

Role of Fluoroquinolones in Sputum Culture Conversion in MDR-TB Patients

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Abstract

Background: Tuberculosis (TB) is an infectious disease caused by mycobacterium tuberculosis with a high incidence rate in India. In recent times, reducing the emergence of multi drug resistant TB (MDR-TB) poses a great challenge.

Aims and objectives: To study the 3rd & 6th month sputum culture status, after starting Category IV regimen and factors responsible for culture conversion of MDR-TB patients.

Material and Methods: We enrolled a total of 200 patients. Out of these, 3 patients were baseline XDR-TB, so excluded and 176 patients completed the study. All MDR/rifampicin resistant pulmonary TB patients >14 years of age receiving category IV regimen & willing to give consent for participation were included in the study. Patients with extrapulmonary TB were excluded. Majority of the patients (89.20%) patients remained negative at 3rd and 6th month.

Results: We found a significant association between delayed culture conversion and former smokers with >20 pack year smoking history compared to early converters with persistent culture negative at 6 months. At baseline, fluoroquinolone resistance was independently found to be significantly associated with adverse effect on culture conversion in the first 6 months. Also, there was significant association ($p = 0.02$) in patients showing culture positivity at 6th month following early negative cultures and current alcohol intake (within the last 6months) as well as with HIV positivity and cough > 2month. Female gender, conversion of sputum culture from positive to negative and radiological improvement was found to be positive predictors of a successful treatment outcome. While smoking habit and alcohol consumption was negative predictors of successful treatment outcome. Thirty five (26%) patients developed ADRs that required withdrawal of causal drug.

Conclusion: This study presented with the various factors associated with early and delayed culture conversion and culture reversion of MDR-TB patients.

Keywords: multidrug resistance tuberculosis, sputum culture

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Introduction

Tuberculosis (TB) is a global issue, particularly for the developing countries. In 2015 global incidence of TB was 10.4 million and in India it was 2.84 million. [1] In recent times, reducing the emergence of multi drug resistant TB (MDR-TB) poses a great challenge. Recently, in India the incidence of MDR-TB is about 2.84% (2.28-3.50 %) among new TB cases and 11.62% (10.21-13.15%) among previously treated TB patients. [2]

The regimen for MDR-TB is also known as category IV regimen under the national program in India, i.e., Programmatic Management of Drug Resistant TB (PMDT). [3] Similarly, category V is the name given to the regimen for Extensively Drug Resistant TB (XDR-TB). [3]

The MDR-TB patients are followed up by sputum culture for AFB monthly from 3rd to 7th month and then every 3 months interval from 9th month to end of treatment. [3] At the end of IP, if the latest culture result is positive, then extension of IP using Kanamycin. [2] IP can extend up to maximum of three months, then patient will be initiated on CP irrespective of culture result. [3]

If a patient remains culture positive at 6 months, adherence and dose of the patient is reviewed along with clinical and radiological response. Factors associated with failure/delayed sputum culture conversion are poor treatment adherence, irregular supply of drugs, modified treatment for adverse effect, malabsorption, ignorance, social barrier, co-morbidities, co-infections & drug resistance. The knowledge of various factors associated with MDR TB and culture status help in rational planning of follow-up investigations to identify early non-responders and patients most likely to benefit from the proposed shorter regimen for MDR-TB that had been proposed by WHO in May 2016. [4] The aim of the present study the status of 3rd and 6th month sputum culture of MDR-PTB

patients and the relationship between these two reports and with other factors associated with successful culture conversion.

Material and Methods

The prospective, observational, longitudinal study was conducted at the DR TB center of RBIPMT, Delhi and attached the KCC OPD along with laboratory support from New Delhi Tuberculosis Centre. All MDR-PTB/RR-TB patients who were registered at RBIPMT DR-TB centre and whose treatment duration was 3 months or less, patients with MDR/rifampicin resistant pulmonary TB patients >14 years of age receiving category IV regimen & willing to give consent for participation were included in the study. Patients with extrapulmonary TB were excluded. This study recruited a total of 200 patients during 1st April 2016 to 31st August 2016.

Various factors related to patients like, demographic profile, clinical examination, pre-treatment evaluation, BMI, CXR, addiction status, co-morbidities, sputum microbiology and treatment regimen status were recorded at baseline, 3rd and 6th month.

Results of 3rd and 6th month culture reports were obtained and patients divided into 4 groups. Group 1: 3rd month culture -ve, 6th month culture -ve; Group 2: 3rd month culture -ve, 6th month culture +ve; Group 3: 3rd month culture +ve, 6th month culture -ve; Group 4: 3rd month culture +ve, 6th month culture +ve.

Statistical analysis

Each group assessed for possible factors by relevant statistical tests. After the collection of the patient data, statistical analysis of the available data was done using Microsoft Excel software. Various distribution analysis was done regarding parameters like age, sex, BMI, addiction as well as

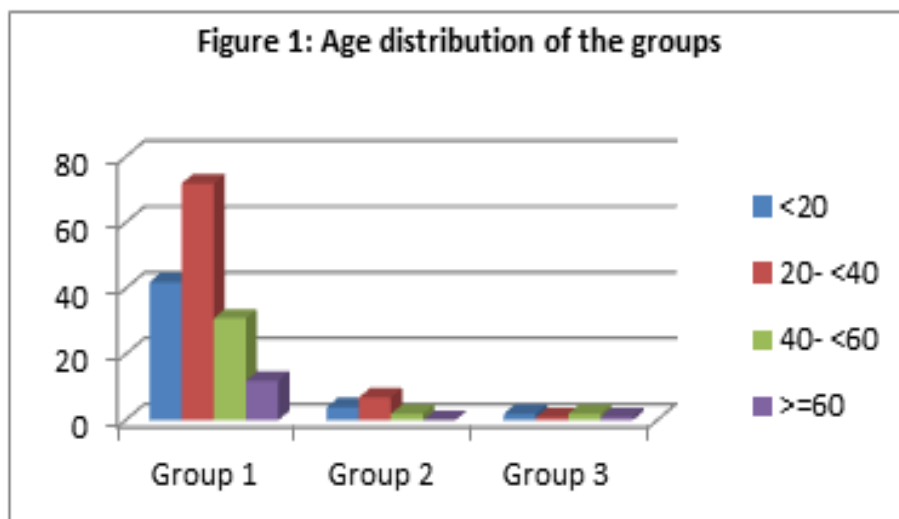
other demographic parameters. P value of <0.05 is considered as significant.

Results

A total of 200 patients were enrolled in the present study, out of which 3 had baseline XDR pattern so were excluded from the

final analysis. During the study, 12 patients were lost to follow up, 9 died in between so a total of 176 patients completed the study.

Group 1: 157 patients, Group 2: 13 patients, Group 3: 6 patients, Group 4: 0 patients



Out of 176 patients, 48 patients were in age group <20 years age, 80 patients were in 20-40 age, 35 patients in 40-60 age group and 30 patients > 60 years (figure 1). There was no significant difference between the

groups in respect of age at the start of treatment.

Various parameters, their prevalence in all groups as well as the significance of the intergroup differences are shown in table 1.

Table 1: Various parameters and their inter-relationship between the groups

Criteria		Group 1	Group 2	Group 3	*P value		
					1 vs 2	1 vs3	2 vs 3
Smoking	Never	125	11	5	0.66	0.82	0.94
	Quit>1yr ago,<20 pack yr	21	1	0	0.56	1	1
	Quit>1yr ago,>20 pack yr	1	0	1	1	0.0005	1
	Current smoker,<10 pack yr	7	0	0	1	1	1
	Current smoker,10-20 pack yr	0	1	0	0.18	1	1
	Total	157	13	6			
Alcohol intake	Never	134	11	6	0.94	1	1
	Quit 6 th month ago	22	1	0	0.52	1	1
	Current	1	1	0	0.02	1	1
	Total	157	13	6			
BMI	<18.5	113	11	3	0.32	0.24	0.11
	18.5-24.99	39	0	2	1	0.63	1
	>25	5	2	1	0.033	0.13	0.94
	Total	157	13	6			

HIV	Yes	1	1	0	0.023	1	1
	No	156	12	6			
	Total	157	13	6			
Albumin (mg/dl)	<3	1	2	0	0.0001	1	1
	3-5	135	9	6	0.11	1	1
	>5	21	2	0	0.84	1	1
	Total	157	13	6			
Cough	<2month	69	2	4	0.044	0.27	0.025
	>2month	88	11	4			
	Total	157	13	6			
Chest X-Ray Cavity	No cavity	130	7	3	0.01	0.04	0.87
	Cavity	27	6	3			
Chest X ray, Extent of lesions	Less extensive	125	7	4	0.03	0.44	0.6
	More extensive	32	6	2			
Sputum smear	negative	34	3	1	0.9	0.77	0.75
	Scanty, 1+ & 2+	109	6	4	0.08	0.89	0.40
	3+	14	4	1	0.013	0.51	0.51
	Total	157	13	6			
Base line DST	Ofx-s, km-s	134	6	4	0.0004	0.21	0.4
	Ofx-R, Km-s	23	7	2			
	Total	157	13	6			
Weight change	Loss or no gain	3	2	4	0.006	<0.0001	0.03
	<5kg	151	11	2	0.06	<0.0001	0.025
	>=5kg	3	0	0	1	1	1
	Total	157	13	6			
Side-effects	Vomiting	2	1	5	0.09	<0.0001	0.0009
	Ototoxicity	4	0	0	1	1	1
	Psychosis	2	0	0	1	1	1
	Liver toxicity	1	0	0	1	1	1
	None	148	12	1	0.77	<0.0001	0.0009
	Total	157	13	6			

There was significant association between delayed culture conversion and former smokers with >20 pack year smoking history compared to early converters with persistent culture negative at 6 months. It was also observed that there was significant association ($p = 0.02$) in patients showing culture positivity at 6th month following early negative cultures and current alcohol intake (within the last 6 months) as

compared to early culture conversion with persistent negative cultures. We found a significant association between culture positivity at 6th month following early negative culture and HIV positivity compared to early conversion with persistent negative cultures.

There was significant association between baseline albumin <3 gram/dl and culture positivity at 6th month following early

negative culture compared to early conversion and persistent negative culture. It was seen that cough >2 months was significantly associated with culture positivity at 6th month after early negative culture compared to early persistent or delayed conversion.

Presence of cavity on chest X-ray was significantly associated with delayed culture conversion and 6th month culture positivity after early negative culture; compared to early conversion with persistent culture negative. There was significant association between 6th month culture positivity after early negative culture; with sputum smear 3+ at diagnosis compared to early conversion with persistent culture negative. Baseline Ofloxacin resistance was significantly associated with culture positivity at 6th month after early negative cultures; compared to early conversion with persistent negative cultures. It is to be noted that there were no patients who had Kanamycin resistance with Ofloxacin sensitive pattern.

Weight loss or failure to gain weight in the first 3 months was significantly associated with delayed conversion and 6th month culture positivity after early negative culture; compared to early conversion with persistent negative culture. Weight gain in the first 3 months was significantly associated with early conversion with persistent negative culture and with delayed conversion as compared to conversion at 3 months followed by culture positivity at 6 months.

Presence of vomiting in first 3 months was significantly associated with delayed conversion compared to early conversion with persistent negative cultures; and culture positivity at 6th month with early negative cultures; and absence of vomiting.

Discussion

We observed in the present study that various combinations of predisposing and existing factors were significantly

associated with delayed conversion like, cough >2 month, chest pain, cavity on chest x-ray at baseline; sputum 3+ at baseline, cavity on chest x-ray and extensive lesion in chest x-ray at baseline; absence of weight gain during first 3 months and presence of Cough >2 months at baseline. Baseline factors independently associated with adverse culture outcomes included baseline Fluoroquinolone resistance, baseline low serum albumin and HIV positivity. Factors during follow up independently associated with adverse culture outcomes included presence of vomiting and replacement of cycloserine.

This study provided information about the type of MDR/RR TB patient who converts early and remains converted on 4th and 5th months cultures and thus the PMDT may consider omitting the 4th and 5th month follow up cultures in this subgroup of patients thereby reducing the laboratory load in view of the currently limited laboratory capacity.

In a systematic review and meta-analysis done by James c et al [5], studies on outcomes of DR-TB were included (31 treatment programmes from 21 countries). 62% patients had successful outcomes, but the rate of default was 13%, and there was a high death rate of 9%. Gender, DM, alcohol use, HIV co infection, BMI, smear positivity, cavitations, prior treatment, more than six drugs resistance, fluoroquinolone use and extensive drug resistant TB (XDR-TB) were related to treatment outcome. The following factors were associated with poor treatment outcome: male gender, alcohol abuse, low BMI, smear positivity, fluoroquinolone resistance, and X-DR resistant pattern. The following factors were statistically associated with successful outcome: surgical intervention, Fluoroquinolone use, no prior TB treatment[5].

In a study done by Gadallah MA et al, [6] half of the cases showed moderate or extensive lung lesions, and 15.8% were

diabetics. A total of 158 patients (69.3%) had successful outcome including 119 cured and 39 completing treatment. Predictors of unsuccessful outcome were: delay in sputum conversion (more than 2 months), moderate or extensive lung lesion, and diabetes mellitus. Bacteriological improvement as well as the infectious status of patients was found to be a significant predictor for treatment outcome. [6]

In a study done by Jain k et al [7], they observed that 39% MDR TB patients were cured while 5% completed successful treatment. Out of 89 patients with sputum culture conversion, majority (73%) turned negative within first 3 months. Female gender, conversion of sputum culture from positive to negative and radiological improvement was found to be positive predictors of a successful treatment outcome. [8] While smoking habit and alcohol consumption was negative predictors of successful treatment outcome. Thirty five (26%) patients developed ADRs that required withdrawal of causal drug. The most common ADR was joint pain due to pyrazinamide followed by neurological and psychiatric disturbances due to Cycloserine. [7]

Conclusion

This study presented with the various factors associated with MDR-TB treatment outcome as well as its positive as well as negative association with the culture status of the patients. This information should be taken in to consideration while individualizing the patient treatment case to case basis to optimize the maximum treatment outcome.

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