International Journal of Research in Medical Sciences
Lakhani P et al. Int J Res Med Sci. 2019 Mar;7(3):687-693
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20190918

Original Research Article

An observational study to analyze predisposing factors, causality, severity and preventability of adverse drug reactions among multidrug resistant tuberculosis patients treated under RNTCP program in Northern India

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Received: 18 December 2018
Accepted: 29 January 2019

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ABSTRACT

Background: There were 4.1% of all new cases and 19% of previously treated patients were diagnosed with either multidrug resistant or rifampicin resistant tuberculosis in 2016. In the state of Uttar Pradesh, there were 2.16 new cases and 44,531 previously treated cases. The objectives of the study were to assess the predisposing factors, causality assessment, severity grading and avoidability 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 for 12 months at a tertiary care hospital. The patients with MDR tuberculosis on treatment with DOTS Plus regimen under RNTCP and who met the inclusion exclusion criteria were recruited after informed consent. ADRs were monitored daily till the patients remained admitted and thereafter monthly. Predisposing factors were recorded. Causality assessment was performed by Naranjo scale and WHO UMC scale, severity by Hartwig's scale and avoidability by Halla's scale.
Results: There were 115 patients were recruited, 70 developed at least one ADR. 98 ADRs were reported. The commonest ADR reported were – gastrointestinal (38.76%), neurological (21.24%) and hepatobiliary (8.16%). Diabetes and HIV predisposed to development of ADRs. 58.18% ADRs were classified as possible and 37.5% as probable by Naranjo's scale. 51.02% ADRs were classified as probable and 42.83% as possible by WHO-UMC. 56% were classified as mild, 36% moderate, and 6% severe via Hartwig's scale. 51 ADRs were classified as avoidable and 40 ADRs were possibly avoidable.
Conclusions: Monitoring and assessment of ADRs is necessary to promote awareness, curb resistance and maintain adherence.

Keywords: ADR assessment, MDR-TB, Naranjo's scale, Tuberculosis, WHO-UMC scale

INTRODUCTION

MDR-TB is defined by WHO as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs. MDR-TB is primarily the result of incorrect treatment. This may be in form of fewer medications than the standard regimen, inadequate duration of treatment and inconsistent medication.

According to the world health organization in the year of 2016, 4.1% of all new cases and 19% of previously treated patients were found to have multidrug resistant or rifampicin resistant tuberculosis MDR/RR TB out of these 2,40,00 succumbed. A Further frightening situation is that nearly 6.2% of the cases with MDR-TB also have XDR-TB.[1]

In order to fight the growing menace of multidrug resistant tuberculosis in the country, India launched the DOTS-Plus Program in the year 2007.The DOTS-Plus program is a supplement to DOTS program that has additional components for MDR management and treatment. Directly observed therapy for patients with tuberculosis is a better alternative to self-administered treatment because it allows a close monitoring of the patient and emergent adverse events.[2]

The intensive phase of DOTS-Plus regimen contain Kanamycin (inj.), Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol, Cycloserine (total six drugs) that lasts for 6-9 months and continuation phase contain Levofloxacin, Ethionamide, Ethambutol, Cycloserine (total four drugs) that lasts for 18 months. Treatment of MDR-TB tends to be more complicated difficult, challenging and costlier than tuberculosis treatment in patients without resistance.[3]

Since MDR-TB needs long term treatment, occurrence of adverse events adds to the morbidity and mortality of the patients. Occurrence of adverse events may reduce the treatment adherence. Less treatment adherence is one of the important causes responsible for low success rate of therapeutic benefits. Treatment adherence is an important aspect to prevent the conversion from MDR to extensively drug-resistant TB (XDR TB).

Looking on the importance of ADRs in successful treatment it becomes important to conduct regular screening for early detection and management of ADR. Factors such as malnutrition and co-infection with HIV further predispose a patient to adverse drug events.

Due to the spread of MDR-TB globally, more and more genetically diverse population groups are being exposed to drugs used for treatment, thereby increasing the possibility of new or serious ADRs. Causality assessment is an important procedure to determine whether a particular drug has resulted in a particular ADR. Various algorithms are utilized including Naranjo's, WHO Uppsala Monitoring Center (WHO-UMC), Jone's algorithm, Yale algorithm and quantitative approach algorithm. Based on these tools, the score can be definite, probable, possible or doubtful. Naranjo's causality assessment is an assessment scale based on a battery of graded questions which take into account factors such as temporal association of drug administration and event occurrence, possibility of presence alternative causes, drug levels, dose response relationship in the form of dechallenge and rechallenge and previous patient relationship with the drug. The WHO-UMC tool is a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

Severity attributed to ADRs describes the everyday impact of the ADR on the patient's life. Seven levels of ADR were categorized by J Seigel and PJ Schneider, out of which ADRs belonging to Level 1 and 2 are classified as less severe, levels 3 and 4 as moderate and levels 5,6 and 7 as severe.

Avoidability scales can help predict the adverse effects and guide the physician to take appropriate steps in order to prevent them.

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 identifying predisposing factors, causality assessment, severity grading and avoidability of the adverse drug reactions (ADRs) of the antitubercular drugs in MDR-TB patients in a tertiary care hospital of northern India.

METHODS

The study undertaken was a prospective observational type conducted at a tertiary care hospital of northern India. It was conducted by department of pharmacology and therapeutics in collaboration with the department of respiratory medicine at King George's Medical University, Lucknow, Uttar Pradesh. The study was carried out after getting ethical clearance from institutional ethics committee. The patients with proven MDR tuberculosis were put on treatment with DOTS Plus regimen under RNTCP. Out of these only patients who gave consent and fulfilled the inclusion/exclusion criteria for the study were recruited.

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

The total duration of study was 12 months (May 2016 to April 2017). The patients were monitored throughout treatment period. Before the patients were started on DOTS-Plus regimen, they were submitted to pretreatment investigation such as, sputum smear, liver function tests, kidney function tests, thyroid function tests, blood sugar levels (fasting and postprandial), psychiatric screening, HIV seropositivity test and chest X-ray. Patients were allotted a unique patient identification number for ease of follow up. Initially, they were monitored daily for any adverse drug reactions till the patients remained admit in ward. Once discharged, patients were followed up on a monthly basis. During subsequent visits biochemical investigations were repeated. Any adverse effects encountered by patients were recorded. Patients with severe adverse drug reactions were referred to concerned clinical departments and followed up regularly. The patients were interviewed and data was captured onto the CDSCO Suspected Adverse drug reaction reporting form.

Causality assessment was done using Naranjo's causality assessment scale and WHO-UMC causality assessment system. Severity of ADRs was assessed using modified hartwig and siegel severity scale which classifies the ADR as mild, moderate and severe divided into 7 subclassification. Avoidability of ADRs was assessed by using hallas's avoidability scale which classifies the ADR as- definitely avoidable, possibly avoidable, not avoidable and unevaluable.

RESULTS

A total of 115 patients were enrolled during the 12-month study, during which 98 adverse drug reactions were encountered in 70 patients. The adverse drug reaction that were seen were - 38 (38.76%) cases of gastrointestinal adverse drug reactions (nausea and vomiting, epigastric pain, diarrhea and abdominal pain), 8 (8.16%) jaundice/hepatitis, 7 (7.14%) Impaired hearing/vertigo, 21 (21.24%) central nervous system adverse drug reaction (headache, seizures, psychosis, depression), 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. 76.19% of patients with comorbid diabetes developed ADR. 73.33% of patients with HIV developed ADR (Table 1, Table 2).

Table 1: MDT-TB and diabetes mellitus.

ADR	TB with DM	TM without DM	Total
Present	16 (76.17)	54(57.44)	70 (60.86)
Absent	5(23.80)	40(42.55)	45 (39.13)
Total	21(18.26)	94 (81.73)	115

χ^2=1.806; p value=0.179

Table 2: MDR-TB and HIV.

ADR	TB with HIV	TM without HIV	Total
Present	11(73.33)	59(59.00)	70(60.86)
Absent	4(26.66)	41(41.00)	45(39.13)
Total	15 (13.04)	100 (86.95)	115

χ2=0.604; p value=0.437

Table 3: Naranjo Scale.

ADRs	No. of ADRs (%)				Total (%)
	Definite	Probable	Possible	Doubtful	
Nausea and Vomitting	-	6(6.12)	7(7.14)	2(2.04)	15(15.30)
Epigastric Pain	-	4(4.08)	3(3.06)	1(1.02)	8(8.16)
Diarrhoea	-	6(6.12)	3(3.06)	-	9(9.18)
Abdominal Pain	-	4(4.08)	2(2.04)	-	6(6.12)
Jaundice/Hepatitis	-	3(3.06)	5(5.10)	-	8(8.16)
Impaired Hearing/Vertigo	-	3(3.06)	4(4.08)	-	7(7.14)
Headache	-	4(4.08)	8(8.16)	-	12(12.24)
Seizures	-	-	3(3.06)	-	3(3.06)
Psychosis	-	-	2(2.04)	-	2(2.04)
Depression	-	1(1.02)	3(3.06)	-	4(4.08)
Peripheral Neuropathy	-	1(1.02)	5(5.10)	-	6(6.12)
Rash and itching	-	2(2.04)	4(4.08)	-	6(6.12)
Arthralgia	-	2(2.04)	3(3.06)	-	5(5.10)
Renal Impairment	-	1(1.02)	2(2.04)	-	3(3.06)
Hypothyroidism	-	-	2(2.04)	-	2(2.04)
Blurred Vision	-	-	2(2.04)	-	2(2.04)
	-	37(37.75)	58(59.18)	3(3.06)	98(100.00)

Table 4: WHO-UMC Scale.

S. No	ADRs	Number of ADRs (%)						Total (%)
		Certain	Probable	Possible	Unlikely	Unclassified	Unclassifiable	
1	Nausea and Vomiting	-	5(5.10)	7(7.14)	2(2.04)	1(1.02)	-	15(15.30)
2	Epigastric pain	-	5(5.10)	2(2.04)	1(1.02)	-	-	8(8.16)
3	Diarrhoea	-	4(4.08)	3(3.06)	2(2.04)		-	9(9.18)
4	Abdominal pain	-	4(4.08)	1(1.02)	1(1.02)	-	-	6(6.12)
5	Jaundice/hepatitis	-	6(6.12)	2(2.04)	-	-	-	8(8.16)
6	Impaired hearing/vertigo	-	4(4.08)	3(3.06)	-	-	-	7(7.14)
7	Headache	-	6(6.12)	6(6.12)	-	-	-	12(12.24)
8	Seizures	-	2(2.04)	1(1.02)	-	-	-	3(3.06)
9	Psychosis	-	-	2(2.04)	-	-	-	2(2.04)
10	Depression	-	2(2.04)	2(2.04)	-	-	-	4(4.08)
11	Peripheral neuropathy	-	4(4.08)	2(2.04)	-	-	-	6(6.12)
12	Rash and itching	-	3(3.06)	3(3.06)	-	-	-	6(6.12)
13	Arthralgia	-	2(2.04)	3(3.06)	-	-	-	5(5.10)
14	Renal impairment	-	1(1.02)	2(2.04)	-	-	-	3(3.06)
15	Hypothyroidism	-	1(1.02)	1(1.02)	-	-	-	2(2.04)
16	Blurred vision	-	1(1.02)	1(1.02)	-	-	-	2(2.04)
Total		0	50(51.02)	41(41.83)	6(6.12)	1(1.02)	0	98(100.00)

Table 5: Comparison of Naranjo and WHO-UMC.

WHO-UMC causality criteria	Number of ADRs (%)	Naranjo algorithm	Number of ADRs (%)
Certain	0	Definite	0
Probable	50(51.02)	Probable	37(37.75)
Possible	41(41.83)	Possible	58(59.18)
Unlikely	6(6.13)	Doubtful	3(3.06)
Unclassified	1(1.02)		
Unclassifiable	0		
Total	98(100.00)		98(100.00)

- Number of observed agreements: 37 (18.88% of the observations)
- Number of agreements expected by chance: 43.5 (22.19% of the observations)
- Kappa = -0.043
- P value = 0.784
- SE of kappa = 0.023
- 95% confidence interval: From -0.087 to 0.002
- The strength of agreement is worse than what you expect to see by chance alone.
- Assessed this way, the strength of agreement is considered to be 'poor'

As per naranjo's algorithm 37.75% of the ADRs were categorized as "probable" with score ranging from 5-8, 58.18% of the ADRs were categorized as "possible" with score ranging from 1-4, 3.06% of the ADRs were categorized as "certain" (Table 3). As per WHO-UMC causality assessment scale 51.02% of the ADRs were categorized as "probable", 41.83% of the ADRs were categorized as "possible", 6.12% of the ADRs were categorized as "unlikely", 1.02% of the ADRs were categorized as "unclassified". No ADRs were categorised in "certain" and "unclassifiable" (Table 4).

The agreement between the two scales was the highest for "possible" category (92.7%) and no agreement at all for "certain" category. Overall disagreement in causality assessment was found in 45 cases (Table 5). There was ''poor'' agreement between naranjo and WHO-UMC.

Table 6: Hartwig's Scale: severity.

Severity of ADRs	No. of ADRs (%)
Mild	56(57.14)
Moderate	36(35.73)
Severe	6(6.12)
Total	98(100.00)

Table 7: Halla's avoidability assessment scale.

Avoidability of ADRs	No. of ADRs (%)
Definitely Avoidable	2(2.04)
Possibly Avoidable	40(40.8)
Not Avoidable	51(52.04)
Not Evaluable	5(5.10)
Total	98(100.00)

Using modified hartwig and siegel scale, which is a standard scale for severity assessment. It was observed that out of 98 ADR reports, 56 cases (57.14%) were mild,

36 cases (35.73%) were moderate and 6 cases (6.12%) were severe (Table 6).

Using hallas avoidability assessment scale, 51 ADRs were classified as 'not avoidable', 40 ADRs were 'possibly avoidable', 5 ADRs were 'not evaluable', and 2 were 'definitely avoidable' (Table 7).

DISCUSSION

Incidence of ADRs was more in patients with diabetes mellitus (76.19%) than in patients without diabetes mellitus (57.44%). Incidence of ADRs was more in patients with HIV (73.33%) than in patients without HIV (59.00%). Both HIV as well as diabetes could increase the risk of ADR due to overlapping toxicities from polypharmacy-related treatment. High risk of ADRs can also manifest because of poor clinical conditions and advanced disease at presentation. Although numerous studies are available which portray similar results, further research is required to understand the mechanisms related to an increased rate of ADR in MDR-TB patients with concomitant diabetes and HIV. 38 out of 98 (38.76%) ADRs were gastrointestinal ADRs. Nausea and vomiting were the most common complaints comprised of 13.04% of all ADRs, epigastric pain comprised 6.95%, diarrhea 7.82%, followed by abdominal pain 5.21%. They were mild but required immediate treatment. These were recorded within the first week of initiation of treatment. No alteration was required in the DOTS-Plus treatment. Quinolones and ethionamide have a probable causal relationship with gastrointestinal symptoms. Gastrointestinal ADRs can be avoided by administering these drugs one hour after one tablet of domperidone and proton pump inhibitor or H_2 inhibitor. Other ADR monitoring studies also showed gastrointestinal ADRs like Dela AI et al, (24.5%), Rathod KB et al, (33.96%), Verma et al, (51.11%) and Yang TW et al (18.4%).[4-7]

Hepatotoxicity is defined as 1.5 times rise in pretreatment alanine transaminase (ALT) levels. Jaundice or hepatitis comprised of 8.16% of all ADR. Pyrazinamide induced hepatotoxicity has a probable causal relationship. As per assessment, hepatotoxicity belonged to 'not avoidable' category with severity level 4. Incidence of hepatitis was comparable in other studies such as Yang TW et al, (3.9%), Dela AI et al, (2.04%), and in Waghmare MA et al, (2.8%).[4,7,8] In Verma et al, hepatotoxicity comprised of 33.33% of all ADRs.[6]

Oto-vestibular toxicity was observed in 6.08% patients. This can be attributed to kanamycin. Two patients had associated tinnitus. Ototoxicity was seen as early as 2 months and as late as 12 months.13.33% patients required withdrawal of kanamycin. Kanamycin was replaced with PAS (P-aminosalicylic acid). Vertigo has a definite causal relationship with kanamycin as all aminoglycosides are known to be vestibulotoxic with level 2 severity. Although kanamycin ototoxicity is well known, it is not avoidable, because of the lack of other drugs equally effective. Similar results were observed in study by Waghmare MA et al, (17%), Rathod KB et al, (5.66%) and Kapadia Vishakha K (4.76%).[5,8,9]

Central Nervous System (CNS) adverse drug reaction were second most common ADR observed in 18.26% patients similar to results observed in studies by Kapadia Vishakha K (35.2%), Rathod KB et al, (5.28%), Verma et al, (22.22%) and Jain et al, (25%).[5,6,9,10] Headache was observed in 10.43% patients, depression in 3.47% patients, seizures were seen in 2.60% patients and psychosis was seen in 2.04% patients. Psychiatric illness is a known adverse drug reaction of cycloserine.[11] All patients with CNS ADRs required withdrawal of cycloserine which was replaced with PAS. Psychiatric manifestations were seen as early as 7 days and late as 10 months. Occurrence of psychosis was an unpredictable adverse event and grouped as 'not avoidable' ADR with severity level 4.

Peripheral neuropathy was seen in 5.12% patients. Two patients required pyrazinamide withdrawal for this ADR. Peripheral neuropathy predominantly of sensory type developed over seven months of initiation of drug treatment. Ethionamide was found to have probable causal relationship. As ethionamide is structurally related to isoniazid, it interferes with the utilization of pyridoxine (vitamin B6) and its increased excretion in urine. Neuropathy was treated by additional 100 mg dose of pyridoxine without any alteration in MDR-TB treatment. Afterward, increasing the dose of pyridoxine from the beginning of therapy made this mild level 1 ADR avoidable. Similar studies where peripheral neuropathy was observed are Singh et al, (2.22%), Waghmare MA et al, (3.8%) and Rathod KB et al, (1.88%).[5,8,12]

Cutaneous reactions were seen in 5.21% patients. Pruritis without rash was seen in 5 patients and pruritis with rash was seen in 1 patient. All responded to anti allergic medication (cetrizine) and none required withdrawal of drug. Localised erythematous rash with severity level 1 occurred within seven days to two months of starting DOTS-Plus treatment. Pyrazinamide and quinolones had probable causal relationship. Incidence of rash due to pyrazinamide ranged from 0.1-28.88%% in other studies namely Rathod KB and Verma et al.[5,6] The most frequent adverse dermatological effects of pyrazinamide are burning sensation, hypersensitivity dermatitis and photoallergy. But in this study, we found mild erythematous rashes which did not require alteration in drug regimen. However, this ADR, being unpredictable, became not avoidable.

Arthralgia was observed in 4.34% patients. Arthralgia was seen in 3/5 (60.00%) patients as early as 1 month, 1/5 (20.00%) at 4 months, 1/5 (20.00%) at 6 months. None of the patients required withdrawal of drug. All patients responded to NSAIDS (non-steroidal anti-inflammatory drugs). Arthralgia with severity level 3 showed probable causal relationship with pyrazinamide

and quinolones. Mostly, weight bearing joints were affected within fifteen days of starting the treatment. Pyrazinamide produces arthralgia and arthritis by increasing serum uric acid levels. Being unpredictable, arthralgia was also not avoidable. Similar results were observed in studies by Verma et al, (4.44%), Kapadia Vishakha K (7.94) and Rathod KB et al, (4.15%).[5,6,9]

Renal involvement was seen in the form of borderline derangement of serum creatinine which improved in few weeks in 2.60% patients and none required withdrawal of injection kanamycin. Renal impairment with severity level 2 was detected by monthly renal function tests (serum urea and creatinine rise over 150 mg/dl and 90 mg/dl respectively) done for first three months of starting treatment. Non-oliguric or polyuric presentation was quite common. Kanamycin had probable causal relationship. Aminoglycosides firstly cause tubular cytotoxicity by apoptosis and necrosis of these cells; that is followed by reduced glomerular filtration, induced by vascular and mesangial contraction.[13] Renal function impairment were also seen in Kapadia Vishakha K (1.58%), Singh et al, (2.22%), Rathod KB et al, (1.13%), Verma et al, (4.44%) and Waghmare MA (0.9%).[5,6,8,9,12]

Hypothyroidism was seen in 1.73% patients at the end of the fourth month of initiating drug therapy. The offending drug for hypothyroidism having level 3 severity was ethionamide with probable causal relationship. Ethionamide, being similar in the structure to other thioamides, such as propylthiouracil and methimazole, could inhibit thyroid hormone synthesis through an analogue mechanism of inhibition of iodine organification.[14] As it was an unpredictable event in the course of a complete DOTS-Plus treatment, this ADR was categorized as not avoidable. Similar studies that reported hypothyroidism include Waghmare MA (6.6%) and Kapadia Vishakha K et al, (1.58%).[8,9]

Visual disturbance was found in two patients at the end of one month. It had definite causal relationship with ethambutol with severity level 2. As it was an unpredictable event in the course of a complete DOTS-Plus treatment, this ADR was categorized as 'not avoidable'. Visual disturbances were also reported by similar studies namely Kapadia Vishakha K et al, (3.17%) and Verma et al, (11.11%).[6,9]

In order to ascertain the success of any treatment regimen, it is necessary to ascertain all the factors associated with the disease and treatment. With the help of real-life accounts of patients, the physician can be in a better position to decide what is best for a particular patient and expect the worst. Adverse drug reactions stand to be a great de-motivator for the patients and may cause a decrease in the overall adherence to treatment. This gives rise to more resistance. Therefore, patients need to be properly treated for the ADRs as well as proper counselling should take place.

ACKNOWLEDGEMENTS

Authors would like to thank their chief guide Prof. Rakesh K. Dixit, whose valuable inputs and insights made this project possible. Authors would also like to extend their gratitude and heartfelt thanks to Prof. Surya Kant, Dr. Ajay Verma, Prof. Amod K. Sachan and Prof. Rajendra Nath for constantly guiding them. Lastly, they would like to thank their colleagues.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of K. G. M. U. Lucknow, India

REFERENCES

1. World Health Organization. Drug-resistant TB: Totally drug-resistant TB FAQ. Geneva: World Health Organization; 2016. Available at: http://www.who.int/tb/areas-of-work/drug-resistant-tb/totally-drug-resistant-tb-faq/en/ (Accessed 3 November 2018).
2. World Health Organization. Drug-resistant TB: global situation. Geneva: World Health Organization; 2016. Available at https://www.who.int/tb/areas-of-work/drug-resistant-tb/global-situation/en/ (Accessed 3 November 2018).
3. Guidelines for the programmatic management of drug-resistant tuberculosis- 2011 update. Geneva: World Health Organization; 2011:1-44. Available at: http://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf?sequence=1 (Accessed 15 November 2018).
4. Dela AI, Tank NKD, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: A four year retrospective study. Lung India. 2017;34(6):522-6. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5684809/ Accessed 15 November 2018
5. 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 Oct;1(6):253-7.
6. Verma R, Mahor GR, Shrivastava AK, Pathak P. Adverse drug reactions associated with first line anti-tubercular drugs in a tertiary care hospital of central India: a study of clinical presentations, causality, and severity. Asian J Pharm Clin Res. 2014;7(5):140-3.
7. Yang TW, Park HO, Jang HN, Yang JH, Kim SH, Moon SH, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis referral hospital in South Korea: A

retrospective study. Medicine (Baltimore). 2017;96(28):e7482. Available atL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5515762/ Accessed 15 November 2018

8. Waghmare MA, Utpat K, Joshi JM. Treatment outcomes of drug-resistant pulmonary tuberculosis under programmatic management of multidrug-resistant tuberculosis, at tertiary care center in Mumbai. Med J DY Patil Univ. 2017;10:41-5.
9. Kapadia VK, Tripathi SB. Adverse Drug Reactions and Outcome Analysis of MDR TB Patients on DOTS Plus Regimen. Ntl J Com-munity Med. 2015;7(1):5-9.
10. Jain K, Desai M, Solanki R, Dikshit RK. Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis. J Pharmacol Pharmacother. 2014;5(2):145-9. Available at: http://www.jpharmacol.com/article.asp?issn=0976-500X;year=2014;volume=5;issue=2;spage=145;epage=149;aulast=Jain Accessed 15 November 2018
11. Vega P, Sweetland A, Acha J. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004;8:749-58. PMid:15182146.
12. 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. Available at: http://www.lungindia.com/article.asp?issn=0970-2113;year=2007;volume=24;issue=2;spage=54;epage=57;aulast=Singh Accessed 18 November 2018
13. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011;79(1):33-45. Available at: https://www.kidney-international.org/article/S0085-2538(15)54676-0/fulltext. (Accessed 18 November 2018).
14. 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. Int J Tuberc Lung Dis. 2012;16(4):468-72. PMid:22326109.

Cite this article as: Lakhani P, Singh D, Barua S, Jain S, Kant S, Verma A, et al. An observational study to analyze predisposing factors, causality, severity and preventability of adverse drug reactions among multidrug resistant tuberculosis patients treated under RNTCP program in Northern India. Int J Res Med Sci 2019;7:687-93.