

In our study, three patients (incidence: 2.67%) developed hepatotoxicity (Table 3). All three reactions occurred in intensive phase of regimen. Immediately, all anti TB drugs were stopped & patients were referred for evaluation. Liver function tests were carried out in all of them & elevated enzyme levels were found in all of them. All three cases were diagnosed as hepatotoxicity as per study definition. One patient of them defaulted after that & could not be put back on DOTS regime even after several attempts made by DOTS personnel. In remaining two patients, treatment was withheld & both were put on different regime (EMB, SM & ofloxacin on a daily basis) by pulmonary department. Liver enzymes returned to normal in 15-20 days in both patients. Then reintroduction of INH, RFP & PZA were tried out in stepwise manner as per hospital protocol. In both patients, RFP turned out to be offending agent. After that both patients decided to continue on daily regimen suggested by pulmonary department & defaulted from DOTS. It is well-known that INH, RFP & PZA are the most common potential drugs that cause hepatic injury.[29,31] The exact mechanism of antituberculosis drug-induced hepatotoxicity (ATDH)

is unknown, but toxic metabolites are suggested to play a crucial role in the development, at least in the case of INH.[30-32] Incidence of hepatotoxicity in our study is 2.67% which is less compared to other studies.[7,8,12-17] Important reasons could be less sample size & exclusion of HIV patients. HIV patients are at increased risk of hepatotoxicity.[31] Among the most widely accepted risk factors for ATDH are advanced age (above 60 years), female sex and low body mass index or malnutrition.[31,33] Previous history of hepatitis & alcohol consumption are also considered important risk factors though reports are inconclusive.[30,31-33] In our study, all three patients were male in age group of 18-40 years. Except for alcohol consumption, other risk factors were absent in all three patients.

In our study, two patients (incidence: 1.3%) developed peripheral neuropathy (Table 3). It occurred in 2nd month. Both were given pyridoxine 100 mg/day.

Peripheral neuropathy is a known ADR of INH.[29] Though uncommon (<0.2%) at currently prescribed dosages, risk increases in the presence of associated conditions, such as advanced age, diabetes mellitus, alcoholism, nutritional deficiency, slow acetylator phenotype, HIV infection, kidney failure, pregnancy, and breastfeeding.[30,32] In present study, one of patients had low baseline weight (38 kg) & the other was alcoholic. In one Indian study by Shinde et al.,[28] peripheral neuropathy occurred in 5% patients despite prophylactic pyridoxine supplementation.

In our study, two patients (incidence: 1.3%) complained of drowsiness in the 2nd week of treatment (Table 3). It was a mild reaction & no symptomatic treatment was given. Drowsiness is an ADR of Isoniazid.[29] Incidence of 1.3% in our study is comparable to other studies.[6,7,12-14]

In present study, one patient had complaints of hearing loss in 7th week (Table 3). This was confirmed by audiometry test. As this was elderly patient on Category II patient and only few doses were left, considering potential benefit–risk ratio physician opted for continuing the drugs. Ototoxicity is known ADR of SM.[29] Incidence of 0.67% in our study is less compared to other studies.[6,13] This could be because of less number of patients of Category II in our study.

Causality assessment

The Naranjo algorithm[22] & WHO-UMC[23] scales are most widely used in carrying out the causality assessment of ADRs.

As per Naranjo algorithm (Table 4), majority of ADRs 32 (91.43%)were "possible." 3(8.57%) ADRs were "probable." No ADR fell into "certain" category. "Probable" ADRs included two cases of hepatotoxicity and one case of ototoxicity. As per WHO-UMC scale (Table 5), majority of ADRs 32 (91.43%) were "possible," 2 (5.71%) ADRs were "certain" and 1 (2.86%) was "probable." "Certain" ADRs included two cases of hepatotoxicity. Reason for majority of ADRs falling into "possible" category was that dechallenge and/or rechallenge were not tried in most of the cases.

Table 4: Causality assessment by Naranjo algorithm.

Type of ADRs	Frequency of ADR	Definite	Probable	Possible
GI intolerance (nausea/vomiting/gastritis)	19	0	0	19
Arthralgia	4	0	0	4
Itching with or without rash	4	0	0	4
Hepatotoxicity	3	0	2	1
Peripheral neuropathy	2	0	0	2
Drowsiness	2	0	0	2
Ototoxicity	1	0	1	0
Total	35	0	3	32

Table 5: Causality assessment by WHO-UMC scale.

Type of ADRs	Frequency of ADR	Certain	Probable	Possible
GI intolerance (nausea/vomiting/gastritis)	19	0	0	19
Arthralgia	4	0	0	4
Itching with or without rash	4	0	0	4
Hepatotoxicity	3	2	0	1
Peripheral neuropathy	2	0	0	2
Drowsiness	1	0	1	0
Ototoxicity	2	0	0	2
Total	35	2	1	32

Severity assessment scale

In order to take proper initiatives toward the management of ADRs, it is necessary to study the severity of ADRs. Modified Hartwig and Siegel scale[24] is widely used for this purpose. As shown in Figure 2, majority of the cases were 'moderate' 17 (48.57%). This was followed by "mild": 15 ADRs (42.86%) and 3 ADRs were (8.57%) 'severe'.

Influence of possible risk factors for developing ADRs

As shown in Table 2, female gender was found to be a significant risk factor for developing ADRs (OR: 3.08, 95% confidence interval [CI]: 1.33-7.12, p<0.001). Female gender has been associated with increased occurrence of ADRs.[7,13] Though many studies couldn't find any significant association between them. However some studies like the one conducted by Tak et al.[34] showed higher incidence in males (70%). This may be because predisposing factors like smoking and alcoholism are more common in males. These contradictory findings, although inconclusive, suggest that closer monitoring of females during anti-TB therapy is warranted.

Alcoholic patients had more risk for developing ADRs compared to non-alcoholic patients (OR: 2.02, 95% CI: 0.81-5.04) though statistically it was not significant (Table 2). Alcohol is considered an important risk factor for adverse effects especially for hepatotoxicity.[7,33] Counseling for it is of utmost importance.

In case of age group of patients, patients aged 60 years or older had more chance of developing ADRs compared to age group between 18 and 40 years (OR: 2.00, 95% CI: 0.34 - 11.85) though statistically it was not significant (Table 2). Patients in 40-60 years age group had least risk in all three age groups. Some other studies have shown that elderly patients are at more risk for adverse effects & the frequency of adverse reactions was shown to increase in a progressive and direct form in relationship to age.[5,6,8,14]

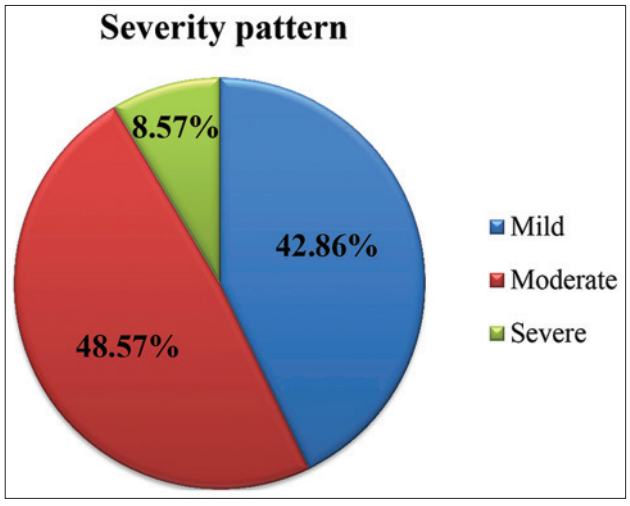

Figure 2: Severity assessment by modified Hartwig and Siegel scale.

Category II patients was also found to be a risk factor for developing ADR compared to cat I patients (OR: 1.36, 95% CI: 0.52-3.56) though statistically it was not significant (Table 2). Category II patient was associated with more occurrence of ADRs in many similar studies.[6,12-14] This may be related to more number of drugs and longer duration of treatment. It is prudent to be more vigilant during entire treatment period of Category II patients.

Impact of ADRs on treatment regimen

In present study, 5 (3.33%) patients defaulted from DOTS regimen because of ADRs which is a significant finding. Hepatotoxicity was a major reason for defaulting from DOTS (three patients, 60%). Persistent GI intolerance and itching with rash were the culprit in one patient each. In 20 cases out of 35 ADRs (57.14%), some form of symptomatic treatment was required. In 13 cases out of 35 ADRs (37.14%), additional investigations were advised. All these increase economic burden on both national health programs & patients.

We have already discussed characteristics of each ADR in detail. Primary reason given by all patients who defaulted were fear of more ADRs & decreased trust in treatment regime. Though it is important to note that only one patient completely stopped taking any further treatment for TB, other four patients opted for private practitioners for their further treatment. ADRs are regarded as one of the major factors for poor adherence to TB treatment as per WHO report.[10] Severe ADRs like hepatotoxicity are known to affect patient compliance adversely.[5,31,33] Non-adherence due to ADRs may lead to extension of treatment duration, drug resistance, treatment failures, and relapses.[11] Hence, it is prudent to be more cautious for patient developing severe ADRs.

Limitations

Regular biochemical investigations were not carried out in our study, so ADRs like asymptomatic hepatitis, thrombocytopenia might have been missed.

We excluded high risk categories for ADRs like HIV positive patients, pediatric population, and extra pulmonary cases. So our incidence may not be true reflection of entire population.

CONCLUSION

The incidence of ADRs due to DOTS therapy was 19.33% & total 35 ADRs had occurred in our study. ADRs may result in an increase in health care services and affect the anti-TB treatment pattern. Patients with ADRs were more susceptible to develop unfavorable anti-TB outcomes. This

emphasize the importance of developing strategies to deal with ADRs both to improve the quality of patient care and to control TB safely.

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