SAS Journal of Medicine (SASJM) **ISSN 2454-5112**
Abbreviated Key Title: SAS J. Med.

A Unit of Scholars Academic and Scientific Society, India

Assessment of Adverse Drug Reactions during CAT IV Regimen in Cases of MDR-TB

Dr. H.K. Sethy[1*], Dr. Milan Mishra[1], Dr. M.R. Pattnaik[2], Dr. Lincy Rajan[3], Dr. Jithendra Patra[4], Dr. Kali Prasad Pattnaik[5], Dr. Suchismita Panda[6]
[1-4]Departments of Pulmonary Medicine, SCB Medical College, Cuttack, India
[5]Department of Pharmacology, SCB Medical College, Cuttack, India
[6]Department of Biochemistry, SCB Medical College, Cuttack, India

Original Research Article

***Corresponding author**
Dr. H.K. Sethy

Article History
Received: 08.02.2018
Accepted: 19.02.2018
Published: 28.02.2018

DOI:
10.21276/sasjm.2018.4.2.2

Abstract: Tuberculosis is continuing to be major global health problem, in spite of implementation of effective drug regimen as per RNTCP guide lines. MDR-TB is now a great threat to mankind and drugs challenged against it have potential adverse reactions. If such reactions are not assessed or managed properly, it may lead to repeated drug interruptions and poor outcome. The objective of our study is to assess the causality, severity and preventability of the adverse drug reactions of CAT IV regimen during treatment of MDR-TB patients. It is a prospective hospital based, observational study conducted in DR TB centre, Department of Pulmonary Medicine, SCB Medical College, Cuttack during the period from July 2015 to March 2017. We included 59 newly diagnosed MDR-TB cases having adverse drug reactions after excluding comorbid conditions and other medications. All adverse reactions are identified, diagnosed clinically or by laboratory parameters and assessed during the course of treatment. Majority had single (42.4%) or multiple (44%) adverse drug reactions. The most common adverse drug reaction was Gastritis in 74.6% cases followed by Hearing loss (18.6%), Dizziness (16.9%) and Joint pain (13.6%). 83.5% of events of ADR showed *possible* causal association. 79.4% of events of ADR were of moderate severity and 20.6%of ADR had severe reaction. 45.3% of ADRs were definitely preventable, 39.2% of ADR were probably preventable and 15.5% were not preventable. Tuberculosis is curable if RNTCP guideline is strictly followed. The major issue in management of MDR cases is its prolonged treatment course of 18-24 months with multiple drugs carrying weak potency but major toxicity leading to poor adherance and treatment failure. Successful management of ADR without interruption of available standardized drugs can result in good treatment outcome.
Keywords: MDR-TB, ADR, Assessment, Causality, Severity, Preventability, Outcome.

INTRODUCTION

Tuberculosis (TB) is as old as mankind and still remains as a major global public health problem in spite of its curability and continuous human efforts through national TB control programmes. It is one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease [1]. Each year TB adds 10.4 million new cases affecting 90% of cases of adults and 10% of children and the male: female ratio is 1.6:1[1].

MDR-TB, one of TB phenotypes is now a great threat to mankind and progressively rising in all countries of the world in spite of man's continuous effort. There are 3.9% of new cases and 21% of previously treated cases of MDR/RR-TB (2015 Global report)[1]. 45% cases of global MDR/RR-TB cases are seen in China, India and the Russian Federation. There were about 250 000 (range, 160 000–340 000) deaths from MDR/RR-TB reported in 2015 [1]. The confirmatory diagnosis only can be possible by presently available culture and molecular DST. The treatment is combination of multiple second line drugs according to DST result. Success rate with a recommended MDR-TB regimen is 40 to 52%[2]. A timely diagnosis and correct treatment can cure most cases. The major drawback is poor adherance due to adverse drug reactions (ADR) to SLDs. Studies from different parts of world suggest that more than 5% of patients on anti-tubercular drugs developed ADRs [3-5]. It has been reported that there is 15% probability of adverse drug reactions occurring in a patients on a multiple Anti-TB Drug Regimen which tends to occur in the first three months of treatment [6]. Various studies reveal ADRs account for 5% of all hospital admissions and cause death in 0.1% of medical and 0.01% of surgical cases [7]. It has also been found that 50% of ADRs are preventable [8].

Treatment of MDR/RR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. Second line drugs are frequently associated with high rates of unacceptable adverse drug reactions, needing interruption and change of regimen. Therefore, it is imperative to prevent adverse drug reactions during the treatment course with meticulous monitoring and to treat ADR aggressively once it develops, to ensure complete adherence and good treatment outcome [9,10].

Our study was conducted to analyse the pattern of adverse drug reactions, periodic estimation of various parameters, to determine severity of the adverse drug reactions, to establish the casual relationship between the drug administration and adverse events and to assess the preventability of adverse drug reactions to CAT IV drugs among MDR TB patients at DR-TB Centre, Department of Pulmonary Medicine, SCB Medical College and Hospital, Cuttack.

MATERIALS & METHODS

It was a prospective, hospital based, observational study conducted in the Department of Pulmonary Medicine, S.C.B. Medical College and Hospital, Cuttack during the period July 2015 to March 2017.

Inclusion Criteria

All newly diagnosed patients with MDR-TB on Category-IV DOTS as per the RNTCP Guidelines were included in the study, after explaining the drug effects and obtaining written consent,

Exclusion Criteria

Patients with co-morbid conditions i.e. Diabetes mellitus, Renal failure, Hypothyroidism, Allergy and those receiving drugs like ART, steroids, etc. and herbal products or any other supplements were excluded. The study proposal was submitted and approved by the Institutional Ethics Committee of SCB MCH, Cuttack.

PRETREATMENT EVALUATION

All newly diagnosed MDR cases by LPA/Culture, referred from District Tuberculosis Centers were admitted for pre-treatment evaluation into DR-TB center. Patients' data, detailed history and meticulous physical examination, the investigations like Complete blood count, FBS and 1 hour PPBS, renal and liver function tests, serum electrolytes(sodium and potassium), chest x-ray, urine(routine and microscopic examination),serum TSH level, viral screen (HIV, HBsAg, HCV), pregnancy test (for all women of childbearing age group) were done. CAT IV DOTS was initiated after clearance was obtained from various disciplines particularly ENT (Audiometry), Ophthalmology (Funduscopy), Psychiatry and Gynecology (for all female patients) consultations and approval of the treatment protocol by DR-TB site committee, SCB MCH, Cuttack. All patients were observed for adverse drug reactions. ADRs were recognized at the earliest by close monitoring without any leading questions to elicit the specific drug reactions. All the events of ADRs, either reported or observed were managed in accordance with PMDT-RNTCP Guidelines of India (May 2012). The average hospital stay was 10 to 12 days including the mandatory 7 day observation period after starting CAT IV drugs according to PMDT guidelines. There after patients were referred back to DTOs with 7 days medication and prior information via email.

All the patients were followed up every three months during the study period from the date of initiation of medication. On every follow-up, patients were subjected to the proceedings as in pretreatment evaluation. Tests for HIV, HBsAg and HCV were done at 6 month intervals to study latent/recent infections. Serum FT3 and FT4 levels were assessed, where TSH level was abnormal. Whenever deemed essential the consultation with concerned discipline was entertained.

REPORTING OF ADRs

Various modes of reporting system were adopted including use of ADR notification form, telephone reporting, direct access, referral of patients and personal meeting at every quarter so as to ease the reporting of "suspected" ADRs. The different hematological, biochemical, hormonal, audiometric, and ophthalmological data were analyzed. Details of data pertaining to the reported ADR were collected and documented in ADR documentation form (Suspected ADR Reporting Form, Version 1.3 developed by Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission). The contents of ADR documentation form are: patient demography, description of event, medications suspected, medication used prior to the reaction with their complete dosing regimens, co-morbidities, risk factors involved, patient allergy status, causality category, severity, predictability, preventability, management of reported adverse reaction, outcome of management and follow up details. Finally the reported events were subjected to evaluation and analyzed to confirm the implicated drug that caused the "suspected" adverse reaction.

Reportable Criteria for ADR

WHO definition of an ADR was adopted as a criterion for reporting any suspected reaction. An adverse drug reaction is defined as "one which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".

Assessment of ADR Reports

All the reported events were evaluated to explore the likely involvement of suspected drug in causing the reported event.

Causality Assessment

The causality relationship between suspected drug and reaction was established by using WHO-UMC causality assessment system and Naranjo Adverse drug reaction probability Scale. Drugs were evaluated individually for causality, and points were deducted if another factor was suspected to have resulted in the adverse event, thereby weakening the causal association. The Naranjo scale classifies the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose-response relationships and previous patient experience with the medication. The ADR was assigned to a probability category from the total score as follows: *definite* ≥9, *probable* 5-8, *possible* 1-4 and *doubtful* if the score is 0. The scale does not account drug-drug interactions. But in our study we had not performed the drug levels because of no availability of facility.

- **Assessment of Severity**

The severity of reported reactions was assessed by using Hartwig and Siegel Severity Assessment scale and was categorized into mild, moderate and severe after assignment of level of severity.

- **Assessment of Preventability**

The preventability of reported ADRs was assessed by using Modified Schumock and Thornton scale and was categorized as definitely preventable, probably preventable and not preventable.

STATISTICAL ANALYSIS

All data were tabulated in master chart using Microsoft Office Excel 2007 and analyzed using SPSS version 21.0 statistical software. Descriptive statistics was used to analyze the data. Results were expressed as either percentage or mean ± standard deviation (SD). A p value of less than 0.05 was considered significant.

RESULTS

All total of 59 newly diagnosed MDR cases (by LPA/Culture) were included in the study. Majority of patients were in the age group 15-24 years (35.6%) followed by 25-34 years (23.7%).There was no remarkable difference between male and female (M:F 1.03:1).

Most of them were in the weight band 26-45 kg (66.1%) followed by 46-70 kg (32.2%). BMI revealed majority cases belonging to very severely underweight and Underweight groups each(35.6%,n=21), followed by normal (23.7%,n=14). No significant difference was observed in socioeconomic status category (below poverty line and above poverty line (45.8% vs. 54.2%). Only 16 patients (27.1%) were to found have addiction (smoking, alcohol, tobacco).

Out of 59 patients enrolled in the study, majority belonged to previously treated cases, in which the Relapse was 39.0%, Treatment failure was 28.8% and treatment after default (TAD) was only 18.6%. New cases accounted for 11.9%.

ADR to Cat IV drugs was found in majority of patients (41.4%) who had received ATT between 1 month to 6 months in past during their lifetime. Only 6.9% patients had received ATT for more than 14 months. One patient (1.7%) had received no anti-tubercular drugs.

In our study, 62.7% patients reported having no history of contact with tuberculosis, while 13.6% of the cases reported contact with MDR TB cases and 23.7% had history of contact with drug susceptible cases. Out of total 59 cases, 57 were Pulmonary MDR TB cases, in which majority (86%) belonged to criteria B followed by criteria A in 14% cases (as RNTCP PMDT criteria for MDR TB suspect does not apply to two cases of extra pulmonary MDR TB 3.4% out of total 59 cases).

In our study 86.4% of the patients were found to develop acquired multidrug resistance on the basis of LPA result. All patients were followed up every three months during the course of Cat IV treatment. Total number of follow-ups was 92. Two patients (3.4%) completed four quarterly follow-ups and in 10 cases (17%) follow-up could not be done due to death (n=2), follow-up date falling outside study period (n=5), not giving consent for follow-up (n=2), and default due to ADR (n=1).

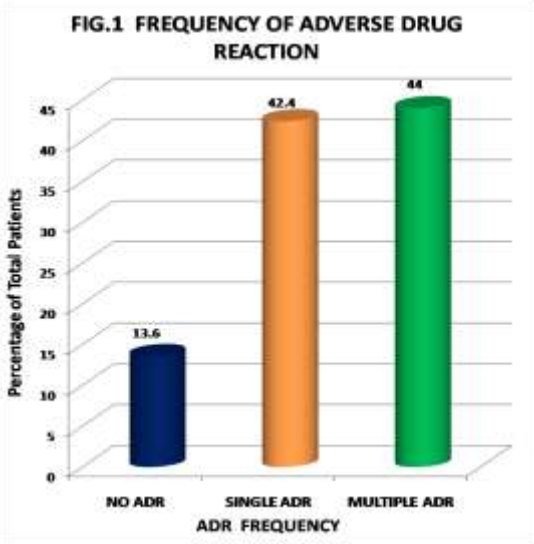
On quarterly follow-up of patients, the only hematological abnormalities were Anemia in 10.2% cases, Hypokalemia the most common biochemical abnormality found in 47.4% patients closely followed by Hyponatremia (40.7%). Raised level of serum alkaline phosphatase was found in 23.7% of cases. None of the patients had risen in serum urea or creatinine**.** 6.8% (n=4) cases who were thyroid at pretreatment evaluation, reported abnormal thyroid function test while on CAT-IV DOTS.

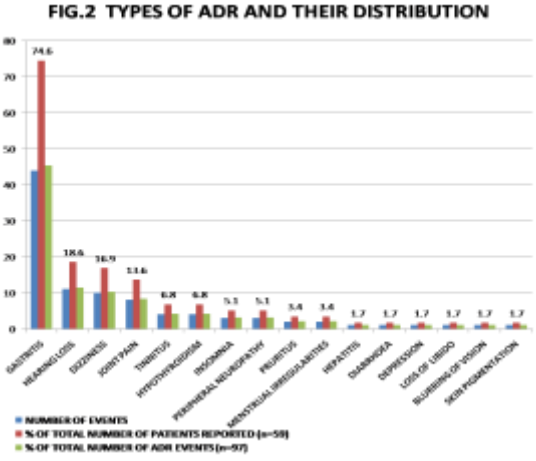
In this study 44% of patients reported multiple events of ADR and 42.4% reported single events of ADR [Fig.1]. The most common adverse drug reaction was Gastritis (74.6%) followed by Hearing loss (18.6%), Dizziness (16.9%) and Joint pain (13.6%)[Fig.2]. In this study, 77.3% events of ADR occurred within the period of 1 week to 3 months of starting CAT IV DOTS [Fig.3].

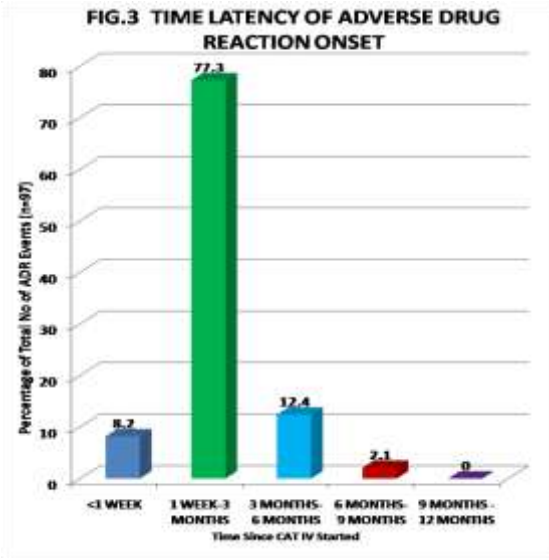
Using WHO-UMC CAUSALITY ASSESSMENT SYSTEM, 83.5% of events of ADR showed *possible* causal association with the drug and 16.5% showed *probable causal association* [Fig.4]. Similar results were also obtained by using NARANJO ADVERSE DRUG REACTION PROBABILITY SCALE [Fig.5]. Applying HARTWIG SIEGEL

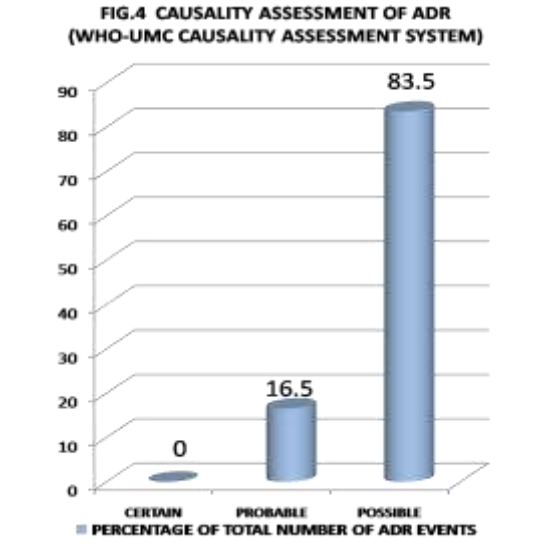
SEVERITY ASSESSMENT SCALE, 79.4% of events of ADR was found to be of moderate ADR(LEVEL 3&4) and only 20.6% of cases were found to have Severe ADR(LEVEL 5,6)[Fig.6]. Applying *Modified Schumock and Thornton scale*, 45.3% of ADRs were definitely preventable, 39.2% of ADR were probably preventable and 15.5% were not preventable [Fig.7].

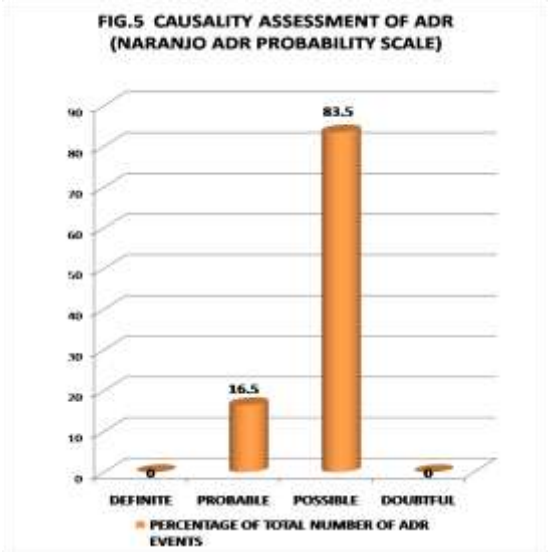
On analyzing adherence to initial therapy in relation to ADR, it was observed that out of 59 patients, only 1.7% (n=1) defaulted due to ADR and 13.6% (n=8) who developed no ADR, initial therapy was continued without any intervention, but majority of cases (62.7%) with 16 types of ADR and 97 events were managed with ancillary medication and supportive treatment. Only in 4 cases (6.8%), initial therapy was changed with omission of offending drug. PAS was substituted for Ethionamide and Pyrazinamide in one case of hepatitis and Kanamycin was substituted by PAS in three cases of hearing loss[Fig.8].

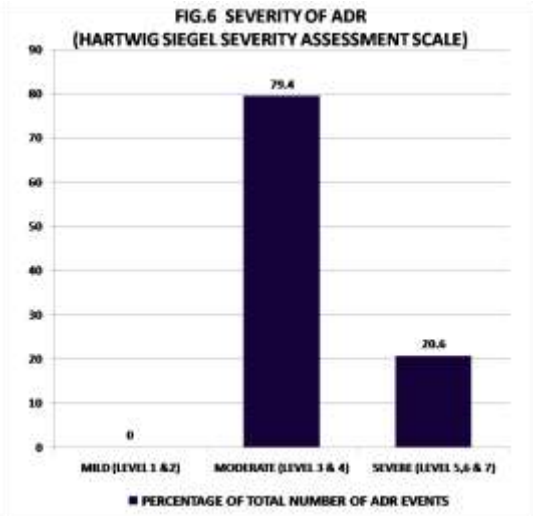


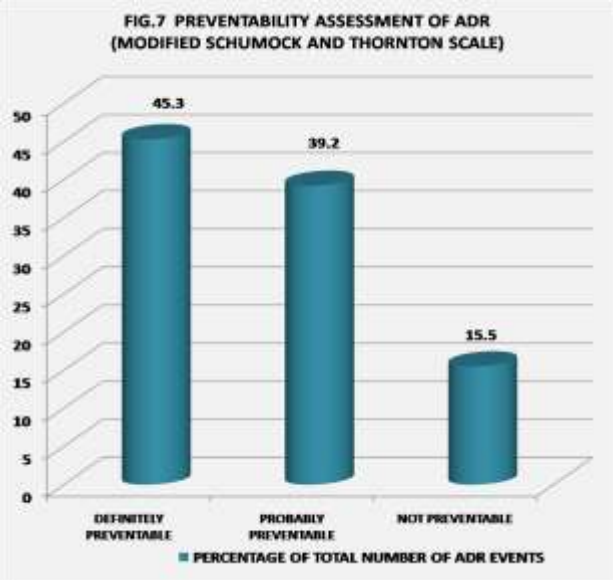


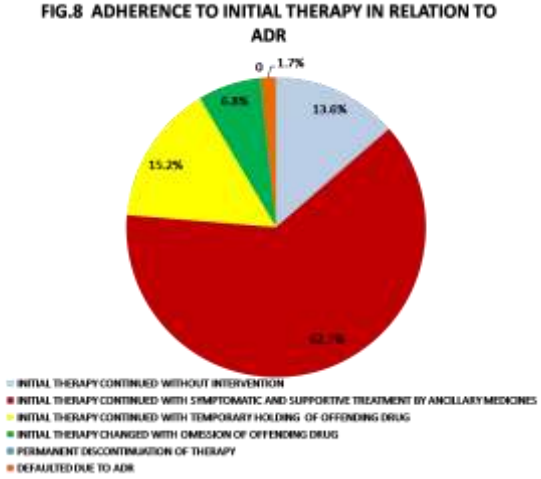












DISCUSSION

No age is immune for Tuberculosis. M. tab once entered into the body, cannot be eradicated. But can be contained and at any point of time can be reactivated depending on host immunity or bacterial virulence. Chemotherapy is the only cure which needs multiple drugs to kill the bacillus, the most hardy and complex organism. No drugs are free of their ADRs at prophylactic, therapeutic and physiological doses and they developed DR if taken irregularly or inadequately. The drugs implicated against MDR-TB are more bulky, less potent but more toxic and need longer duration of treatment. The ADRs may be of same or different phenotypes for same drug or combination of drugs. ADR is the most common cause of Non-adherence, progression of disease, increased mortality and subsequent development of DR if patient survived. Hence early detection and treatment is mandatory to prevent the spread and most lethal effect of MDR-TB in community.

Among 59 MDR-TB patients included in our study, the mean age was 32.24±15 years (range 14-70 years). There is no significant difference in proportion between male and female (50.8% vs. 49.2%). Majority of patients were in the age group of 15-24 years (35.6%) followed by 25-34 years (23.7%). At initiation of CAT IV DOTS, the mean weight was 42.7±9.7 kg, majority were in the weight band 26-45 kg (66.1%) followed by 46-70 kg(32.2%). The mean BMI of our study population was 16.7±3.1 kg/m2.The number of patients below poverty line and above poverty line was almost equal (45.8% vs. 54.2%) with the balance slightly edged in favor of APL category. 16 patients (27.1%) were addicted to alcohol/tobacco chewing/smoking. Alcohol was the leading addiction (13.6%) followed by tobacco chewing (11.8%) and smoking. Smoking was the least event in our study, probably due to the fact that near 50% of study population was female having tobacco chewing habit rather than smoking and alcohol was used by both sexes. The Retreatment cases were 88.1% and New cases accounted for 11.9% which is an alarmingly high number when compared to latest global rate (3.9%) and national rate (2.5%)[11].

Majority of our patients were belonged to the Relapse category (39.0%) followed by treatment failure (28.8%) and treatment after default (18.6%). Higher number of relapse cases which were thought to be having DS-TB, were found to be DR-TB. The majority of patients (62.7%) had no history of contact with tuberculosis, 13.6% had contact with MDR TB cases and 23.7% had history of contact with drug susceptible cases**.** Thus 13.6% and 86.4% of the patients were found to have primary and acquired multidrug resistance respectively on the basis of LPA result as against the report by Hire *et al*, 2014[12] (5.4% primary and 94.5% Acquired resistance) and Tag El Din *et al*, 2015[13] (4.7% primary and 95.3% Acquired resistance). The higher percentage of primary resistance reported in our study might be due to clustering of cases in families. Majority of patients (86%) belonged to criteria B followed by criteria A (14%), out of the 57 Pulmonary MDR TB cases except two cases of extra pulmonary

MDR TB (3.4%) as far as The RNTCP PMDT criteria for MDR TB suspect[11] is concerned.

In our study, all patients were followed up every three months during the course of treatment to observe ADRs. While 32.2%, 32.2%, 15.2%, 3.4% patients completed first, second, third and fourth follow-up respectively, only one patient defaulted due to ADR and 2 patients died before follow-up. Tag El Din *et al.* 2015[13] reported 104(97.2%), 89(83.2%), 49(45.8%) and 26(24.3%) patients completed first, second, third and fourth follow-up. The trend in follow-ups were seen to be more initially but fallen as the duration of treatment found to be longer.

In our study, total number of ADR events was 97 in 59 patients over 92 follow-ups. 86.4% of patients developed events of ADR and 13.6% had no ADR which was comparable with Tag El Din et al, 2015 (ADR in 94.4% and no ADR in 5.6%)[13] and Nathan son *et al*. 2004 (ADR in 86% and no ADR in 14%)[14]. The most common ADR was Gastritis (74.6%) followed by Hearing loss (18.6%), Dizziness (16.9%) ,Joint pain (13.6%), tinnitus(6.8%), hypothyroidism(6.8%), peripheral neuropathy(5.1%), hepatitis(1.7%), depression(1.7%) and blurring of vision(1.7%). Akshata *et al*. [15] found among 607 patients GI ADR in 71.1%, arthralgia in 14%, depression in 13%, peripheral neuropathy in 5.85%. Shin *et al*, reported among 244 patients ADR occurred in 179 with nausea and vomiting in 75.4%, arthralgia in 47.1%, hypothyroidism in 17.2% and hepatotoxicity in 16.8% [16]. Tag El Din *et al*, 2015 reported ADR in 101 out of 107 patients with GI ADR in 57%, peripheral neuropathy in 53.3%, Ototoxicity in 17.8% and hypothyroidism in 10.3% of patients [13]. The reasons for the heterogeneity in the prevalence and distribution of ADRs across various studies are unclear, but might be related to several possible factors such as: a). Differences in definitions of adverse event terminologies across settings; b)whether the adverse event was symptomatic and c)patient-reported (subjective) or clinician-validated (objective); d)whether all or only the severe and serious adverse events were studied; e)variations in the use of specific anti-TB agents in different regimens; f) differences in co-morbidities and other covariates between different study settings; g) host factors like different ethnicity leading to variation in pharmacodynamics and pharmacokinetics of drugs; h) environmental factors and genetic predisposition. Socioeconomic Circumstances and Burden of Chronic Disease are also suspected factors in genesis of some ADRs like gastritis and depression.

Both from clinical and pharmacovigilance point of view, the time window of initial 3 months for ADRs is very crucial. In our study, 77.3% events of adverse drug reaction occurred within the period of 1wk to 3 months of starting CAT IV DOTS. While 8.2% of ADR events occurred within 1wk of starting the regimen, 12.4% events within the period of 3 to 6 months, only 2.1% events between 6 to 9 months of initiation of CAT IV DOTS and there were no ADR events between 9 to 12 months. Tag El Din *et al*, 2015 reported most adverse reactions occurred during the first 3 months of treatment [13]. Sigdel *et al*, 2016 reported most of the ADRs were observed within 5 months of starting MDR TB treatment regimen [17]. Isaakidis *et al*. 2012 reported adverse effects occurred between 2nd to 4th months of MDR-TB treatment initiation [18]. Van der Walt *et al*, 2013 reported adverse effects occurred during the first 4 months of MDR-TB treatment [19] and Torun *et al*, reported most adverse effects began within 4 months after beginning of treatment [20].

Carrying out causality assessment using standard methods/scales is one of the best ways to establish the causal relationship between a drug and its adverse event. In our study, using WHO-UMC causality assessment system 83.5% showed *possible* causal association with the drug and 16.5% showed *probable causal association*. Sood *et al*. who reported in 69.3% cases ADR events had possible association and in 30.7% cases had probable association with the suspected drug and no definite association was proved in any event[21]. Zala *et al*. 2015 reported causality association in 61.16% of ADR events were certain, in 26.45% events were probable and in rest 12.4% were possible [22]. Using Naranjo adverse drug reaction probability scale, *probable* and *possible causal* association was observed in 16.5% and 83.5% of events of ADR respectively. This result was in partial agreement with Sigdel et al, 2016 (35% probable and 65% possible) [17] and Shinde *et al*. (39.45% probable and 60.55% possible)[23]. Hire *et al*. 2014 reported definite, probable and possible association in 10.9%, 84.4% and 4.7% events respectively [12] and Zala *et al*. 2015 reported definite, probable, possible and doubtful association in 57.85%, 26.45%, 9.09% and 6.61% events respectively [22]. In contrast to above studies, no definite causal association was found in our study as we did not perform therapeutic drug monitoring (TDM) owing to resource constraints or drug withdrawal and challenge keeping in view the seriousness and chronicity of MDR TB and risk of development of XDR TB. In majority of countries, there can be established possible or probable causal association between the drug and ADR because it is difficult to prove certain association owing to resource constraints.

The Cause of ADRs plays a vital role in management of ADRs and if not detected in an early date, the ADR will course to greater severity resulting in less chance of survival of the patient. Host factors like different ethnicity leading to variation in pharmacodynamics and pharmacokinetics of drugs, environmental factors, genetic predisposition, socioeconomic circumstances and burden of Chronic Diseases influence and potentiate the degree of reaction leading to increased mortality if proper history, meticulous physical examination and close follow ups if not carried out by health care workers. Control of

severity in late stage is very difficult to manage. The evaluation of different levels of severity heralds the knowledge about ignorancy from both sides of patients and physicians, socioeconomic status of the patients and poor team effort. Our study using HARTWIG SIEGEL SEVERITY ASSESSMENT SCALE showed 66% of events of ADR in LEVEL 4, 13.4% in LEVEL 3 and 20.6% of ADR events in LEVEL 5,6 signifying Severe ADR. There were no ADR events of LEVEL 1,2 OR 7. Hire *et al*. [12] reported most of the ADR events in LEVEL 3 (56.3%) followed by level 4(23.4%), level 1(10.9%) and level 2(9.4%) of total ADR events. Sigdel *et al*. reported major ADR events in LEVEL 1 (86.77%) followed by level 3 11.76%) and level 4 (1.47%) of total ADR events[17] and Shinde *et al*. 2017 reported most of the events in LEVEL 4 (51.38%) followed by level 1 (35.78%) and level 6 (12.84%) of total ADR events[23]. The reasons for such discrepancy in the level of severity of ADRs across various studies might be related to whether ADR is symptomatic and patient-reported (subjective) or clinician-validated (objective), whether all or only the severe and serious adverse events were studied, variations in use of specific anti-TB agents in different regimens, differences in associated co-morbidities and other covariates between different study settings.

In order to take proper initiatives towards the management of ADRs, it is necessary to study the severity. In our study, 79.4% of events of ADR were moderately severe, 20.6% were severe and none of the ADR events qualified as mild. Hire *et al*. 2014 reported most of the events as moderate (79.9%) and as mild in 20.3% of events [12]. Sigdel *et al.* reported 86.77% mild and 13.23% as moderate [17]. Shinde *et al.* reported 35.78% mild, 51.38% moderate and 12.84% severe [23] and Zala *et al*. reported 28.93% mild, 51.24% moderate and 23.14% as severe [22]. In our study, Severe adverse drug reaction had no effect on mortality and majority of the ADR are moderate in severity that were managed by either symptomatic and/or supportive treatment with ancillary drugs or temporary discontinuation of offending drug on in-patient or out-patient basis depending on the type of ADR. Early diagnosis, reporting and treatment of ADR are crucial to ensure adherence.

Using Modified schumock and thornton scale the preventability of ADR events was assessed in our study. In 45.3% of events, the ADRs were definitely preventable**,** 39.2% of events were probably preventable and 15.5% were not preventable. Zala *et al*. Reported 15.7% of ADR events as definitely preventable, 36.36% as probably preventable and 47.93% as not preventable [22]. Compliance of patients for drug administration in relation to food, alcoholism, motivation of the patient towards treatment, awareness of patient/ attendant about ADR, alertness of healthcare staff towards ADR and their effort towards patient education for prevention of ADR are most important factors to take preventive measures against the events and to ensure treatment adherance.

In our study, 6.8%(n=4) who were euthyroid at pretreatment evaluation, reported abnormal thyroid function test while on CAT-IV DOTS in contrast to RNTCP guidelines which states hypothyroidism is a rare ADR (<1%)[24] but almost nearer to Tag El Din *et al*. (10.3%)[13]. Hypothyroidism may be more common during MDR-TB treatment than previously recognized. Screening all patients, even those without symptoms, for hypothyroidism within 2–3 months of starting MDRTB treatment should be considered until prospective studies can inform screening guidelines [25].

On quarterly follow-up of our patients, anemia was found in 10.2% of patients in contrast to Sigdel *et al*. (5.71%)[17]. Hypokalemia was 47.4% in contrast to Shin *et al*. (33.2%)[16] and Shin and Furin *et al*, (31.3%)[27] while Hyponatremia was in 40.7% of cases in contrast to Tag El Din *et al*. (0.9%)[13]. Raised level of serum alkaline phosphatase was found in 23.7% of cases, whereas hepatitis in 1.7% of cases. There was no history of pre-existing liver disease in the study population. Granulomatous hepatitis due to tubercular involvement of liver can give rise to isolated rise in serum ALP [28]. Also other undiagnosed disease conditions like osteoporosis or malignancy may have contributed to this rise in serum ALP. Hyperuricemia was found in 11.9% of total patients (total events of ADR vs total arthralgia cases: 7.2% vs 87.5% of) whereas by Ahmad *et al.* (total events of ADR vs total arthralgia cases: 20.44% vs 84.1%)[29] and Zala *et al.* (Total events of ADR vs total arthralgia cases: 14.9% vs 100%)[22]. In our study, 13.5% patients had hypoproteinemia and hypoalbuminemia as opposed to Tag El Din et al, 2015 who reported hypoalbuminemia in 5.6% of their study population and 1.7% of total patients reported hepatitis(raised bilirubin, SGOT and SGPT) but none of the patients reported nephrotoxicity(raised urea and creatinine)[13]. In study by Nathanson *et al.* Hepatitis was 2.2% and nephrotoxicity was 1.2%[14], whereas Shin *et al.* Found Hepatitis in 16.8% and nephrotoxicity in 9.8% of patients [16].

On analyzing adherence to initial therapy in relation to ADR, it was observed that out of 59 patients only one (1.7%) defaulted due to ADR. In 8 patients (13.6%) having no ADR, initial therapy was continued without any intervention. In majority of cases, ADR was managed with ancillary medication and supportive treatment along with temporary withdrawal of suspected offending drug wherever required and reintroduction cautiously after the ADR subsided (62.7%). Only in 4 cases (6.8%) initial regimen was changed with omission of offending drug. Our results are in close agreement with Akshata *et al*. 2015 who reported default in 1.7% because of ADR and change in regimen in 10.5% of cases [15] and Ahmad *et al*. reported default in 3.87%

because of ADR and change in regimen in 11% of study population [29].

Shin *et al.* [16] reported modification of regimen in 55.1% and 28.7% of total cases respectively. Comparatively, minimal modification of TB treatment regimen (6.8%) in our study indicates the aggressive management of MDR-TB at the study site through pharmacological and psychological supportive therapy and correcting contributing factors that compromised clinical efficacy of MDR TB treatment regimens. Also differences in training and ability of health care workers to detect adverse events and the use of different treatment regimens with different combinations of drugs are factors contributing to this variation.

In our study out of 59 patients and 97 events of ADR, the drug regimen was changed in only 4 cases (6.8% of patients, 4.1% of events of ADR). In one case of hepatitis, Ethionamide and Pyrazinamide were withdrawn and PAS introduced. In three cases of hearing loss Kanamycin was substituted by PAS. Our results are in concordance with Akshata *et al*. who reported change in regimen in 10.5% of cases [15] and Ahmad *et al.* 2016 who reported change in regimen in 11% of study population [29]. With proper ADR preventive measures and aggressive ADR management plans in place there arises very few occasions for change of regimen due to ADR.

CONCLUSION

MDR TB is man-made and has multifactorial reasons. Non-adherance to CAT-IV regimen for MDR-TB is frequent due to its pronged course and drug toxicity, resulting in treatment failure. ADRs are the most important cause for non-adherance. Early detection and assessment of ADRs due to individual drugs are essential components for successful treatment outcome.The time window from one week to three months of initiation of CAT IV DOTS is crucial for both clinical and pharmacovigilance point of view to watch for ADR and its management. Definite causal assessment is not possible in resource limited countries. In our study, more than 50% ADRs were definitely preventable inspite of majority of cases with moderate severity and without definite causal assessment, with ancillary drugs or temporary withdrawal of offending drug. Early reporting, diagnosis and treatment of ADR are more vital for effective treatment and outcome in MDR TB cases.

REFERENCES

1. WHO Global Tuberculosis Report. 2016;5,38,78-81
2. Guidelines- DOTS-Plus 2010. Revised National Tuberculosis Control Programme New Delhi: Government of India; 2010. Available from *http://www.tbcindia.nic.in/pdfs/DOTS_Plus_Guidelines*_Jan2010.pdf
3. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tubercle and Lung Disease. 1996 Feb 1;77(1):37-42.
4. Dhingra VK, Rajpal S, Aggarwal N, Aggarwaln JK, Shadab K, Jain SK. Adverse drug reactions observed during DOTS. The Journal of communicable diseases. 2004 Dec;36(4):251-9.
5. Chukanov VI, Kaminskaia GO, Livchane E. Frequency and pattern of adverse reactions due to treatment of patients with pulmonary tuberculosis with antitubercular reserve drugs. Problemy tuberkuleza i boleznei legkikh. 2004(10):6-10.
6. Hoffman GS, Sechler JM, Gallin JI, Shelhamer JH, Suffredini A, Ognibene FP, Baltaro RJ, Fleisher TA, Leavitt RY, Travis WD, Barile MF. Bronchoalveolar lavage analysis in Wegener's granulomatosis. Am Rev Respir Dis. 1991;143:401-7.
7. Pirmohamed M. Breckenridge AM. Kitteringham NR. Park BK. Adverse drug reactions a Clinical review. BMJ. 1998;25(316):214.
8. Winterstein AG, Sauer BC, Hepler CD, Poole C. Preventable drug-related hospital admissions. Annals of Pharmacotherapy. 2002 Jul;36(7-8):1238-48.
9. Prasad R. Management of multi-drug resistant tuberculosis: practitioner's view point. Indian Journal of Tuberculosis. 2007 Jan 26;54(1):3.
10. Rathod KB, Borkar MS, Lamb AR, Suryavanshi SL, Surwade GA, Pandey VR. Adverse events among patients of multi drug resistant tuberculosis receiving second line anti TB treatment. International Journal of Scientific Reports. 2015 Oct 22;1(6):253-7.
11. Joseph P, Desai VB, Mohan NS, Fredrick JS, Ramachandran R, Raman B, Wares F, Ramachandran R, Thomas A. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. The Indian journal of medical research. 2011 May;133(5):529.
12. Hire R, Kale AS, Dakhale GN, Gaikwad N. A prospective, observational study of adverse reactions to drug regimen for multi-drug resistant pulmonary tuberculosis in Central India. Mediterranean journal of hematology and infectious diseases. 2014;6(1).
13. El Din MA, El Maraghy AA, Hay AH. Adverse reactions among patients being treated for multi-drug resistant tuberculosis at Abbassia Chest Hospital. Egyptian Journal of Chest Diseases and Tuberculosis. 2015 Oct 1;64(4):939-52.
14. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, Vink K, Jaramillo E, Espinal MA. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. The International Journal of Tuberculosis and Lung Disease. 2004 Nov 1;8(11):1382-4.
15. Akshata JS, Chakrabarthy A, Swapna R, Buggi S, Somashekar M. Adverse drug reactions in management of multi drug resistant tuberculosis, in

tertiary chest institute. Journal of Tuberculosis Research. 2015 Apr 16;3(02):27.
16. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, Barnashov A, Karpeichik Y, Andreev YG, Golubchikova VT, Tonkel TP. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. The International Journal of Tuberculosis and Lung Disease. 2007 Dec 1;11(12):1314-20.
17. Sigdel M, Dhakal SR, Kandel P, Maharjhan N, Khan GM. A Study of Adverse Drug Reactions Caused by Second Line Anti-Tubercular Drugs Used in Nepal. International Journal of Health Sciences and Research (IJHSR). 2016;6(1):201-8.
18. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J, Saranchuk P, Da Silva E, Khan S, Paryani R, Udwadia Z, Migliori GB. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PloS one. 2012 Jul 11;7(7):e40781.
19. Van der Walt M, Lancaster J, Odendaal R, Davis JG, Shean K, Farley J. Serious treatment related adverse drug reactions amongst anti-retroviral naïve MDR-TB patients. PLoS One. 2013 Apr 3;8(4):e58817.
20. Törün T, Güngör G, Özmen I, Bölükbaşı Y, Maden E, Bıçakçı B, Atac G, Sevim T, Tahaoğlu K. Side effects associated with the treatment of multidrug-resistant tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2005 Dec 1;9(12):1373-7.
21. Sood A, Bansal R, Sharma A, Himani H, Bhagra S, Kansal D. Profile of adverse drug reactions in patients on anti-tubercular drugs in a sub Himalayan rural tertiary care teaching hospital. International Journal of Research in Medical Sciences. 2016 Dec 19;4(10):4465-71.
22. Zala AC, Manvar R, Patel D, Patel D, Gamit N. A prospective-observational study to assess the prevalence of adverse drug reactions in MDR-TB patients at tertiary care hospital in India. American Journal of Pharmacology and Pharmacotherapeutics. 2015;2(4):112-9.
23. Shinde MP, Halasawadekar NR, Ramanand SJ, Pore SM, Ramanand JB, Patil PT, Kumbhar AV. A study of adverse drug reactions in patients receiving treatment for multi-drug resistant tuberculosis. International Journal of Basic & Clinical Pharmacology. 2017 Jan 28;6(2):354-8.
24. Sachdeva KS, Kumar A, Dewan P, Kumar A, Satyanarayana S. New vision for Revised National Tuberculosis Control Programme (RNTCP): universal access-"reaching the un-reached". The Indian journal of medical research. 2012 May;135(5):690.
25. Satti H, Mafukidze A, Jooste PL, McLaughlin MM, Farmer PE, Seung KJ. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. The International Journal of Tuberculosis and Lung Disease. 2012 Apr 1;16(4):468-72.
26. Alli JA, Kehinde AO, Kosoko AM, Ademowo OG. Oxidative stress and reduced vitamins C and E levels are associated with multi-drug resistant tuberculosis. Journal of tuberculosis research. 2014 Mar 21;2(01):52.
27. Shin S, Furin J, Alcántara F, Hyson A, Joseph K, Sánchez E, Rich M. Hypokalemia among patients receiving treatment for multidrug-resistant tuberculosis. Chest. 2004 Mar 1;125(3):974-80.
28. Sherlock S, Dooley J. Diseases of the liver and biliary system. John Wiley & Sons; 2008 Apr 15.
29. Ahmad N, Javaid A, Sulaiman SA, Afridi AK, Khan AH. Occurrence, management, and risk factors for adverse drug reactions in multidrug resistant tuberculosis patients. American journal of therapeutics. 2016 Feb 29.