Research Article

Profile of adverse drug reactions in multiple drug resistant tuberculosis patients at drug resistant-tuberculosis center - Miraj, Maharashtra

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ABSTRACT

Background: Drug resistant tuberculosis (DR-TB) has been an emerging global public health threat and area of serious concern on to global efforts of TB control initiative. **Objectives:** To elucidate the profile of adverse drug reactions (ADRs) associated with antitubercular treatment regime for DR-TB. **Materials and Methods:** A retrospective, record-based, observational type of epidemiological study was conducted on multi DR (MDR)-TB patients. The sample size includes, total of 468 patients were admitted in DR-TB center Miraj during year 1st July 2013 to 30th June 2015. A structured pro forma was designed and utilized to collect the data that include variables on ADR profile of diagnosed MDR-TB cases on supervised DOTS-Plus regimen under programmatic management of DR-TB under Revised National Tuberculosis Control Program. The data were analyzed into frequency percentage distribution and presented in tabular form. **Results:** Out of total 468 MDR-TB patients, 12.82% were reported with ADRs. Out of total 109 ADRs, gastrointestinal upset was maximum, 5.98% followed by psychosis 4.91%, hearing impairment 2.99%, and rest were in between 0.21% and 1.49%, respectively. Max, 56.67% ADRs were seen in undernourished patients with major involvement pertained to central nervous system. Around, 50% ADRs were managed by symptomatically, whereas others were managed by changing the antitubercular drug (33.33%), use of vitamin B6 and use of antidepressant. **Conclusion:** Early detection, management and reporting of ADRs remain key factors in the management of MDR-TB with remarkable relevance to prevent emergence threat of global MDR-TB.

KEY WORDS: Multi Drug Resistant Tuberculosis; Drug Sensitivity Testing; Adverse Drug Reactions; Drug Resistant Tuberculosis Center

INTRODUCTION

Emergence of drug resistant tuberculosis (DR-TB), particularly multi DR TB (MDR-TB) and more recently extensively DR-TB, has been an area of growing concern and is posing a threat to global efforts of TB control.[1] In 2014, 9.6 million people felt ill with TB and 1.5 million died from the disease. Over 95% of TB deaths occur in low- and middle-income countries and it is among the top five causes of death for women aged 15-44. In 2014, an estimated 1 million children became ill with TB and 140,000 children died of TB. TB is a leading killer of human immunodeficiency virus (HIV) positive people in 2015, 1 in 3 HIV deaths were due to TB. Globally in 2014, an estimated 480,000 people developed MDR-TB.[2]

India is the country with the highest burden of TB, according to the World Health Organization statistics for year 2013

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with an estimated incidence of 2.1 million cases of TB for India, out of a global incidence of 9 million with estimated TB prevalent cases of 2.6 million.[1] It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB.[3] Globally, 5% of TB cases were estimated to have had MDR-TB in 2014. Drug resistance surveillance data show that an estimated 480,000 people developed MDR-TB in 2014 and 190,000 people died as a result of MDR-TB.[4,5] Drug resistance in MDR-TB is manmade and is a consequence of suboptimal regimens and treatment interruptions.[6] Recently, the burden of resistant TB is again emerging big challenge to India and by considering this government of India announces TB as a notifiable disease in year 2012.[7]

The study aimed to disseminate the profile of adverse drug reactions (ADRs) in MDR-TB patients under DOTS-plus therapy for early diagnosis and immediate action for further improving the compliance to MDT and complete cure of TB.

MATERIALS AND METHODS

This was a retrospective, record-based study of MDR-TB patients who were admitted in DR-TB center Miraj since year 1st July 2013 to 30th June 2015. A sample size include, 436 MDR-TB patients registered under DR-TB center Miraj during study period, who were ≥10 years of age and registered for treatment with MDR-TB regimen at DOTS-plus site Miraj, which includes patient drain from Sangli (rural and corporation), Kolhapur (rural and corporation), Sindhudurg district, etc.

Exclusion Criteria

Those patients who were transferred out, who did not give consent for the interview and age <10 years.

A pretested structured pro forma was designed that include the variables on demographic and ADR profile of diagnosed DR-TB cases on supervised antitubercular drug regimen under programmatic management of DR-TB under Revised National TB Control Programme. The data were collected by investigator by viewing the records of study subject and analyzed into frequency percentage distribution and presented in tabular form.

Ethical Consideration

The study was approved by the Institutional Ethics Committee of Government Medical College (GMC) Miraj.

MDR-TB Case

A TB patient whose sputum is culture positive for mycobacterium TB bacilli and resistant *in vitro* to isoniazid and rifampicin with or without resistance to other antitubercular drugs based on drug susceptibility testing (DST) results from a Revised National Tuberculosis Control Program (RNTCP) certified culture and DST laboratory.

As rifampicin resistance is quite rare without Isoniazid resistance, RNTCP has taken the programmatic decision that patients who have any rifampicin resistance, should also take to be resistant to isoniazid and managed as if they are an MDR-TB case. In this study, we followed the same protocol.[8]

ADRs[9,10]

Any noxious or unintended response to a drug which occurs at doses normally used in human for the prophylaxis, diagnosed or treatment of disease or for the modification of physiological function.

RESULTS

A total of 468 MDT-TB patients were registered for DOTS-plus therapy during the study period ranges from 10 to 75 years with mean age, 34.5 years, respectively.

According to Table 1, maximum, 61.32% MDR-TB cases were belonged male population with mean age 34.58 years. Maximum, 63.32% of patients were undernourished (body mass index ≤18.5 kg/m^2) with mean weight 42.42 kg. Out of total 468 patients, 12.82% were reported with ADRs to DOTS-plus therapy. A total of 60 patients were experienced ADR under DOTS-plus therapy with mean age 35.27 years. Maximum, 56.67% were belonged to male gender and high proportion, 56.67% of undernourished with mean weight 42.78 kg.

Table 2 shows, most commonly affected system was central nervous system (CNS), which contributed 41.28% of total ADRs followed by gastrointestinal and Oto-Rhino-Vestibular system affecting ADRs were 25.68% and 19.26%, respectively. ADRs reported related to skeletal and dermatological system was 6.42% and 4.58%.

Out of 468 MDR-TB patients receiving DOTS-plus therapy, 5.98% were reported gastrointestinal upset as major ADR followed by psychosis and ototoxicity by 4.91% and 2.98%, respectively. However, rest all ADRs reported by patients were ranges from 0.21% to 1.49%, respectively. The mean duration (months) of initiation of DOTS-plus therapy and occurrence of ADRs were depression was maximum, 11.11 followed by suicidal (9.6), psychosis (9.3) and ototoxicity (5.7), respectively. Around 50% ADRs were managed by symptomatically, whereas others were managed by changing the antitubercular drugs (33.33%), use of vitamin B6 and antidepressant (Table 3).

Table 1: Demographic characteristics of MDR-TB patients (*n*=468)

Study characteristics	Frequency (%)
Age (years)	
Mean±SD	34.58±13.03
Range	10-75
Gender	
Male	287 (61.32)
Female	187 (38.68)
Weight (kg)	
Mean±SD	42.42±9.72
Range	16-70
BMI (kg/m^2)	
≤18.5	298 (63.68)
18.5-24.9	155 (33.12)
≥25	15 (3.20)
ADR reporting patients	60 (12.82)
Number of total ADRs	109
Characteristics patients experienced at least one ADR (*n*=60)	
Age (years)	
Mean	35.27±12.10
Range	19-68
Gender	
Male	34 (56.67)
Female	26 (43.33)
Weight (kg)	
Mean	42.78±10.81
Range	22-70
BMI (kg/m^2)	
≤18.5	34 (56.67)
18.5-24.9	21 (35)
≥25	5 (8.33)

MDR-TB: Multi drug resistant-tuberculosis, SD: Standard deviation, BMI: Body mass index, ADR: Adverse drug reactions

DISCUSSION

This study revealed, total 468 patients were received DOTS-plus drug treatment for MDR-TB at DR-TB center Miraj since year 1st July 2013 to 30th June 2015 with mean age 34.58 ± 13.03 years, ranges from 10 to 75 years. The percentage of male patients was greater, 61.32% than female patients, 38.68%. A study conducted by Vishakha and Sanjay.[11] also reported higher percentage of male, 63.49% than female, 36.51%. The high proportion of case load in economically productive age group and male population could be due to poverty, illiteracy, ignorance, addictions, risk-taking behavior, noncompliance, and poor adherence to treatment. The mean weight of study population was 42.42 ± 9.72 kg which ranges from 16 to 70 kg. Similar finding has also been reported by Vishakha and Sanjay et al.[11] as mean weight 41.80 ± 10.82 kg.

Study depicted, 12.82% patients were developed at least one ADR and total 109 ADRs were reported in this study. The percentages of ADRs in patients receiving MDR-TB therapy reported by Furin et al.,[12] Shin et al.[13] and Torun et al.[14] were 100%, 73.3% and 69.2%, respectively. The percentage of ADRs are less in our study as compare to others could be due to better tolerance of drugs, motivation, and better awareness of patient regarding drugs and their consumption and this could be possible due to better knowledge and communication of health-care staff under National Health Programme.[15] The trained health workforce along with adequate health infrastructure, positive attitude of health personals toward TB and strong political will is a big strength for low incidence of ADRs in this study. Motivation and implementation of information, education, and communication activities through public and private health-care sector increased early reporting of ADRs. Higher rate of ADRs, in the study conducted by Torun et al.,[14] could be due use to different aminoglycosides such as kanamycin, capreomycin, amikacin, and streptomycin were used for longer duration (up to 12 months), which could have resulted in increased number of ototoxicity (41.8%).

Maximum, 56.67% patients showing ADRs were undernourished and it can be assumed that the recommended doses used for these patients could be higher with respect to their body weights. It can further be recommended that treating these patient needs administrating lower doses of drugs that could minimize occurrence ADRs, without compromising therapeutic efficacy (--- other studies).

In this study, gastrointestinal (GI) upset (nausea and vomiting) was the most common ADR. In our study, 28 (5.98%) patients complained of GI upset. All these patients were treated symptomatically and none of the patients required drug withdrawal. GI upset was the most common ADR reported in the earlier studies by Furin et al.,[12] Shin et al.,[13] Thomas et al.,[16] Vishakha and Sanjay et al.,[11] and Yew et al.[17] The percentages of GI upset in their studies were 100%, 75.4%, 67%, 22.22%, 20%, respectively. As compared to these previous studies, the occurrence of GI upset in this study is lower. This can be explained on the basis of that our data included hospitalized patients. There was a possibility that the minor GI upset ADR in some patients would have been observed and treated by health providers working at the periphery. In addition to these higher rates of GI upset in Furin et al.[12] and Shin et al.,[13] studies could be due para-aminosalicylic acid (PAS) administered as primary drug and in our study PAS was used only as a replacement drug.

In this study, most commonly affected system was CNS, 41.28% and common offending drugs were cycloserine, fluoroquinolones, and ethionamide. In the cases of psychosis, depression and suicidal thoughts, the first offending drug was

Table 2: System wise distribution of all adverse drug reactions (*n*=109)

System	Manifestations/ADRs	Frequency of ADRs (%)
Central nervous system	Psychosis, depression, suicidal thoughts, seizures, insomnia, headache, peripheral neuropathy, etc.	45 (41.28)
Gastrointestinal tract	Nausea and vomiting	28 (25.68)
Oto-Rhino-Vestibular	Giddiness, tinnitus, and impaired hearing	21 (19.26)
Skeletal system	Arthralgia	7 (6.42)
Dermatological	Rashes, acne vulgaris	5 (4.58)
Endocrine system	Gynecomastia	2 (1.83)
Ophthalmological system	Visual blurring	1 (0.91)

ADR: Adverse drug reactions

Table 3: Specification distribution of ADRs in patients receiving MDR-TB therapy

Adverse drug reaction	Number of patients with ADR (%)*	Mean duration, range from initiation of therapy (months)	Action taken for ADR
Gastrointestinal upset	28 (5.98)	Not available	Symptomatic treatment
Psychosis	23 (4.91)	9.3±6.5, (0.23-19.4)	Cs replaced by PAS (*n*=17), antipsychoticstarted
Ototoxicity	14 (2.99)	8.7±5.4, (1.4-17.78)	Km replaced by PAS (*n*=14)
Insomnia	7 (1.49)	5.7±5.1, (0.5-13.1)	Symptomatic treatment
Arthralgia	7 (1.49)	4.7±2.8, (0.9-8.5)	Symptomatic treatment
Giddiness	7 (1.49)	2.99±2.1, (1.2-7.8)	Symptomatic treatment
Depression	6 (1.28)	11.11±5.39, (3.92-19.63)	Antidepressants started
Headache	4 (0.85)	Not available	Symptomatic treatment
Skin rash	4 (0.85)	Not available	Symptomatic treatment
Peripheral neuropathy	2 (0.43)	Not available	Pyridoxine 100 mg/day
Gynecomastia	2 (0.43)	5.21±3.09, (2.07-5.31)	Ethionamide replaced by PAS (*n*=2)
Suicidal ideation	2 (0.43)	9.68±8.17, (2.3-18.47)	Antidepressants started
Convulsions started	1 (0.21)	Not available	Lvx replaced by PAS, anticonvulsant
Acne vulgaris	1 (0.21)	Not available	Symptomatic treatment
Visual disturbances	1 (0.21)	Not available	Ethambutol stopped and PAS added

*Indicate the sum of percentage exceeds the percentage of patients who developed at least one ADR (12.82%, Table 3) as some patients experienced more than one ADR considered. PAS: Para-aminosalicylic acid, ADR: Adverse drug reactions, MDR-TB: Multi drug resistant-tuberculosis

cycloserine. Psychosis (4.91%) was the second most common ADR in our study. Higher rates of psychosis have been reported in the studies conducted by Shin et al.[13] (11.9%) and Furin et al.[12] (10%). This discrepancy could be due to fixed and higher dose of cycloserine (1000 mg) used in their patients. The mean duration of onset of psychosis was 9.3 ± 6.5 months. While the mean duration of onset of psychosis was 3 ± 4.4 months and 3.3 months in studies conducted by Furin et al.[12] and Shin et al.,[13] respectively. The higher mean interval in this study indicates delayed onset of psychosis which could be due to lower dose and weight band wise titration of dose of cycloserine, as opposed to fixed and higher dose of cycloserine used in the previous studies as mentioned above. In this study, all patients showing psychosis were treated with antipsychotic drugs. It was observed that psychosis was the most common ADR leading to drug withdrawal (17 patients).

In this study, two (0.43%) patients were complained of suicidal thoughts. The other ADRs related to CNS were insomnia (1.49%), headache (0.85%), and seizures. Insomnia and headache were attributed to cycloserine. Insomnia and headache were treated symptomatically. ADR of convulsion is attributed to Levofloxacin. In this study, one case (0.21%) of convulsions was reported. Levofloxacin was replaced by PAS and anticonvulsant drug was given in this patient. ADRs otovestibular system related ADRs in this study were Ototoxicity and giddiness (Table 3). Ototoxicity was the third most common ADR (2.99%) in our study (Table 3). It has proven a clear association of Ototoxicity with the use of Kanamycin and other aminoglycosides.[18] Very high rate of Ototoxicity was reported by Torun et al.[14] (41.8%). This could be attributed to the higher dose (1000 mg) and extended exposure (up to 12 months) to aminoglycosides in their study. This is consistent with findings by Moore et al.,[19] who showed an association between Ototoxicity and cumulative duration of aminoglycosides. In patients with Ototoxicity Kanamycin were replaced by PAS in all 14 patients. Ototoxicity was the second most common ADR

resulting in drug withdrawal. In this study, giddiness was reported in 7 (1.49%) patients. In none of these patient Kanamycin removed, pyrazinamide and levofloxacin can cause arthralgia.

In this study, 7 (1.49%) patients complained of arthralgia and their symptoms were relieved with nonsteroidal anti-inflammatory drugs. In this study, the ADRs related to dermatological system were reported in 5 (1.07%) cases. These patients were treated symptomatically. Similar rate of ADRs related to dermatological system was reported by Vishakha and Sanjay et al.[11] (1.58%). In this study, gynecomastia as ADR was reported in two (0.43%) cases (Table 3). In both these cases, Ethionamide was replaced by PAS. None of the previous studies had reported the occurrence of gynecomastia. The large sample size (468) of our study as compared to the previous similar studies conducted by Torun et al. (13) (263 patients), Shin et al. (12) (244 patients), Vishakha and Sanjay et al.[11] (63 patients), and Furin et al.[12] (60 patients) could have facilitated detection of this uncommon ADR. Peripheral neuropathy observed in two (0.43%) patients.

In this study, all patients on MDR-TB therapy received tab pyridoxine 100 mg. In addition, 100 mg was given in cases of peripheral neuropathy. Higher rate of peripheral neuropathy reported in studies conducted by Furin et al.[12] (20%), Shin et al.[13] (4.1%), and Torun et al.[14] (3%) could be due to lack of inclusion pyridoxine or lower dose of pyridoxine. Visual disturbance is a known ADR to ethambutol was reported one (0.21%) case in this study. This was attributed to use of ethambutol. Ethambutol replaced by PAS in this patient. Hepatotoxicity was not reported in this study. Both Furin et al.[12] and Vishakha and Sanjay et al.[11] have reported hepatotoxicity in single case (1.7% and 1.58%, respectively).

Hypothyroidism is attributed to use of PAS and ethionamide for prolonged duration. In this study, hypothyroidism was not reported. Higher rates of hypothyroidism reported in studies conducted by Shin et al.[13] (17.2%) and Furin et al.[12] (10%). This could be due to use of PAS as primary drug and higher dose of ethionamide in their study.

Limitations

Data are generated from tertiary health-care center attended patients mainly coming from rural area.

CONCLUSION

The study concluded that percentage of patients showing ADRs to MDR-TB therapy was 12.82% which was lowest than ever reported in the previous studies. MDR-TB cases with under nutrition should be cautiously treated with drug dose adjustment to minimize ADRs. Most of the ADRs could be managed symptomatically with minimal interventions even by peripheral health-care providers with proper sensitization, motivation, training, and retraining.

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