Original Research Article

To study the profile of multi-drug resistant tuberculosis (MDR) TB patients on shorter regimen at a tertiary care Centre of North India

Prashant Yadav, Aditya Kumar Gautam[1]*, Ashish Kumar Gupta[1], Adesh Kumar[1], Shashank Kumar Rai[1], Naresh Pal Singh[2]

[1]Dept. of Respiratory Medicine, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India
[2]Dept. of Community Medicine, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India

ARTICLE INFO

ABSTRACT

Background: The effectiveness of shorter regimen for the treatment of MDR-TB patients was found in the study done by Damien Foundation in Bangladesh, therefore we planned to study the profile MDR-TB patients who were taking shorter regimen so that various factors can be explored related to this regimen in Indian scenario.

Material and Methods: This was a prospective longitudinal study done in respiratory medicine department between January 2020 to December 2021. There were 177 patients of MDR/ RR pulmonary TB were identified and as per inclusion criteria and based on exclusion criteria 84 patients were excluded therefore our study population comprised of 93 remaining patients those who filled the study protocol, their treatment (Injectable shorter regimen) and follow up investigations done as per programmatic management of drug resistant TB guideline of National TB elimination programme.

Results and Observation: There were 55(59%) males and 38(41%) were females and mean age of patient was 31 ± 15.11 years (range 4-82 years). Out of 93 patients 27(29%) were smokers and 25(27%) were alcoholics and the most common symptom was fever 92(98.9%). The most common comorbidity was diabetes mellitus 11(11.9%). The most common minor side effect seen was GI intolerance in 41(44.1%) patients.

Conclusion: Out of 93 patients 76.3% (71) were cured and 23.7% (22) patients were failed to cure. The association between smoking and treatment outcome was statistically significant (p value=0.013). The association between treatment outcome and previous history of adequate treatment was found to be significant (p=0.016).

1. Introduction

In 2014, 480,000 people were developed multidrug resistant tuberculosis (MDR-TB) globally, Out of 26% (123,000 people) were notified only and 111000 (23%) were started on treatment. The treatment of drug sensitive TB can be done with current standards of care in an effective way but on the other hand outcome of MDR TB treatment is not good and approximately less than fifty percent patients of MDR TB patients have successful outcome only.[1]

The duration of management of MDRTB more than 20 months with 8 months intensive is recommended in newly diagnosed MDR TB patient by world health organisation, although these are conditional recommendations and needs further research.[2,3]

There are several factors for poor compliance of MDR TB regimen as many costly drugs which have potential adverse effect are being used for longer duration, therefore

successful outcome of MDR TB treatment is less. To overcome these issues research was done by Damien foundation over a period of 12 years in Bangladesh and they found effective 9 months regimen for management of MDR TB patients.[4,5] The further evaluation of This 9 months regimen of MDR TB is being conducted in west African regions and they found sputum culture conversion in 96% cases at the end of 4th month of treatment. A recent meta-analysis reported 54% treatment success rate among MDR TB patients.[6]

The effectiveness of shorter regimen for the treatment of MDR-TB patients was found in the study done by Damien Foundation in Bangladesh, therefore we planned to study the profile MDR-TB patients who were taking shorter regimen so that various factors can be explored related to this regimen in Indian scenario.

2. Materials Methods

2.1. Study design

Prospective, longitudinal study.

2.2. Study duration

January 2020 to December 2021.

2.3. Place of study

Respiratory medicine department of tertiary care centre.

2.4. Study subjects

All the MDR/ Rifampicin (RR) TB patients who attended OPD or admitted in IPD of Respiratory medicine fulfilled the inclusion criteria were recruited.

2.5. Inclusion criteria

1. Patients who provided consent to participate in the study
2. All MDR/RR Pulmonary TB patients who were kept on shorter regimen (injectable) and of >18 years of age.
3. Patients who were hemodynamically stable.

2.6. Exclusion criteria

1. Those MDR / RR pulmonary TB case who had additional drug resistance to levofloxacin / High dose moxifloxacin (Mfx^h), Kanamycin (Km) / Capreomycin (Cm) /Amikacin (Am) or inhA or Pyarazinamide.
2. Those MDR / RR TB Pulmonary TB patients who took second-line drugs as:-High dose moxifloxacin (Mfx^h), Kanamycin, Ethionamide, or Clofazimine (Cfz) of more than 1 month.
3. Central Nervous System TB or Disseminated TB
4. Intolerance to any drug in the shorter MDR TB regimen

5. Those patients having Pregnant and Extrapulmonary tuberculosis.
6. Those who did not give consent.
7. Age <18 years of age.
8. Lost to follow up
9. Death

2.7. Ethical consideration

The ethical committee of the University's gave clearance for the study and written informed consent was taken from each subject before their enrolment.

2.8. Methodology

There were 177 patients of MDR/ RR pulmonary TB were identified and as per inclusion criteria and based on exclusion criteria 84 patients were excluded therefore our study population comprised of 93 remaining patients those who filled the study protocol. Those who were excluded (84) patients among them 24 patients were died, 21 participant were did not come for follow up and in 39 patients treatment regimen were changed. Out of 39 treatment regimen changed in 10 patients due to ototoxicity, in 5 patients due to renal toxicity and in 11 patients there were additional resistant during course of treatment and 13 patients came to culture positive at 6 month. (Figure 1)
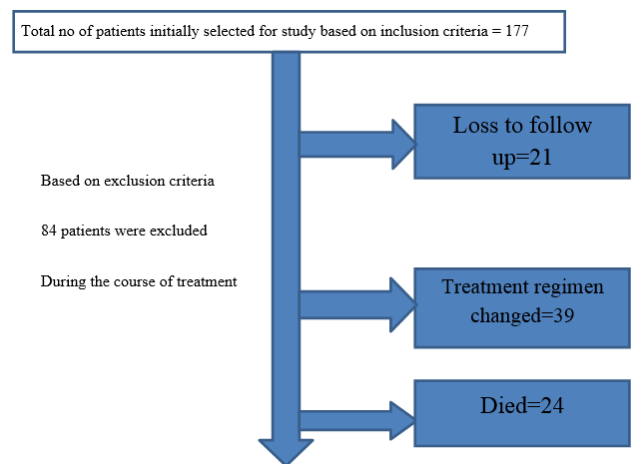
Figure 1:

Patient completed treatment and follow up (study population n) =93. (Figure 1)

Detailed history and physical examination , Height / weight, Complete blood count (CBC), Liver function test (LFT), Kidney function test (KFT) , Random blood sugar, Human immunodeficiency virus (HIV) testing, thyroid profile (TSH), chest x-ray, audiometery, psychiatric assessment, urine routine microscopy, urine pregnancy test(in reproductive age group females), ECG, and ophthalmological assessment were done. Treatment

Table 1: Shorter regimen (Injectable)

Regimen	Duration
Intensive Phase (4-6 month)	
Injection Kanamycin / High dose Moxifloxacin / Clofazimine / Ethionamide / Pyrazinamide /Ethambutol / High dose Isoniazid	**9-11 months**
Continuation Phase (5 month)	
High dose Moxifloxacin / Clofazimine/ Pyrazinamide/ Ethambutol	

Table 2: Drug Dosage & Weight Band

S.No.	Drugs	16-29 Kg	30-45kg	46-70kg	>70 kg
1.	Inj. Kanamycin	500 mg	750 mg	750 mg	1000mg
2	High Dose Moxifloxacin	400 mg	600 mg	800 mg	800 mg
3	Clofazimine	50 mg	100 mg	100 mg	200 mg
4	Pyarazinamide	750 mg	1250 mg	1750 mg	2000 mg
5	High Dose Isoniazid	300 mg	600 mg	600 mg	900 mg
6	Ethionamide	375 mg	500 mg	750 mg	1000 mg
7	Ethambutol	400 mg	800 mg	1200 mg	1600 mg

Regimen was started as per weight band.[7] (Tables 1 and 2).

In follow up visit weight was measured monthly in Intensive Phase (IP) and quarterly in continuation phase (CP). Serum creatinine was monitored monthly till second line injectable (SLI) completed. Audiometry was done as and whenever clinically indicated till SLI course completed. UPT, serum electrolyte, ECG and CBC / Platlets were done as and when clinically indicated. TSH and LFT were done at the end of IP, and as when indicated. Chest X-ray was done at end of IP, end of treatment and as when indicated.

Sputum smear examination was done at Monthly from 3rd month onwards till end of IP (Monthly in extended IP only if previous month Sputum smear positive). Sputum culture was done at end of IP, end of extended IP and end of treatment. First Line probe Assay (LPA) & Second Line LPA and Liquid Culture Drug Susceptibility Test (Moxifloxacin 1.0, Linezolid, Clofazimine & pyrazinamide) if smear /culture positive at end of IP, end of extended IP and end of treatment done as per programmatic management of drug resistant TB guideline of National TB elimination programme.[7]

All the collected data were entered in Microsoft Excel 2019 worksheet, SPSS software was utilised for statistical analysis. Chi-square test, Student t test and Z test were used to analyse the collected data. p value <0.05 was considered significant.

3. Results and Observation

The mean age of study participants was 31±15.11 years. Maximum patients 67 (72%) were in the age group of 18-45 years. There were 59.1% male and 40.9% were female. There were 57 (61.3%) of Above Poverty Line and 36 (30.1%) Below Poverty Line patients and 78.50% were literate and 21.5% were illiterate. There were 71% patients who had body mass index less than 18.5kg/m^2.

There were 27(29%) smoker and 25(27%) were alcoholic. The association between history of smoking and treatment outcome was significant i.e. (P=.013) and between alcohol and treatment outcome was not significant. (p=0.55) History of previous Antitubercular treatment were found in 61(65.5%) patients. Out of these, 40(65.5%) patients were adequately treated and rest 21(34.5%) were inadequately treated. Among patients who were adequately treated previously, 28 (70%) were cured and 12(30%) were failed to cure. While patients who were inadequately treated 8(38.1%) were cured and 13(61.9%) were failed to cure . Thirty two (34.4%) patients had no history of ATT intake out of which 26(81.3%) were cured and 6(18.7%) were failed to cure. The association between history of ATT intake and treatment outcome was not significant i.e. (P=.420) but the association between previous history of ATT intake as adequate and treatment outcome was significant (P=0.016). (Table 3)

The most common clinical symptom was fever (98.9%) and Cough (92.5%) and their association with treatment outcome was not significant. The most common chest X-ray finding was nodules (26.9%) followed by Cavity (20.4%) and consolidation (14%) and association between radiological findings and treatment outcome was not significant. (0.909)

The most common comorbidity among study participants was diabetes mellitus (10.75%), followed by COPD (7%) and Asthma (7%) and association of comorbidity and treatment outcome was not significant. (0.091) (Table 5)

At 3 month 12 (12.9%) patients had sputum smear examination positive and other 81(87.1%) patients had sputum smear examination negative. At 4 month 89 (95.7%) patients were sputum smear examination negative and 4(4.3%) patients remain sputum smear examination positive therefore in these 4(4.3%) patients intensive phase were extended for 1 month. At 5 month 92 (98.9%)

Table 3: Socio-demographic profile of the study Patients and their association with Treatment Outcome

S.No.	Variable	Sub-group	Frequency (%)	Treatment outcome		Chi square test p value
				Cured	Not cured	
1.	Gender	Male	55 (59.1%)	40(43)	15(16.1)	0.323
		Female	38 (40.9%)	31(33.3)	7(7.5)	
2.	Age groups	<18 years	9 (9.7%)	9(9.7)	0(0)	0.113
		18-45 years	67 (72%)	52(55.9)	15(16.1)	
		46-60 years	13 (14%)	8(8.6)	5(5.4)	
		>60 years	4 (4.3%)	2(2.2)	2(2.2)	
3.	Socio-economic status	Above poverty line (APL)	57 (61.3%)	43(46.2)	14(15.1)	0.796
		Below poverty line (BPL)	36 (38.7%)	28(30.1)	8(8.6)	
4.	Educational status	Illiterate	20 (21.5%)	13(14)	7(7.5)	0.178
		Litrate	73(78.5%)	58(62.4)	15(16.1)	
5.	Occupational status	Farmer	21(22.6%)	16(17.2)	5(5.4)	0.665
		Student	23(24.7%)	19(20.4)	4(4.3)	
		Labourer	11(11.8%)	7(7.5)	4(4.3)	
		Service	12(12.9%)	8(8.6)	4(4.3)	
		House wife	26(28%)	21(22.6)	5(5.4)	
6.	Body mass index (BMI)	<18.5kg/m^2	66(71%)	52(55.9)	14(15.1)	0.386
		18.5-24.9kg/m^2	27(29%)	19(20.4)	8(8.6)	
7.	Behavioural Factors	Smoker	27(29%)	16(17.2)	11(11.8)	**0.013**
		Nonsmoker	66(71%)	55(59.1)	11(11.8)	
		Alcoholics	25(27%)	18(19.4)	7(7.5)	0.55
8.	Previous history of ATT	Present (61) Adequately		28(70)	12(30)	**0.016**
		Inadequately		08(38)	13(62)	
		Absent (32)	—	26(81.3)	6(18.70)	0.42

Table 4: Comorbidity and their association with treatment outcome

S.No.	Variables	Sub group	Frequency (%)	Treatment outcome		Chi-square test (P value)
				Cured N (%)	Not cured N (%)	
1.	Comorbidity	Diabetes mellitus(DM)	8(8.6%)	4(4.3)	4(4.3)	0.091
		HIV	2(2.2%)	0(0)	2(2.2)	
		COPD	7(7.5%)	4(4.3)	3(3.2)	
		Asthma	7(7.5%)	6(6.5)	1(1.1)	
		Hypertension	5(5.4%)	3(3.2)	2(2.2)	
		CAD	2(2.2%)	2(2.2)	0(0)	
		Hepatitis B	1(1.1%)	1(1.1)	0(0)	
		COPD and DM	2(2.2%)	1(1.1)	1(1.1)	
		COPD and Hypertension	1(1.1%)	0(0)	1(1.1)	
		Asthma and DM	1(1.1%)	0(0)	1(1.1)	

patients were sputum smear examination negative only 1 (1.1%) patients remained sputum smear examination positive therefore intensive phase was extended for 1 more month. At 6 month all 93(100%) patients were sputum smear examination negative and all these 93(100%) patients completed their continuation phase treatment of 5months . At end of treatment 20(21.5%) patients were sputum smear examination positive and 73(78.5%) patients were sputum smear examination negative. (Table 5)

At 3 month 4(4.3%) patients were culture positive and 89 (95.7%) patients were culture negative. At 6 month all 93 patients were culture negative. At the end of treatment 22(23.6%) patients were culture positive and 71(76.3%) patients were culture negative. So in 22 (23.7%) patients culture reversion occurred despite taking complete course of treatment. (Table 6)

In our study of 93 patients, 81(87.1%) patients had one or more minor side effects, which were managed and in 12.9% Patients there were no side effects. The most common minor side effect seen was gastrointestinal intolerance in 41(44.1%) patients out of which 32(78%) were cured while 9 (22%) were failed to cure.

Eleven (11.8%) patients had skin rashes out of which 9(81.8%) were cured and 2(18.2%) were failed to cure. Fifteen (16.2%) patients had neurological side effect out of which 10 (66.6%) were cured and 5(33.4%) were failed to cure. Sixteen (17.2%) patients had psychiatric illness out of which 11(68.8%) were cured and 5(31.2%) were failed to cure. Eight (8.6%) patients had skin pigmentation out of which 5(62.5%) were cured and 3(37.5%) were failed to cure. (Figure 2) Those patient had ototoxicity and renal toxicity already excluded from our study.
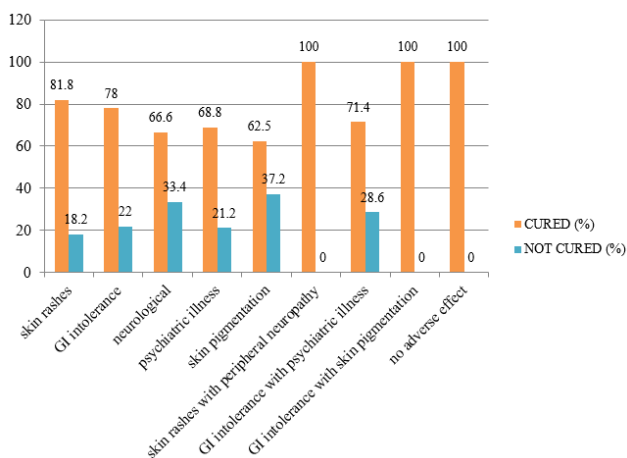
Figure 2: Clustered bar showing relation of treatment outcome with adverse drug reaction

In the present study, out of 93 patients, 56 (60%) patients completed their treatment in 272 days (9 month), 84 (90%) completed their treatment in 299 days (10 month), 89 (96%) completed their treatment in 331days (11 month) and 93 (100%) patients completed their treatment within 363 days (12 month). Treatment prolongation was due to extension of the intensive phage among patients with delayed sputum smear and culture conversion.

4. Discussion

In our study, the mean age of study population was 31±15.11 years with 59% males and 41% females. The association between treatment outcome and age group, gender were not significant (P=0.113, 0.323 respectively), similar observation reported by other previous studies.[8,9]

In the present study, 66(71%) patients had BMI <18.5kg/m^2 while 27(29%) had BMI 18.5-24.9kg/m^2. Mean BMI was 17.3±2.1 (range=12.8-22.6). The association between BMI and treatment outcome was not significant (p value=0.386), however Kuaban C et al. found 62(43%) patients had a BMI below 18.5 kg/m2, while rest 82 (57%) had BMI >18.5kg/m^2 in his study.[8]

In the present study, 25(26.9%) patients were alcoholics, 27(29%) patients were smokers. The association between treatment outcome and alcoholics was not significant (p value=0.5) while association between treatment outcome and smokers was significant (p value=0.013). However Singh et al. found 13(13.3%) patients were alcoholics and 4(4.1%) patients were diabetics in his study.[9]

In this study 10(10.8%) patients were diabetics, 10(10.8%) patients were COPD, 7(7.5%) patients were asthmatics and 2(2.2%) patients had HIV, The association between treatment outcome and comorbidity was not significant (p value=0.091). In this study Chest X-ray finding were unilateral in 2(2.2%) cases and bilateral in 25(97.8%) and the most common radiological finding was nodules in 25 (26.9%) cases .The association between treatment outcome and X-ray finding were not significant (p value=0.909). Singh et al. in their study found Unilateral in 5(5.1%) cases and Bilateral in 93(94.9%) cases, however he reported most common finding was consolidation 70(71.4%) in his study.[9]

In the present study, out of 93 patients, sputum microscopy conversion was 87.1% (n=81/93), 95.7% (n=89/93), 98.9% (n=92/93), 100% (n=93/93) at 3-month, 4-month, 5 month, and 6 month respectively. While culture conversion at 3 month was 95.7% (n=89/93). So sputum smear conversion and culture conversion rates of our study were in concordance with other studies.[8,9] Aung KJM et. reported culture conversion in 93% cases at 2 month of treatment while microscopy were also negative at 4 month in more than 90% patients.[10] Kuaban C et al. found culture conversion in 99.2% by the end of the third month.[8]

Singh et al. in their study found that sputum smear and culture conversion rates were 75/81 (92.5%) and 71/81 (87.7%), respectively.[9,11] In other previous studies also culture conversion rates were in between 74% to 92%.[11–14]

Table 5: Sputum smears status during course of treatment of study subjects: (N=93)

S.No.	Month	Smear Positive n (%)	Smear Negative n (%)
1.	3 month	12(12.9)	81(87.1)
2.	4 month	4(4.3)	89(95.7)
3.	5 month	1(1.1)	92(98.9)
4.	6 month	0(0)	93(100)
5.	At end of treatment	20(21.5)	73(78.5)

Table 6: Sputum culture status during course of treatment of study subjects: (N=93)

S.No.	Variables	Positive n (%)	Negative n (%)
1.	At 3 month	4(4.3)	89(95.7)
2.	At 6 month	0(0)	93(100)
3.	At end of treatment	22(23.6)	71(76.4)

In this study, out of 93 patients 76.3% were cured and 23.7% were failed treatment. Singh et al. reported 71(74.5%) successfully cured and 10(10.2%) failed, whereas 7 (7.1%) defaulted and 10(10.2%) died at the completion of treatment.[9] Kuaban C et al. in their study found that out of 150 patients 134(89%) successfully completed treatment, 10 died, 5 were lost to follow up.[8] Aung KJM et al. in their study found that 84.5% (n=435/515) had successful treatment outcome and 1.4% (n=7/515) patients failed treatment while 5.6% (n=29/515) patients died during treatment, 7.8% (n=40/515) patients defaulted treatment and 0.8% (n=4/515) relapsed.[10]

Failure rate is higher in our study than study done by Singh et al, Kuaban C et al and Aung KJM et al while cured rate of our study were slightly lower than these studies.[8–10] In our study the patients who died during treatment(21) and the patient who were lost to follow up (21) were excluded, otherwise our success rate would have been less than these study.

In the present study, out of 93 patients 81 had some minor side effects out of which most common side effect was GI intolerance which was seen in 44.1%(n=41/93) patients, The adverse reaction seen in our study were in concordance with study done by Singh et al and Anug KJM et al.[9,10] Those patients who had major side effects during treatment, their treatment regimen were changed and they were excluded.[15]

5. Conclusion

1. Mean age of study participants were 31±15.11 years (range 4-82 years) with 59% (55) males and 41% (38) females. The association between treatment outcome and age group, gender, were not significant (p value=0.113, 0.323, respectively).
2. Out of 93 patients 76.3% (71) patients were cured and 23.7% (22) patients were failed to cure. The association of treatment outcome with socioeconomic status of study participant, educational status of study participants, occupation, alcohol intake, symptoms, and chest x-ray finding were not statistically significant

(p value <0.05).
3. The association between smoking and treatment outcome was statistically significant (p value=0 013).
4. The association between treatment outcome and previous history of adequate treatment was significant (p=0 016).
5. The association between treatment outcome and side effects was not significant (P=0 501).

6. Source of Funding

None.

7. Conflict of Interest

None.

.

References

1. 1.World Health Organization. Global Tuberculosis Report 2015. Geneva, World Health Organization, 2015. 20th ed. World Health Organization. Available from: https://apps.who.int/iris/handle/10665/191102.
2. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 Update. Geneva, World Health Organization, 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501583.
3. Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J*. 2011;38(3):516–28.
4. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarkar MR, Daru P, et al. highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182(5):684–92.
5. Trébucq A, Schwoebel V, Kuaban C, Noeske J, Ciza F, Hassane S, et al. Expanding shortened MDR-TB treatment: the West African experience. *Int J Tuberc Lung Dis*. 2014;18(1):S15.
6. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Becerra MC, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012;9(8):1001300. doi:10.1371/journal.pmed.1001300.
7. Guideline for PMDT in India 2017 Central TB Division; https://tbcindia.gov.in.>index1>sublinked=4780.
8. Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Foe JA, Trebuck A, et al. High effectiveness of a 12-month regimen for MDR-TB patients

in Cameroon. *Int J Tuberc Lung Dis*. 2015;19(5):517–24.

9. Singh A, Prasad R, Kushwaha RA, Srivastava R, Giridhar BH, Balasubramanian V, et al. Treatment outcome of multidrugresistant tuberculosis with modified DOTSplus strategy: A 2 years' experience. *Lung India*. 2019;36(5):384–92.

10. Aung KJM, Van Deun A, Declercq E, Sarkar MR, Das PK, Hossain MA, et al. Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis*. 2014;18(10):1180–7.

11. Dhingra VK, Rajpal S, Mittal A, Hanif M. Outcome of multi-drug resistant tuberculosis cases treated by individualized regimens at a tertiary level clinic. *Indian J Tuberc*. 2008;55(1):15–21.

12. Arora VK, Sarin R, Singla R, Khalid UK, Mathuria K, Singla N, et al. DOTS-plus for patients with multidrug-resistant tuberculosis in India: early results after three years. *Indian J Chest Dis Allied Sci*. 2007;49:75–9.

13. Prasad R, Verma SK, Sahai S, Kumar S, Jain A. Efficacy and safety of kanamycin, ethionamide, PAS and cycloserine in multidrug-resistant pulmonary tuberculosis patients. *Indian J Chest Dis Allied Sci*. 2006;48(3):183–6.

14. Thomas A, Ramachandran R, Rehaman F, Jaggarajamma K, Santha T, Selvakumar N, et al. Management of multi drug resistance tuberculosis in the field: Tuberculosis research centre experience. *Indian J Tuberc*. 2007;54(3):117–24.

15. Brown MT, Bussell JK. Medication Adherence: WHO Cares? *Mayo Clin Proc*. 2011;86(4):304–14.

Author biography

Prashant Yadav, Assistant Professor

Aditya Kumar Gautam, Associate Professor

Ashish Kumar Gupta, Professor (Junior Grade)

Adesh Kumar, Professor

Shashank Kumar Rai, Junior Resident

Naresh Pal Singh, Professor