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Original Research Article

An observational study to find out incidence and pattern of adverse drug reactions among multidrug resistant tuberculosis patients treated under revised national TB control program of India

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ABSTRACT

Background: Between 2006 and 2015, the prevalence of MDR-TB has been found to be as high as 39.9% in some states. Approximately 35.8% of all previously treated patients developed MDR-TB. The objective of the present study was to identify demographic and health characteristics of patients as well as incidence and pattern of the adverse drug reactions caused by antitubercular drugs in MDR-TB patients in a tertiary care hospital of northern India.
Methods: This 12 months study of observational study was conducted at a DOTS centre. MDR-TB diagnosed patients treated with DOTS Plus regimen were enrolled after getting informed consent. Patient information was recorded. Patient follow-up was conducted to identify the incidence and pattern of ADRs.
Results: A total of 115 patients were enrolled. Maximum number of cases were in the 31-40 age group (25.21%) followed by the 41-50 age group (20.86%). 76 (66.08%) were males and 39 (33.91%) were females. 52 patients (45.21%) had concomitant diseases, out of which 15 (13.04%) were HIV positive and 21 (18.26%) were diabetic. 70 patients (60.86%) developed ADRs. The adverse drug reaction that were seen are -38 (38.76%) cases of gastrointestinal adverse drug reactions, 8 (8.16%) jaundice/hepatitis, 7 (7.14%) impaired hearing/vertigo, 21 (21.24%) central nervous system adverse drug reaction, 6 (6.12%) peripheral neuropathy, 6 (6.12%) rash and itching, 5 (5.10%) arthralgia, 3 (3.06%) renal impairment, 2 (2.04%) hypothyroidism and 2 (2.04%) blurred vision.
Conclusions: Determining which population groups are affected most by ADRs can help physicians to better monitor and make an early diagnosis to reduce ADR-related morbidity and mortality.

Keywords: ADR, DOTS-Plus, MDR-TB, RNTCP, Tuberculosis

INTRODUCTION

Drug resistant tuberculosis (DR-TB) can be of several types. Rifampicin-resistant TB (RR-TB) refers to *Mycobacterium tuberculosis* strains that are resistant to rifampicin. Multidrug resistant TB (MDR-TB) refers to strains that are resistant to both rifampicin and isoniazid. Extensively drug resistant (XDR-TB) refer to strains resistant to fluoroquinolones -ofloxacin, levofloxacin, or moxifloxacin- and any second-line injectable - kanamycin, amikacin, or capreomycin- in addition to rifampicin-isoniazid resistance. Totally drug resistant TB, also known as extremely drug resistant TB or super-XDR-TB (TDR-TB or XXDR-TB) refer to strains resistant to all of the first and second line drugs. In India, multidrug tuberculosis shows an alarming trend and is slowly turning into a significant public health problem.

Since 2006 to 2015, the prevalence of MDR-TB was as high as 39.9% among all TB patients in certain states. Nearly 35.8% of all previously treated patients developed MDR-TB.[1] In 2016, incidence of MDR-TB or Rifampicin

Resistant Tuberculosis (RR-TB) was 1,47,000 which was the highest among all countries.[2]

The first attempt at controlling tuberculosis was made in 1929 when India joined the International Union Against Tuberculosis. The first established national program was in the year 1959 - National TB control Programme (NTP). The current national program is Revised National TB Control Program (RNTCP) and future control strategies include the implementation of National Strategic Plan 2017-2025.[3]

In spite of several decades of attempts at controlling tuberculosis, the disease has still managed to evade being eradicated. 40% of the population in India suffers from TB. Majority of the proportion have latent TB.[4] TB causes two deaths in every three minutes, making India the country with the highest burden of TB.[5] In 2016, 2.79 million individuals were newly diagnosed with TB, a figure that has increased when compared to the estimated 2.2 million incident cases in 2014.[4,6] 85% of confirmed new TB patients are treated successfully whereas the treatment success rate of previously treated TB patients is 70%.[4]

However, encouraging trends suggest that incidence rates of TB have been steadily declining. Data suggests that the incidence has reduced from 289 per lakh in 2000 to about 217 per lakh in 2015. Mortality rates have declined as well. 56 per lac per year in 2000 has declined to 36 per lac per year in 2015.[7]

Special measures are being undertaken to control MDR-TB. RNTCP has established the Programmatic Management of Drug Resistant TB (PMDT) in 2012, formerly known as DOTS Plus to better address MDR-TB diagnosis, management and treatment while simultaneously integrating basic TB control services. Under this scheme, patients diagnosed with TB are also checked for drug-resistant strains, so that misdiagnosis followed by improper treatment and further spread does not occur.[8]

The failure of tuberculosis treatment can be attributed to several reasons. These can be categorized broadly under doctor-related, drug- related and patient -related. Doctor related treatment failure include initiating improper treatment owing to inappropriate guidelines, non-compliance with guidelines and absence of guidelines. Drug-related treatment failures include poor quality, irregular supply, wrong dose or combination, drug resistance and adverse drug reactions. Patient-related causes include lack of information, lack of money either for treatment or transport, actual or presumed side effects, lack of commitment to the long course and duration of drug intake, and social barriers. Failure of treatment contributes significantly to drug resistance.

Adverse effects contribute to morbidity patient and poor adherence. According to a study by WHO, the common adverse effects seen are nausea/vomiting, diarrhoea, arthralgia, dizziness/vertigo and hearing disturbances, headache, sleep disturbances, electrolyte disturbances, electrolyte disturbances, abdominal pain, anorexia, gastritis, peripheral neuropathy, depression, tinnitus, allergic reaction, rash, visual disturbances, seizures, hypothyroidism, psychosis, hepatitis and renal failure/nephrotoxicity.[9]

Regarding adverse effects of any treatment, it is important to remind ourselves of the Latin phrase '*Primum non nocere*' which means "first, to do no harm". Apart from clinical diagnosis, advising laboratory tests for confirmation and instituting therapeutic management, the cautious physician also takes part in the monitoring and reporting adverse drug reactions (ADR) which completes the holistic approach to healthcare. However, a large proportion of physicians do not actively participate in ADR monitoring and reporting due to several reasons - inadequate knowledge about drugs, fear of reporting, lack of self-confidence, lack of initiative and drive to report, inadequate skills to identify ADRs, poor understanding of ADR reporting form and lack of awareness about the national pharmacovigilance program and how to report.[10]

It is important to remedy the shortcomings, most of which can be easily solved by routine awareness workshops and CMEs. With the help of proper monitoring and reporting, data can be generated regarding various aspects of treatment. Generating data pertaining to local population can give us better insights about the penetration of the national programme, the success rates of the treatment, the degree of resistance, the rate of spread of MDR-TB and the various adverse drug reactions. With this data, current loopholes can be identified, and better national programs can be designed. In the year of 2016, RNTCP covered a population 21.78 crores in the state of Uttar Pradesh. Out of the population covered, TB emerged in 2.16 lakh incident new cases and 44,531 previously treated cases.[4]

The present study was conducted to find out various aspects of adverse effects associated with MDR tuberculosis treatment under DOTs plus program. The objectives of the present study were to identify demographic and health characteristics of patients receiving antitubercular drugs and the incidence and pattern of the adverse drug reactions (ADRs) of the antitubercular drugs in MDR-TB patients in a tertiary care hospital of Northern India.

METHODS

This prospective observational study was conducted on patients diagnosed with MDR tuberculosis and treated with DOTS Plus regimen under the national tuberculosis control program RNTCP. This study was carried out in the Department of Pharmacology and Therapeutics in collaboration with the Department of Respiratory Medicine at King George's Medical University, Lucknow, Uttar Pradesh. The study commenced only after gaining ethical approval from the Institutional Ethics Committee.

The duration of the study spanned 12 months from May 2016 till April 2017. Once diagnosed with MDR-TB - via drug sensitivity tests - and started on DOTS- plus regimen, informed consent was taken from the patient to be enrolled in the study. This was followed by a battery of pre-treatment tests such as sputum smear, thyroid function test, kidney function test, liver function test, psychiatric screening, blood sugar levels (fasting and postprandial), HIV seropositivity and chest X-ray. Each patient was allotted their own patient identification number to ease the follow up process.

Each patient was monitored daily during the initial days of the starting the DOTS-Plus regimen while they were admitted in the hospital. After being discharged, these patients were followed up every month. Several tests were repeated to check for any biochemical abnormalities. Patients with severe adverse drug reactions were treated accordingly or referred to appropriate clinical department if required and were followed up regularly. A detailed interview regarding the ADR would be conducted and recorded in the CDSCO suspected ADR reporting form.

Inclusion criteria

- Newly diagnosed patients of multi-drug resistant pulmonary tuberculosis.
- Patients of either sex with age more than 18 years.
- Patients having normal baseline (pretreatment) parameters like liver function tests, kidney function tests, thyroid function tests, psychiatric screening, and chest X-ray other than blood sugar (fasting and postprandial) and HIV seropositivity.
- Patients having no associated comorbidity except HIV and diabetes mellitus.

Exclusion criteria

- Patients who were unwilling to participate and did not give consent in the study
- Patients who were unable to give interview
- Patients with incomplete medical record
- Patients with chronic liver disease such as cirrhosis, chronic hepatitis and acute viral hepatitis
- Patients with concurrent major debilitating medical illnesses other than diabetes and HIV
- Terminally ill patients.

RESULTS

A total of115 patients were studied during the 12 months study period. Maximum number of cases were in the age group 31-40 years (25.21%) followed by 41-50years (20.86%). Of the total number, 76 (66.08%) were males and 39 (33.91%) were females (Table 1 and Figure 1). Concomitant medical diseases were present in 52 patients (45.21%).

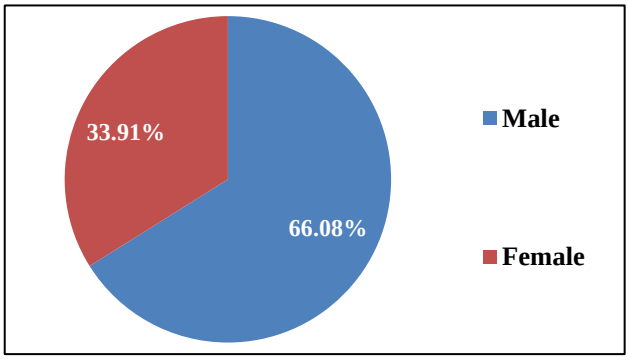

Figure 1: Gender distribution of the patients

Table 1: Demographic characteristics of the patients.

Age	18-30	31-40	41-50	51-60	61-70	71-80	81-90	Above 91
Male (N=76) N (%)	17(77.27)	21(72.41)	15(62.50)	9(45.00)	5(71.42)	3(60.00)	3(60.00)	2(66.66)
Female (N=39) N (%)	5(22.72)	8(27.58)	9(37.50)	11(55.00)	2(28.57)	2(40.00)	2(40.00)	1(33.33)
Total (N=115) N (%)	22(19.13)	29(25.21)	24(20.86)	20(17.39)	7(6.08)	5(4.34)	5(4.34)	3(2.60)

χ^2=5.995; p value=0.540

Table 2: Incidence of adverse drug reaction.

Age	18-30	31-40	41-50	51-60	61-70	71-80	81-90	Above 91
Male (N=31) N (%)	2(33.33)	9(52.94)	7(43.75)	5(31.25)	2(50.00)	1(33.33)	3(60.00)	2(66.66)
Female (N=39) N (%)	4(66.66)	8(47.05)	9(56.25)	11(68.75)	2(50.00)	2(66.66)	2(40.00)	1(33.33)
Total (N=70) N (%)	6(8.57)	17(24.28)	16(22.85)	16(22.85)	4(5.71)	3(4.28)	5(7.14)	3(4.28)

χ^2=3.807; p value=0.802

These included hypertensions, COPD and hyperlipidemia. 36 (31.30%) patients were immunocompromised, of which 15 (13.04%) were HIV positive and 21 (18.26%) were diabetic. Diabetic and HIV positive patients were already known cases and on anti-diabetic medications and anti-retroviral therapy respectively.

Total of 60.86% patients developed ADR. 98 adverse drug reactions were observed in 70 patients. Maximum number of patients with ADRs were in the age group 31-40 (24.28%) followed by 41-50 (22.85%) and 51-60 (22.85%) (Table 2). Of the total number of patients with ADRs in the study males were 31 (40.78%) and females were 39 (100.00%). Out of total 98 ADRs, maximum ADRs were seen in males of age group 41-70 i.e. 35.71% whereas females of same age group constituted 27.55%. Distribution of ADRs in males and females of age group 18-40 was the same i.e. 13.26% each. 46.15% of primary MDR-TB cases and 62.74% secondary MDR-TB cases developed ADR (Table 3).

Table 3: Incidence in primary and secondary MDR-TB (p-value).

ADR	Primary	Secondary	Total
Present	6 (46.15)	64 (62.74)	70 (60.86)
Absent	7 (53.84)	38 (37.25)	45 (39.13)
Total	13	102	115

χ^2=0.727; p value=0.393

Most frequently occurring, 38.76% of the ADRs were gastrointestinal complaints (nausea and vomiting, epigastric pain, diarrhoea and abdominal pain) followed by jaundice and hepatitis occurring in about 8.16% of the patients and the third most commonly observed ADR was impaired hearing/ vertigo (Table 4 and Table 5).

Table 4: Adverse drug reactions: system and individual ADRs.

System	ADR features	No. of ADR (%)	Total ADR in each system (%)
Gastro-intestinal system	Nausea and vomiting	15(15.30)	38 (38.76)
	Epigastric pain	8(8.16)	
	Diarrhoea	9(9.18)	
	Abdominal pain	6(6.12)	
Hepato-biliary system	Jaundice/hepatitis	8(8.16)	8 (8.16)
Oto-vestibular system	Impaired hearing/vertigo	7(7.14)	7(7.14)
Central nervous system	Headache	12(12.24)	21(21.24)
	Seizures	3(3.06)	
	Psychosis	2(2.04)	
	Depression	4(4.08)	
Peripheral nervous system	Peripheral neuropathy	6(6.12)	6(6.12)
Skin and appendages	Rash and itching	6(6.12)	6(6.12)
Skeletal system	Arthralgia	5(5.10)	5(5.10)
Renal system	Renal impairment	3(3.06)	3(3.06)
Endocrine system	Hypothyroidism	2(2.04)	2(2.04)
Ophthalmic	Blurred vision	2(2.04)	2(2.04)
Total		98(100.00)	98(100.00)

DISCUSSION

According to our study, mean age of 46.31±18.54years favors the argument that the disease is common in economically productive age group. This finding is in accordance with similar studies around the world. A study by Cavanaugh et al, in Russia (2002-2005) determined 42years as the mean age.[11] Similar result was shown in study by Masjedi et al (2002-2006) in Iran where mean ages were 44.38±19.05years.[12]

In India, a similar result was seen in a 2010 study by Datta et al, in Kashmir, where the mean age was 39±4.7years.[13] Bhatt GS et al, in Ahmedabad, Gujarat showed a much lower mean age of 33.64±11.03years.[14]

The total number of males in the study was 76 (66.08%) and females were 39 (33.91%). The gender distribution result was similar to the study by Masjedi et al, out of 43, 27 (62.8%) were male and 16 (37.2%) female.[12] Cavanaugh et al, in Russia showed high male predisposition with 83% male and 18% females.[11] A study in Taiwan by Chiang et al, showed 71.9% males and 28.1% females.[15] In the study by Datta et al, in Kashmir showed that ratio of male to female was 29:23.[13]

Table 5: ADRs and age group and gender distribution.

ADR	Age group and gender (%)						Total
	18-40		41-70		71-above		
	Male	Female	Male	Female	Male	Female	
Nausea and vomiting	3(15.00)	2(13.33)	5(33.33)	4(26.66)	1(6.66)	-	15(15.30)
Epigastric pain	1(12.50)	1(12.50)	2(25.00)	3(37.5)	-	1(12.50)	8(8.16)
Diarrhea	2(22.22)	1(11.11)	4(44.44)	2(22.22)	-	-	9(9.18)
Abdominal pain	2(33.33)	-	2(33.33)	2(33.33)	-	-	6(6.12)
Jaundice/hepatitis	-	2(25.00)	3(37.50)	2(25.00)	1(12.50)	-	8(8.16)
Impaired hearing/vertigo	-	2(28.57)	4(57.14)	-	1(14.28)	-	7(7.14)
Headache	1(8.33)	-	4(33.33)	3(25.00)	1(8.33)	3(25.00)	12(12.24)
Seizures	-	1(33.33)	1(33.33)	1(33.33)	-	-	3(3.06)
Psychosis	-	1(50.00)	1(50.00)	-	-	-	2(2.04)
Depression	1(25.00)	1(25.00)	-	1(25.00)	-	1(25.00)	4(4.08)
Peripheral neuropathy	-	1(16.66)	4(66.66)	-	1(16.66)	-	6(6.12)
Rash and itching	2(33.33)	-	1(16..67)	3(50.00)	-	-	6(6.12)
Arthralgia	-	-	2(40.00)	3(60.00)	-	-	5(5.10)
Renal impairment	1(33.33)	-	1(33.33)	1(33.33)	-	-	3(3.06)
Hypothyroidism	-	1(50.00)	-	1(50.00)	-	-	2(2.04)
Blurred vision	-	-	1(50.00)	-	1(50.00)	-	2(2.04)
Total	13(13.26)	13(13.26)	35(35.71)	27(27.55)	9(9.18)	1(1.02)	98(100.00)

Concomitant medical diseases were present in 52 patients (45.21%). These included hypertension, COPD and hyperlipidemia. 36 (31.30%) patients were immunocompromised, of which 21 (18.26%) were diabetic and 15 (13.04%) were HIV positive. In agreement with these results, Sobhy et al, reported that 15% of the studied patients had comorbid diabetes compared to other co-morbidities in MDR-TB patients.[16] Lower percentage of diabetes mellitus was reported by Furin et al, who found comorbid conditions at MDR-TB diagnosis included diabetes (1.7%), HIV (1.7%) and alcoholism (3.3%).[17]

Total of 60.86% patients developed ADR. Majority (42.60%) of the patients with ADR were in the age group of 31-60years. This finding is similar as reported in other studies by Bloss et al, and Nathanson et al, where it ranged from 69% to 86%.[18,19]

Various studies show different results when it comes to prevalence of ADRs. This heterogeneity may be attributed to several factors including but not limited to - variability in terminology for adverse events depending on local language and settings, accuracy of the adverse event-whether the adverse event was patient-reported (subjective) or physician-reported (objective), whether the adverse event data was collected actively by the healthcare professional or reported spontaneously by the patient, whether preference was given to studying only serious adverse event or all adverse events were carefully monitored.

There could be variations in the treatment regimen tailored to each region and presence confounding factors in the form of different co-morbidities and covariates in different study settings.

The total number of males with ADRs in the study was 31 (26.95%) and females were 39 (33.91%). Generally, females are considered to be more at risk of ADRs due to their smaller body size and body weight compared to males. In this study it was also seen, that previously treated cases suffered from more ADRs as compared to new cases.

Adverse drug reactions are common in patients of MDR-TB on DOTs-Plus drug regimen. This may be attributed to poor screening and early detection and loss of valuable time in mitigating adverse drug reactions. There is also a lack of availability of safer alternatives and equally potent drugs in DOTs-Plus drug regimen when compared to DOTS regimen in non-resistant TB.

Awareness about the incidence and pattern and sufficient skills to deal with the same can help the treating physician expect and identify ADRs with more accuracy at an early stage and deal the same with more confidence. The frequency and severity of known ADRs can be reduced by monitoring laboratory and clinical parameters and instituting appropriate measures. This may help improving the compliance and ultimately quality of patient care. Thus, close monitoring and timely management of adverse drug reactions are essential for treatment adherence and to improve outcome in MDR-TB.

The shortcoming of our study was that patients who get admitted to DR TB center of authors' hospital come from rural area. Such patients often do not report minor side

effects due to remote location of the rural area and lack of means of transport. Despite efforts to contact the patients telephonically, it was noted that patients did not report adverse effects they deemed unimportant unless prompted directly with leading questions. However, patients with significant ADRs that required medical attention were noted. The other limitation of the present study was the small sample size and short duration limiting our ability to enroll more patients and detect significant associations

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