Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: A four year retrospective study

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ABSTRACT

Background: Treatment of multidrug-resistant tuberculosis (MDR-TB) requires the use of expensive and toxic second-line anti-tubercular drugs which are given for a longer duration. Adverse drug reactions (ADRs) of second-line antitubercular drugs affect compliance and thereby treatment outcome. We set out to analyze ADRs and treatment outcome of MDR-TB patients receiving directly observed treatments plus therapy. Materials and Methods: A retrospective study of registered MDR-TB cases at district tuberculosis center during 2010–2014 was performed. Data regarding sociodemographic profile, diagnosis, and treatment as well as ADRs were recorded and evaluated. ADRs were evaluated for causality, severity assessment, management aspects, and impact on treatment outcome. Results: In total 147 ADRs were reported among 72 cases. Most commonly observed ADRs were gastrointestinal (24.5%) followed by self reported weakness (21.23%), psychological (14.38%), joint pain (14.38%), and respiratory symptoms. Discontinuation of the drugs due to ADRs was required in 36 (24.48%) events. ADRs were significantly associated with noncompliance and defaulter outcome. Cure rate was higher in MDR-TB cases with ADRs (59.72%) than MDR-TB cases without ADRs (30.18%). Conclusion: Attention needs to be paid for timely recognition and treatment of ADR with minimum modification of treatment regimen. Equal attention should be paid to MDR-TB without ADR cases to raise overall cure rate.

KEY WORDS: Adverse drug reaction, directly observed treatments plus, multidrug-resistant tuberculosis, Revised National Tuberculosis Control Program

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is recognized and being evaluated since 1964. It has been reported frequently during the last four decades. Continuously rising number of MDR TB cases poses a threat to global tuberculosis (TB) control effort. The global incidence of MDR-TB is 3.3% of new cases and 20% of previously treated patients, China and India are the top two countries accounting 50% of MDR TB cases. Treatment of MDR TB requires the use of expensive and toxic second-line anti-tubercular drugs which are given for a longer duration. The Revised National Tuberculosis Control Program (RNTCP) in India follows...
the internationally recommended directly observed treatments (DOTS) plus guidelines for treatment of MDR-TB known as Category IV (CAT IV) regimen from August 2007 onward. During 2014, India achieved complete geographical coverage for diagnostic and treatment services for MDR-TB. The experience of MDR-TB treatment pilot projects has contributed to knowledge about an adverse reaction. However, more data on the characteristics and management of adverse reactions are needed to inform clinicians and program managers as MDR-TB treatment scale-up (MDR Russia). This study was planned to analyze adverse drug reaction (ADR) and treatment outcome of DOT plus therapy to MDR-TB registered cases at district TB center during 2010–2013.

MATERIALS AND METHODS

A retrospective study was conducted to evaluate MDR-TB outcome and analysis of ADR of DOT plus treatment. MDR-TB cases registered at district TB center Rajkot during 2010–2013 (completed course) were included in the study. CAT I and II, extensively drug-resistant (XDR) cases, MDR cases - those who died of natural causes other than disease were excluded from the study. Permission from Institutional Ethic Committee and district TB officer was obtained before the conduct of the study. Data regarding sociodemographic profile (age, gender, weight, past history of disease of drugs), MDR-TB details (causes of MDR-TB, diagnostic details), treatment details, duration as well ADRs, were recorded and evaluated. ADR was evaluated for causality, severity assessment, and management aspects.

RESULTS

In total, 147 MDR-TB cases were registered at diagnostic testing and counseling but as per inclusion criteria, 125 cases were analyzed [Table 1].

A total of 125 drug susceptibility testing (DST) confirmed MDR-TB cases were registered from 2010 to 2013 at district TB center. Among them, 57.6% cases were associated with ADR while 42.4% cases without ADR. Totally 147 ADRs were reported among 72 cases. Majority patients within the age group of 21–40 year with mean age 35.69 ± 12.88. The majority of patients 71.2% were males and remaining were females 28.8%. Among MDR TB cases, 96% of them were previously treated cases (failure, default, and relapse cases) and 4% cases were newly diagnosed MDR TB cases. Defaulters and nonadherence to the treatment were significantly associated with ADR in the study.

The majority patients (53.22%) had two-drug resistance (H and R), and 28.22% had single-drug resistance. Rest of the cases had more than two-drug resistance (H, R, and E/S) found by DST. The cure rate was significantly higher in the patients who had single-drug-resistant (P < 0.05).

| Table 1: Sociodemographic details of multidrug-resistant tuberculosis cases (n=125) |
|-----------------------------------------------|
| Sociodemographic profile | Cases with ADR (72) | Cases without ADR (53) | Total, n (%) |
| Age (years) | | | |
| 1-20 | 6 (4.8) | 6 (4.8) | 12 (9.6) |
| 21-40 | 44 (35.2) | 33 (26.4) | 77 (60.5) |
| 41-60 | 19 (15.2) | 10 (8.0) | 29 (23.2) |
| 61-80 | 3 (2.4) | 3 (2.7) | 7 (5.6) |
| Sex | | | |
| Male | 49 (39.2) | 40 (32) | 89 (71.2) |
| Female | 23 (18.4) | 13 (10.4) | 36 (28.8) |
| Initial weight | | | |
| <45 | 33 (26.4) | 31 (24.8) | 64 (51.2) |
| ≥45 | 39 (31.2) | 22 (17.6) | 61 (48.8) |
| History | | | |
| New cases | 4 (3.2) | 1 (0.8) | 5 (4) |
| Retreatment | 68 (54.4) | 52 (41.6) | 120 (96) |
| Comorbidity | | | |
| HIV | 5 (4) | 2 (1.6) | 7 (5.6) |
| Diabetes | 0 (0) | 2 (1.6) | 2 (1.6) |
| HIV and diabetes | 0 | 0 | 0 |
| Treatment adherence | | | |
| Yes | 57 (45.6) | 22 (17.6) | 79 (63.2) |
| No | 15 (12.0)* | 31 (24.8) | 46 (36.8) |
| Treatment outcome | | | |
| Cure | 43 (59.72) | 16 (30.18) | 59 (47.2) |
| Progress to XDR | 10 (13.88) | 5 (3.66) | 13 (10.4) |
| Transferred out | 1 (0.8) | 6 (4.8) | 7 (5.6) |
| Defaulters | 6 (4.8)† | 11 (8.8) | 17 (13.6) |
| Death | 12 (14.94) | 17 (27.72) | 29 (22.8) |

*Defaulter strongly associated with cases with adverse drug reactions (χ²=20.214, df=5, P=0.001), †Treatment adherence associated with no occurrence of ADR (χ²=18.614, df=1, P=0.000). XDR: Extensively drug-resistant, ADR: Adverse drug reaction.

All the patients received second-line antitubercular drugs (kanamycin [Km], levofloxacin [Lfx], pyrazinamide [Z], ethionamide [Eto], ethambutol [E] and cycloserine [CS], para-aminosalicylic acid [PAS]) on the weight basis as per DOT plus program.

A majority of ADR were of gastrointestinal (GI) (24.5%) followed by weakness (21.23%), psychological (14.38%), joint pain (14.38%), and respiratory (7.8%). Less frequently reported ADRs were ototoxicity (4.1%), blurring of vision (4.1%), headache (4.1%), hepatotoxicity (2.04%), and nephrotoxicity (0.6%). Thirty-six ADRs required discontinuation of the drug. Permanently stopped drugs were CS (psychological ADR), Km (ototoxicity), Eto (GI-ADR), ethambutol and pyrazinamide (joint pain). Psychological ADR, hearing loss, jaundice were found in initial 3 months of starting CAT IV treatment in this study [Table 2].

By the WHO causality assessment, majority (81.50%) ADRs were in “possible” category whereas only 4.7% ADRs were “certain.” Certain ADRs were hearing loss by Km and psychological ADRs by CS. Severity assessment was done by Hartwig and Siegel scale, majority (77.87%) ADRs were mild to moderate while only 23.12% ADRs were severe [Table 3].
DISCUSSION

India has been identified as high burden country for pulmonary TB, MDR-TB, and HIV-TB. MDR-TB and XDR-TB are difficult to treat day by day as it requires prolonged treatment with less efficacious and highly toxic drugs. ADRs associated with these drugs further complicate the picture, resulting in dropouts, insufficient treatment, and thereby affect success rate. The management of ADRs as well as the cost of treating ADRs is an essential component and needs to be addressed. [9]

In this study, the majority of patients were in the economically productive age group (21–40 years) with mean ± standard deviation was 35.69 ± 12.88. Of the study subjects, 2/3 of patients were male. This age group is vulnerable because of economic responsibility and environmental exposure to resistant strain and more prone to addiction such as smoking, alcohol intake, and psychological stress, which results in the weakening of immunity. [9] Immunity plays a major role in the pathogenesis and manifestations of the disease. There was no significant association between age and ADRs as well gender and ADR ($P > 0.05$).
Ninety percent of MDR TB patients were retreated cases. Majority of the patients (52.8%) had two-drug-resistant while single-drug-resistant cases were 28%. ADRs were observed more in cases with single-drug resistance than two-drug-resistant which was not statistically significant \( (P > 0.05) \). A study done by Singh and Joshi in Mumbai showed same results.\(^{[10]} \) Co-morbidity was observed only in 9 (7.2%) patients, among them, ADRs appeared in 5 (55.55%) cases. There was no significant \( (P > 0.05) \) association between comorbidity and ADR.

Treatment outcome profile showed that 59 cases (47.2%) were cured at the end of treatment, among them ADRs were seen in 43 (72.88%). Death rate, default rate, and progress to XDR were 22.8%, 13.6%, 10.4%, respectively. There was significant \( (P < 0.05) \) association between cure and ADRs. Treatment outcomes were significantly better among those who experienced ADRs. Such a result also found in a study done by Shin \textit{et al.} in Russia.\(^{[7]} \) Possible explanation is, those patients who have side effects were followed more closely by TB providers and thereby adherent to treatment, thus increasing the likelihood of a favorable treatment outcome.\(^{[3]} \) ADRs were significantly associated with non-treatment adherence \( (P = 0.00) \) and defaulters outcome \( (P = 0.002) \). A similar result is shown in a study done by Vishakha and Sanjay.\(^{[11]} \)

Individualized regimen was used as per RNTCP which included pyrazinamide, ethambutol, parenteral aminoglycosides (Km), fluoroquinolones (Lfx), Eto, and CS. Seventy-two patients reported 147 ADRs suggesting that each patient had more than one ADR. Most frequently reported ADRs were GI side effects, neuropsychiatric and joint pain, and weakness. Same sets of ADRs were also reported in a study done by Akshata \textit{et al.} in Bengaluru,\(^{[3]} \) by Vishakha and Sanjay in Ahmedabad\(^{[11]} \) and Hoa \textit{et al.} in Vietnam.\(^{[12]} \) In GI system, nausea and vomiting (24.5%) were most common ADR, which were mild–moderate in severity (only 1% ADR was severe) and appeared within 1 month of treatment duration. Abdominal pain and diarrhea was reported in six cases and managed symptomatically. Suspected drug was Eto in 4/30 (13.33%) cases which were discontinued in three cases.

Depression and suicidal tendency was reported in 14.38% cases in the current study. By causality evaluation, it was “certain” in 4.7% cases while “severe” in 6.16% of cases. Severe psychiatric manifestations including hallucinations, anxiety, depression, euphoria, behavioral disorders and suicidal ideation or attempts have been reported to occur in 9.7–50% of individuals receiving CS.\(^{[11-19]} \) Cycloserine which was the suspected drug for psychiatric ADRs had been reported in 10% of the cases in which drug was discontinued in this study. CS-associated neurotoxicity is likely due to diminished central nervous system (CNS) production of gamma-aminobutyric acid caused by inhibition of glutamic decarboxylase. In majority of these cases, the drug was discontinued, with rapid recovery of mental status and no recurring symptoms. Psychiatric symptoms appeared within the first 2 months of treatment in this study. Furthermore, other studies had same duration of occurrence of this ADRs.\(^{[16-19]} \) Increased risk of CNS toxicity may be associated with supratherapeutic levels of CS,\(^{[20]} \) concomitant use of ethambutol,\(^{[21]} \) Isoniazid\(^{[21]} \) or fluoroquinolones\(^{[22]} \) and ethanol ingestion.\(^{[13]} \) In addition to drug toxicity, psychosocial factors contribute to psychiatric complications during MDR-TB therapy, and consequently patients’ adherence to these regimens.\(^{[13-19]} \)

Weakness and joint pain had been reported in 21.23% and 14.38% of the case at 3rd month and 4th month of starting the therapy, respectively. Pyrazinamide and ethambutol have been associated with increasing uric acid levels. Although often it considered asymptomatic, severe hyperuricemia can lead to renal failure. Hence, uric acid level measurement should be done particularly patient with preexisting condition.\(^{[23]} \) Less frequently reported ADRs were ototoxicity (4%), hepatotoxicity (2%), and oculotoxicity (4%) in this study. Ototoxicity, hepatotoxicity, and oculotoxicity appeared within 2 months, 1 month, and 4 months of starting therapy in this study. Respiratory ADRs were seen in 10% (chest pain [4.0%], cough [0.6%], hemoptysis [0.6%], and pneumothorax [0.6%]) cases and appeared after 6 months to 1 year of treatment.

77.3% ADRs were mild to moderate while 22.7% cases were severe ADR reported in this study. A similar study done by Hoa \textit{et al.} showed that mild to moderate ADRs were 58% and severe in 17.73% cases. Severe ADRs were psychological ADR by CS, hearing loss by aminoglycoside, hepatotoxicity, and nausea vomiting by Eto observed in this study.

Causality assessment using the WHO criteria shown 4.79% were “certain,” 13.69% were “probable,” and 81.95% ADRs were “possible” category. Certain ADRs were total seven cases (depression [5], hearing loss [2]). Probable ADRs were in 11/21 (52.38%) (depression, hearing loss in 3/6 [50.0%], nausea and vomiting 4/30 [13.33%], joint pain 2/21 [9.52%], and abdominal pain 1/5 [20.0%]). Rest of the ADRs was classified as possible category.

In general, adverse reactions were managed symptomatically. Offending agents were either reduced in dose or temporarily suspended. In this study, 25 patients needed discontinuation of offending drug. When necessary there was replacement of an alternative drug attempted (e.g. CS stopped, and PAS were added to those patients had depression).

**CONCLUSION**

Cure rate was higher in MDR-TB cases with ADRs than MDR-TB cases without ADR. Attention needs to be paid for timely recognition and treatment of ADR with minimum modification of treatment regimen. Equal attention should be paid to MDR-TB without ADR cases to rise the overall cure rate.
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Study limitations
As this is a retrospective study, we were able to analyze the available data within treatment cards. Under-reporting of ADR as well as reporting bias is possible.

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Conflicts of interest
There are no conflicts of interest.

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