Adverse drug reactions and risk factors for discontinuation of multidrug-resistant tuberculosis regimens in Gujarat, western India

MIHIR PRAFULBHAI RUPANI, JIGNA D. DAVE, VIJAY B. PARMAR, MANINDRA PRATAP SINGH, KHUSHALI DHARMESH PARIKH

ABSTRACT

Background. The predictors for discontinuation of multidrug-resistant tuberculosis (MDR-TB) regimens have not been studied in Gujarat. We aimed to find out the adverse drug reactions (ADRs) and predictors for discontinuation of MDR-TB regimens.

Methods. We conducted this cross-sectional study in Bhavnagar district of Gujarat from September to November 2016 through home visits and personal interviews of 94 patients with MDR-TB.

Results. Sixty-nine patients with MDR-TB (73%) reported ADRs. Tingling (42.6%), headache (37.2%), numbness (36.2%), dizziness (34%) and nausea (33%) were the most common ADRs. Of the 94 patients, 7.4% were compelled to think of discontinuing their treatment due to ADRs; 8.5% had discontinued Cat-I/Cat-II regimen in the past; 11.7% had discontinued their MDR-TB regimen in the past; 13.8% had their drug regimen changed due to ADRs and 94.7% had good adherence to their current regimen (took at least 80% of their doses till date). ADRs were the reason for 75% of the patients who discontinued their Cat-I/Cat-II regimen in the past and 64% of the patients who discontinued their MDR-TB regimen in the past. Tobacco chewing, poor adherence and thought of discontinuing an MDR-TB regimen due to ADRs were significant predictors for discontinuation on bivariate analysis. On multiple logistic regression, none of the predictors were significant.

Conclusions. The frequency of ADRs among patients with MDR-TB is high. ADRs were the primary reason for discontinuing MDR-TB drugs.

Natl Med J India 2020;33:10–14

INTRODUCTION

In India in 2015, an estimated 2.5% of new cases and 16% of previously treated cases had multidrug-resistant tuberculosis (MDR-TB).[1] A study reported that the percentage of adverse drug reactions (ADRs) among patients with MDR-TB stands at 58%.[2] About 18 adverse events have been reported in various other studies.[3] Not much difference has been observed in previous studies with respect to ADRs as far as the comparison between patients with human immunodeficiency virus (HIV) coinfected with TB and those with TB but HIV-non-infected is concerned.[3] Hepatotoxicity due to pyrazinamide and ethambutol has been reported previously.[4] However, another study reported that hepatotoxicity while on an MDR-TB regimen did not result in poor treatment outcomes.[5] We studied the ADRs and predictors for discontinuation of the MDR-TB regimen.

METHODS

Study design and setting

This cross-sectional study was conducted in Bhavnagar district of Gujarat, western India. Bhavnagar district caters to a large number of patients with TB of the same and the surrounding districts of Amreli and Botad. It is situated 255 km southwest of Ahmedabad. The study was conducted through the District TB Centre (DTC) with patients with MDR-TB registered over 3 months (September to November 2016). All 135 patients with MDR-TB registered with the DTC of Bhavnagar district were included in the study.

Inclusion criteria

All patients with MDR-TB above 10 years of age, of either gender, who were on drugs for MDR-TB for at least 2 months (including defaulters), who gave written informed consent were included in the study. The patients were diagnosed as MDR-TB using Cartridge Based-Nucleic Acid Amplification Test (CB-NAAT) at the designated microscopy centre of Sir Takhtsinhji Hospital (government district hospital) of Bhavnagar.

Data collection

Data were collected by a personal interview through home visits of the patients. The home visits in Bhavnagar corporation area were done along with a tuberculosis health visitor (TBHV). The home visits in Bhavnagar rural area were done along with senior treatment supervisors (STSs).

The investigators filled up a one-page questionnaire on ADRs through home visits. The patients' case papers were also checked for additional data such as laboratory investigations. The questionnaire consisted of sociodemographic variables, addiction, HIV status, duration of treatment, drugs currently on

Government Medical College, Bhavnagar 364001, Gujarat, India
MIHIR PRAFULBHAI RUPANI, VIJAY B. PARMAR, MANINDRA PRATAP SINGH Department of Community Medicine
JIGNA D. DAVE Department of Respiratory Medicine
KHUSHALI DHARMESH PARIKH Department of Pathology

Correspondence to KHUSHALI DHARMESH PARIKH; *khushaliparikh@gmail.com*

and ADRs, the reason for stopping the particular drug, previous history of default, the reason for default, etc. Tobacco consumption and alcohol drinking were asked for through a single question but were not quantified. The questionnaire was translated into Gujarati for ease of data collection. The translated questionnaire was validated with concurrent validity. The face validity and content validity were checked by a group of experts and the suggested changes were incorporated. The questionnaire was then pilot tested and necessary corrections done.

Variables

The primary outcome variable was descriptive in nature, wherein the ADRs among patients with MDR-TB have been described. The dichotomous variable of having or not having an ADR was compared with the input variables. The secondary outcome variable was whether patients with MDR-TB were compelled to discontinue treatment due to ADRs, which was expressed as a percentage. Another secondary outcome variable was a dichotomous variable of whether or not patients with MDR-TB discontinued their regimen, which was compared with the input variables. The input variables were sociodemographic variables, weight, duration of treatment, duration of ADRs, HIV status, comorbid conditions and addiction.

Statistical analysis

Independent samples *t*-test was applied for comparison of a continuous variable among the two groups. Chi-square test was applied for comparison of a pair of categorical variables. Mid-P exact p-values were estimated where the assumptions of chi-square tests were not valid (80% of expected cell values were <5 or 1 of the expected cell values was <1). Open Epi software version 2.2 was used to do all the statistical analyses.[6] Multiple logistic regression was done by the 'enter' method, considering discontinuation of the MDR-TB regimen as the dependent variable and entering the following variables as the independent variables (predictors predicting discontinuation) in Step 1: age in years, years of schooling, being single (unmarried), duration of treatment, being in the intensive phase of regimen, presence of ADR and per capita income. Adjusted odds ratios with 95% CI were calculated. A p value <0.05 was considered significant.

Ethical considerations

Approval for carrying out the study was obtained from the Institutional Review Board of the Government Medical College Bhavnagar, Gujarat. Permission for carrying out the study was obtained from the District TB Officer of Bhavnagar district.

Socioeconomic classification

For socioeconomic status, Modified Prasad's classification was used taking All India Consumer Price Index for Industrial Workers value of 268 for August 2016 for Bhavnagar district.[7,8]

RESULTS

Of 135 patients, 18 patients had taken MDR-TB drugs for <2 months; 9 patients were <10 years of age and 14 patients did not give written informed consent to participate in the study. Therefore, 94 patients with MDR-TB were included with a mean (SD) age of 35.9 (14) years. The mean (SD) years of schooling were 4.9 (4) years. The mean (SD) weight of the patients was 46.9 (11) kg. The mean (SD) per capita income of the patients was ₹1927 (1330).

Among the 94 patients with MDR-TB, 56.4% were below 35 years of age; 68.1% were males; 60.6% were literate; 79.8% were married and 59.6% belonged to the upper socioeconomic status (class IV and V) of Modified Prasad's classification. Of the 94 respondents, 34% were homemakers; 28.7% were daily wage labourers and 17% were not doing any work due to the physical weakness caused by MDR-TB (Table I).

On average, the time since diagnosis of MDR-TB was 14.2 months and patients were on MDR-TB drugs for 17.2 months. A majority of them (95%) had taken Cat-I/Cat-II drugs previously, while only 2% had taken MDR-TB drugs before being put on the current regimen. Among the 94 patients, 49% were in the intensive phase; 43% were in the continuation phase and 8% were taking the Modified Cat-IV regimen. Regarding addictions, 20.2% were tobacco chewers, 5.3% were tobacco smokers and 2.1% were addicted to alcohol. Of the 5 patients presenting with comorbid conditions, 3 had diabetes, 1 had HIV and 1 had chronic renal failure. Of the 3 patients with abnormal blood investigations, 1 had a serum creatinine level of 4 g/dl and the other two had serum uric acid level of 10.9 g/dl.

The prevalence of ADRs among patients with MDR-TB was 73% with 69 patients having at least one ADR. Table II lists the ADRs of MDR-TB drugs among the respondents. Only 1 of the 94 patients was coinfected with HIV and was on antiretroviral therapy (ART; tenofovir, lamivudine and efavirenz). The CD4 count of the patient was 94 cells/cmm. The patient had a rash, tingling, numbness, vision changes, fatigue and dizziness as ADRs. Since only one patient had HIV coinfection, no comment could be made on the difference in ADRs due to ART.

TABLE I. Sociodemographic data of the patients (*n*=94)

Characteristic	*n* (%)
Age group (years)	
≤35	53 (56.4)
>35	41 (43.6)
Gender	
Male	64 (68.1)
Female	30 (31.9)
Literacy status	
Illiterate	37 (39.4)
Literate	57 (60.6)
Marital status	
Single	19 (20.2)
Married	75 (79.8)
Occupation	
Homemaker	32 (34)
Daily wage labourer	27 (28.7)
Not working (due to illness)	16 (17)
Diamond worker	6 (6.4)
Salaried employee	5 (5.3)
Retired	5 (5.3)
Student	3 (3.2)
Socioeconomic status	
I	1 (1.1)
II	4 (4.3)
III	33 (35.1)
IV	54 (57.4)
V	2 (2.1)
Socioeconomic status group	
Lower (I to III)	38 (40.4)
Upper (IV and V)	56 (59.6)

TABLE II. Adverse drug reactions in patients (*n*=94) with multidrug-resistant tuberculosis (multiple answers)

Adverse drug reaction	*n* (%)
Tingling	40 (42.6)
Headache	35 (37.2)
Numbness	34 (36.2)
Dizziness	32 (34)
Nausea	31 (33)
Joint pain	24 (25.5)
Vomiting	22 (23.4)
Fatigue	19 (20.2)
Tinnitus	16 (17)
Vision changes	15 (16)
Abdominal pain	14 (14.9)
Loss of appetite	12 (12.8)
Hearing loss	9 (9.6)
Gastritis	8 (8.5)
Physical weakness	8 (8.5)
Depression	6 (6.4)
Psychosis	5 (5.3)
Fever	3 (3.2)
Rash, constipation, itching	2 each (2.1)
Tremors, palpitation	1 each (1.1)

The patients had ADRs for a mean (SD) duration of 15.3 (10) months. Among the 94 patients with MDR-TB, 7.4% were compelled to think of discontinuing the treatment due to ADRs; 8.5% had discontinued their Cat-I/Cat-II regimen in the past; 11.7% had discontinued MDR-TB drugs in the past; 13.8% had their drug regimen changed due to ADRs but 94.7% had good adherence to their present regimen (took at least 80% of their doses till date). ADRs were the reason for 75% of patients discontinuing their Cat-I/Cat-II regimen in the past and 64% of patients discontinuing the MDR-TB regimen in the past (Table III).

The presence/absence of ADRs was not statistically significantly associated with age group, gender, literacy status, marital status, socioeconomic status, drug regimen, presence/absence of a comorbid condition, adherence, tobacco chewing, tobacco smoking and alcohol addiction.

Patients with MDR-TB who had an ADR had a mean (SD) age of 36.7 (13.9) years compared with those who did not have an ADR whose age was 33.6 (14.6) years. This difference was not statistically significant (p=0.35).

Similarly, there was no statistically significant difference among those having ADR(s) and those not having ADR(s) for years of schooling, per capita income, weight, time since diagnosis of MDR-TB and time since starting treatment of MDR-TB.

There was no statistically significant difference among those discontinuing and those not discontinuing their regimen for age, years of schooling, per capita income, weight, time since diagnosis of MDR-TB, time since starting treatment of MDR-TB and time since experiencing ADR(s).

Adherence to an MDR-TB regimen was associated with a 97.7% reduction in risk of discontinuation than those who did not adhere to their regimen. Tobacco chewers were four times more likely to discontinue their MDR-TB regimen than those not chewing tobacco. Those who were compelled to think of discontinuing their regimen due to ADR(s) were seven times more likely to actually discontinue than those who were not compelled to think so. Discontinuation of the MDR-TB regimen was not statistically significantly associated with age group, gender, literacy status, marital status, socioeconomic status, drug regimen, presence/absence of comorbid conditions, tobacco smoking, alcohol addiction, presence/absence of ADRs and change in drug regimen due to ADRs.

On multiple logistic regression, none of the predictors were found to be statistically significantly associated with discontinuation of the MDR-TB regimen (Table IV).

TABLE III. Details of adverse drug reactions (ADRs; *n*=94)

Characteristic	*n* (%)
Adverse drug reactions compelled them to think of discontinuing the MDR-TB drugs	7 (7.4)
Discontinued Cat-I/Cat-II drugs in the past	8 (8.5)
Due to adverse drug reactions	6
Migrated to some other place	2
Discontinued MDR-TB drugs in the past	11 (11.7)
Due to adverse drug reactions	7
Felt cured	2
Migrated to some other place	1
Started treatment from a private practitioner	1
Took at least 80% of doses up till now (adherence)	89 (94.7)
Drug regimen changed due to ADRs	13 (13.8)
Drug stopped due to ADR(s)	*ADR*
Ethionamide	Vomiting, physical weakness
Kanamycin	Swelling at injection site, hearing loss
Levofloxacin	Abdominal pain (liver dysfunction), vomiting, physical weakness
Pyrazinamide	Psychosis, depression, joint pain
Cycloserine	Psychosis
Para-aminosalicylic acid	Vomiting

MDR-TB multidrug-resistant tuberculosis

DISCUSSION

Each drug has a pharmacological action and has some side-effect or ADR attached to it and the treatment regimen of TB is no exception. We assessed the ADRs of patients with MDR-TB to highlight the difference in those with HIV coinfection. We found that 73% of patients with MDR-TB had ADRs. A study in Tamil Nadu found the incidence of ADRs to be 58%.[1] A study done in Lucknow found this to be 47%.[2] A study conducted at the Tuberculosis Chest Institute of Bengaluru reported that the majority of their patients had one or more ADRs.[3] A study in Aurangabad (Maharashtra) reported that nearly 34% of patients received second-line therapy with ADRs.[4] A study in Nagpur, Maharashtra, found 50% of patients with MDR-TB had ADRs.[5] Another study from Maharashtra (Mumbai) reported that 28.8% of patients had ADRs,[6] whereas another study in Mumbai reported 45% ADRs in patients with drug-resistant TB.[7] A study in Ahmedabad conducted at a tertiary care hospital found it in 57.1% of patients.[8] Another study from Ahmedabad reported that 93.8% of patients with MDR-TB had ADRs.[9] A study from New Delhi revealed that all patients with MDR-TB reported ADRs, from as minor as loss of taste to as severe as a psychotic reaction.[10] Bhushan *et al.* in 2014 reported 81.2% of ADRs among patients with drug-resistant TB.[11] Patel *et al.* in 2015 found that in seven districts of Gujarat 54.9% of patients with MDR-TB patients developed ADRs in 2 years of follow-up.[12] The average duration of ADRs was 60–90 days.[12] We found the mean duration of ADRs to be 15.3 months. Thus, various studies in India have reported the prevalence of ADRs to be in the range of 29%–94%.

Only one patient was reactive for HIV in our study, which was also the case in another study done in Ahmedabad.[9] A study from Lucknow mentioned that none of their 98 patients with MDR-TB had HIV coinfection.[2] Hence, to study the difference in ADRs among HIV-infected and non-infected patients with MDR-TB, we need a larger sample size.

A review published by the Indian Council of Medical Research mentions overlapping ADRs in patients put on both anti-TB drugs and ART.[13] A similar finding was reported by a study from Mumbai, where they did not find any statistically significant difference in the occurrence of ADRs between patients with MDR-TB taking either first-line or second-line ART.[14] However, they highlighted the concern of co-administration of tenofovir with aminoglycosides and capreomycin increasing the risk of renal toxicity; co-administration of efavirenz and cycloserine increasing the risk of psychiatric adverse effects; and co-administration of stavudine and ethionamide, cycloserine or high-dose isoniazid increasing the risk of peripheral neuropathy.[14]

Gastrointestinal symptoms were the most commonly reported ADRs in many published studies.[2–5,8–12,14] Peripheral neuropathy (tingling) was the second most common in a study in Mumbai.[14] Headache was the second most common ADR reported in the research conducted in Ahmedabad,[9] which was also the case in our study. We found tingling, headache, numbness, dizziness and nausea to be the most common ADRs.

ADRs were the main reason for discontinuation of treatment of TB in our study. A qualitative study conducted to assess the outcomes of patients with MDR-TB in Nagpur found that 30% of patients felt adverse drug effects as an important barrier to treatment adherence.[15] A study from Bengaluru reported 1.7% of patients discontinuing treatment and 10.5% of patients requiring a change in drug regimen due to ADRs.[3] Another study from Ahmedabad stated that 33% of patients required a change in drug regimen due to ADRs.[8] A study from Punjab reported that 12.1% of patients had to change their drug regimen due to ADRs.[11] The study from Lucknow highlighted that 17.4% of patients required a change in their regimen due to ADRs.[2] The study in Aurangabad stated that 9.4% of patients required a change in regimen due to psychiatric and ototoxic ADRs.[4] The study in Mumbai found that 20% of patients required a change in drug regimen due to moderate-to-severe ADRs.[7] We found that 13.8% of patients with MDR-TB required to change their drug regimen due to ADRs.

A study from Punjab found almost half the male patients (42%) had a history of drug and/or alcohol abuse, 11% were tobacco smokers and 28% were tobacco chewers.[11] We found that 20.2% of patients were tobacco chewers, 5.3% were tobacco smokers and 2.1% were addicted to alcohol. This difference was probably due to the different addictions prevalent in these two states, with alcohol being banned in Gujarat and tobacco chewing being the prevalent practice in Bhavnagar district.[16] Prasad *et al*. reported no statistically significant difference in patients suffering from ADRs with respect to gender, drug addiction, alcohol addiction and age group.[2] Our study also did not find any difference between patients with or without ADRs with respect to their age group, gender, tobacco chewing, tobacco smoking and alcohol addiction.

Limitations

As our study was done in one district, its generalizability to the entire state of Gujarat is questionable. As the sample size was small, our study was not able to compare the ADRs among patients with MDR-TB with or without HIV coinfection.

TABLE IV. Multiple logistic regression for predictors of discontinuation of multidrug-resistant tuberculosis regimen* (*n*=94)

Variable	Beta coefficient	SE (mean)	Wald	Adjusted OR	95% CI	p value
Age (years)	0.016	0.036	0.204	1.016	0.95–1.09	0.652
Years of schooling	0.084	0.111	0.575	1.088	0.87–1.35	0.448
Unmarried (single status)	0.393	0.845	0.216	1.481	0.28–7.7	0.642
Duration of treatment	0.054	0.039	1.917	1.055	0.97–1.14	0.166
Intensive phase of MDR-TB	0.836	0.792	1.115	2.307	0.49–10.8	0.291
ADR present	0.361	0.85	0.18	1.435	0.27–7.6	0.671
Per capita income	0.0	0.0	0.217	1.0	0.99–1.0	0.641
Constant	–4.57	2.06	4.88	0.01	–	0.027

*Omnibus test of model coefficients p=0.813 Hosmer–Lemeshow test p=0.185 Nagelkerke R^2 value 0.075 Classification accuracy 88.3% ADR adverse drug reaction MDR-TB multidrug-resistant tuberculosis CI confidence interval OR odds ratio SE standard error

Conclusions

The frequency of ADRs among patients with MDR-TB is high. Twenty-three patients reported ADRs in our study; tinnitus, headache, numbness, dizziness and nausea were the most common ones. ADRs often compel patients to think of discontinuing treatment and their regimen needs to be changed due to it. ADRs were the main reason for discontinuation of treatment of TB.

A close watch on the occurrence of ADRs and appropriate alteration in treatment of such patients with MDR-TB may allow for a higher compliance to treatment.

ACKNOWLEDGEMENTS

We would like to thank Dr Dixit Kapadia (State TB-HIV coordinator), Dr K.R. Solanki (DTO Bhavnagar), Dr Vikas Sinha (Dean, Government Medical College Bhavnagar), Mr Mahendra Solanki (District TB-HIV supervisor of Bhavnagar), TBHVs of Bhavnagar Corporation and taluka-level STSs of Bhavnagar rural for their guidance and all respondents for their support in the study.

This study was financially supported by The Tuberculosis Association of India, New Delhi.

Conflicts of interest. Nil

REFERENCES

1 Joseph P, Desai VB, Mohan NS, Fredrick JS, Ramachandran R, Raman B, *et al*. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. *Indian J Med Res* 2011;**133:**529–34.
2 Prasad R, Singh A, Srivastava R, Hosmane GB, Kushwaha RA, Jain A. Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis. *Indian J Tuberc* 2016;**63:**106–14.
3 Akshata JS, Chakrabarthy A, Swapna R, Buggi S, Somashekar M. Adverse drug reactions in management of multi drug resistant tuberculosis in tertiary chest institute. *J Tuberc Res* 2015;**3:**27–33.
4 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. *Int J Sci Rep* 2015;**1:**253–7.
5 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. *Mediterr J Hematol Infect Dis* 2014;**6:**e2014061.
6 Singh R, Gothi D, Joshi JM. Multidrug resistant tuberculosis: Role of previous treatment with second line therapy on treatment outcome. *Lung India* 2007;**24:** 54–7.
7 Isaakidis P, Cox HS, Varghese B, Montaldo C, Da Silva E, Mansoor H, *et al*. Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. *PLoS One* 2011; **6:**e28066.
8 Kapadia VK, Tripathi SB. Analysis of 63 patients of MDR TB on DOTS plus regimen: An LG hospital, TB Unit, Ahmedabad experience. *Gujarat Med J* 2013;**68:**52–7.
9 Bhatt G, Vyas S, Trivedil K. An epidemiological study of multi drug resistant tuberculosis cases registered under revised national tuberculosis control programme of Ahmedabad city. *Indian J Tuberc* 2012;**59:**18–27.
10 Singla R, Sarin R, Khalid UK, Mathuria K, Singla N, Jaiswal A, *et al*. Seven-year DOTS-plus pilot experience in India: Results, constraints and issues. *Int J Tuberc Lung Dis* 2009;**13:**976–81.
11 Bhushan B, Chander R, Kajal NC, Ranga V, Gupta A, Bharti H, *et al*. Profile of adverse drug reactions in drug resistant tuberculosis from Punjab. *Indian J Tuberc* 2014;**61:**318–24.
12 Patel SV, Nimavat KB, Patel AB, Shringarpure KS, Mehta KG, Shukla LK. Adverse drug reactions in patients put on multi drug resistant tuberculosis (MDR-TB) treatment in seven districts of central Gujarat. *J Young Pharm* 2015;**7:**425–31.
13 Padmapriyadarsini C, Narendran G, Swaminathan S. Diagnosis and treatment of tuberculosis in HIV co-infected patients. *Indian J Med Res* 2011;**134:**850–65.
14 Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J, Saranchuk P, *et al*. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *PLoS One* 2012;**7:**e40781.
15 Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas A, Kumar AM, Satyanarayana S, *et al.* Patient and provider reported reasons for lost to follow up in MDRTB treatment: A qualitative study from a drug resistant TB centre in India. *PLoS One* 2015;**10:**e0135802.
16. Rupani MD, Parikh KD, Pathak MM, Patel MR, Shah MA. Cross-sectional study on smokeless tobacco use, awareness and expenditure in an urban slum of Bhavnagar, western India. *Natl Med J India* 2019;**32:**137–40.