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Original Research Paper

Clinical, Bacteriological and Radiological Outcome of Patients With Multidrug Resistant Tuberculosis at the end of Intensive Phase of Standardized Regimen at Pmdt Site, Ajmer Rajasthan (India)

Medicine

KEYWORDS : Multi drug resistant tuberculosis, Intensive phase, Treatment outcome, Sputum culture conversion.

Kamendra Singh Pawar — Ex Resident Doctor, Dept. of Respiratory Medicine, Jawahar Lal Nehru Medical College & Associated Group of Hospitals, Ajmer, Rajasthan (India).

Ramakant Dixit — Professor, Dept. of Respiratory Medicine, Jawahar Lal Nehru Medical College & Associated Group of Hospitals, Ajmer, Rajasthan (India).

Neeraj Gupta — Professor, Dept. of Respiratory Medicine, Jawahar Lal Nehru Medical College & Associated Group of Hospitals, Ajmer, Rajasthan (India).

ABSTRACT

Objective: Aim of study was to determine the clinical, bacteriological and radiological outcome of patients with multidrug- resistant tuberculosis (MDR-TB) at the end of intensive phase (IP) of category IV regimen.

Methods: All the eligible patients with pulmonary MDR-TB that were admitted at Programmatic Management of Drug Resistant Tuberculosis (PMDT) site Ajmer (Rajasthan) during last one year were followed up at the end of IP of category IV regimen for sputum conversion, clinical response and radiological assessment. Clinical, bacteriological, radiological and demographic data were retrieved from master charts maintained at PMDT site.

Results: In 109 (84.4%) patients, culture conversion was seen, while 6 (4.6%) patients failed for culture conversion. In 14 (10.8%) culture conversion status was unknown. In most of patients (n=94, 72.8%) culture conversion occurred at 3 months while at 6 months, 109 (84.4%) were culture converted. Clinical (subjective) improvement was seen in 116 (89.9%) patients while no clinical improvement was seen in 13 (10.0%). Radiological improvement was seen in 81(62.7%) patients while no radiological improvement was noticed in 48(37.2%) patients. Both radiological (p value = 0.9597) and clinical (p value = 0.0595) variables were failed for positive correlation with culture conversion at end of IP.

Conclusion: Standardized ambulatory based treatment is highly effective in achieving earlier culture conversions. Both radiological and subjective clinical improvement are seen in majority of patients during IP but failed as a variable in predicting culture conversions at end of IP.

Introduction

Currently, multi drug resistant tuberculosis (MDR-TB) pose a major threat to public health all over world with around 9.9 % strains of Mycobacterium tuberculosis resistant to minimum of single drug in 35 countries or regions.[1] As per world health organization (WHO) estimation based on drug resistance surveillance data, 480,000 persons developed MDR –TB in 2014 and 190,000 lost their lives due to MDR- TB. More than fifty percent contributions to this numbers were from India, China and Russian federation.[2]

The estimated prevalence of drug resistance are around 3% among newly detected cases and around 12-17% in previously treated cases in India.[3] This relatively small odds translates into large number of patient with MDR- TB in country owing to effect of large population of India.[3]

WHO Global TB Report, 2015, says that annual incidence of 2.2 million Tuberculosis cases were estimated to have been occurred in India alone.[4] Indian Revised National Tuberculosis Control Programme (RNTCP) is the largest Directly Observed Treatment Short Course (DOTS) programme in world, and is functioning well as far as disease burden reduction is concerned, achieving objective targets of treatment success and case findings rates as per recent WHO estimates.[4] But whenever the treatment of MDR- TB under programme conditions is considered, the success rates are far below than expected. The cumulative outcomes of 14632/31365(47%) MDR- TB have been declared as cured while 6811(22%) and 6229 (20%) died and defaulted respectively in India till date.[4]

The bacteriological parameters in form of smear microscopy are used for diagnosis, monitoring progress of treatment, and as well for defining its various outcome at the end of treatment for drug susceptible tuberculosis. For the purpose of managing and monitoring treatment of patient with MDR-TB, mycobacterial cultures are primarily used for defining the outcome of treatment for MDR-TB.[5] Patients having been treated for MDR-TB previously, cavitations present on chest radiographs, and having a high colony count of M. tuberculosis on sputum culture suggesting high bacillary load at the start of treatment, drug resistance to greater number of drugs at baseline drug resistance profile, are among variable that were found to be associated with prolongation of sputum culture conversion time while receiving treatment for MDR- TB in study by Holtz et al.[6]

It is of paramount importance to monitor status of sputum culture for mycobacteria based on its both positive as well as negative predictive values during treatment that can help us in guessing its final outcome.[7]

MDR-TB patient while under treatment should be vigilantly monitored and followed up. Parameters namely clinical, microbiological and radiological should be repetitively assessed for monitoring treatment.[8] In India; there is limited data on ambulatory based standardized treatment. This study was planned for initial evaluation of outcome at the end of Intensive Phase (IP) of confirmed MDR- TB patients admitted to Programmatic Management of drug Resistant Tuberculosis (PMDT) site at Ajmer, Rajasthan, India.

Methods:

Objective was to determine the clinical, bacteriological and radiological outcome of patients with MDR-TB at the end of IP of category IV registered at our PMDT site.

Study Design: It was a hospital based analytical, cross sectional type of observational study. Approval from institutional ethical committee was obtained prior to the study. Informed consent of the patient was taken for the study.

Study Duration: All the patients that were admitted at PMDT site Ajmer during the period from 1st Jan. 2012 to

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31st Dec. 2012 were followed up after completion of IP of category IV regimen.

Study Population: All confirmed pulmonary MDR-TB patients admitted to PMDT site Ajmer during specified period were included in the study.

Inclusion criteria:
The patients with documented evidence of pulmonary MDR-TB under RNTCP criteria[3] and who were admitted at PMDT site during specified study period were included in study.

Exclusion criteria:
Those patients who were unwilling to come for follow up

Those patients that were not traceable or lost during follow up or died during IP.

Those patients who were registered at PMDT site Ajmer initially but subsequently transfer out to another reporting unit.

Those patients that were transfer in to PMDT site Ajmer during study period from another reporting unit.

Those patients who were registered at PMDT site Ajmer but not admitted to PMDT site for pretreatment evaluation.

Methodology
The follow up to evaluate outcome was done as per following protocol –

1. Baseline data with specific reference to previous history of anti-tuberculosis treatment, pattern of drug resistance, extent of disease, co-morbid states, socio economic status, smoking and alcohol history, body mass index and baseline hematological investigations and chest radiographs as per RNTCP guidelines were extracted from PMDT site master charts and clinical record sheets.

2. Sputum smear and culture examination were done as per follow up schedule under PMDT.[3]

Sputum specimens were collected and examined by smear and culture at least 30 days apart from the 3rd to 7th month of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) for follow up examinations. In case of extension of IP, the follow up culture months was shifted by every month of extension of IP.[3]

All the follow up culture were done at RNTCP accredited laboratory and performed on conventional solid egg-based Lowenstein-Jensen (LJ) media. Sputum smear for Mycobacterium tuberculosis was done using direct microscopy.

3. All eligible patients were followed up at the end of IP for sputum conversion, clinical response and radiological assessment and hematological investigations for organ dysfunctions.

4. Biochemical parameter during follow up visits as per guidelines[3].

All information to accomplish objective was collected by personal interview of study subjects at PMDT site using pre-designed Performa.

Subjective perception of improvement and no improvement was criteria for clinical outcome in the form of improvement and no improvement.

For bacteriological outcome, smear and culture reports as per follow up schedule under PMDT were reviewed from the Intermediate Reference laboratory, Ajmer and master cards maintained at PMDT site.

Culture and smear reports from 3rd to 7th month of treatment (i.e at the end of the months 3, 4, 5, 6 and 7) were reviewed. Culture conversion was defined as having two consecutive negative cultures taken at least one month apart and smear conversion as having two consecutive negative smears taken at least one month apart.[3] The time interval between the date of start of MDR-TB treatment and the date of first of these two consecutive negative cultures was defined as culture conversion time.[3] Sputum culture conversion and non conversion were taken as criteria for bacteriological outcome.

Chest radiograph posteroanterior (PA) view of every study subject was taken on follow up. The patients were classified as per radiological categories suggested by National Tuberculosis Association of United States of America (1961).[9] Radiological assessment was done by comparing baseline chest radiograph(PA) with follow up chest radiograph(PA) done at end of IP for extent of disease and whether there was regression or progression compared to baseline chest radiograph. Extent of disease, cavitory or noncavitory lesion, unilateral or bilateral involvement, other findings were specifically looked. On appearance of new lesion(s), investigation like hemogram, sputum for aerobic culture and sensitivity, KOH mount, cytology to rule out other pathologies like secondary infections, malignancy, fungal infections were done. Radiological regression was considered as regression of pulmonary lesion(s), decrease in size of cavities or improvement of grading seen on chest radiograph while progression was considered as increase in preexisting pulmonary lesions or appearance of new lesions. Stationary status was considered when having same radiological picture as at treatment initiation with no regression or progression of lesions. This were further segregated into radiological improvement (i.e. regression) and no radiological improvement (i.e. progression and stationary lesions).

Statistical Analysis:
Data collected were entered into Microsoft excel 2010 worksheet in the form of master chart. These were tabulated and analyzed to calculate means, modes, range, standard deviation etc. to represent nominal variables. The statistical software used was openEpi version 3.01. The relation between the bacteriological outcome and variables (clinical and radiological) that may influenced the bacteriological outcome was analyzed using the Mid-P exact test . The p value of less than 0.05 was considered to be statistical significant.

Results
A total of 295 patients were registered during one year. Out of 295 patients, 129 (43.7%) patients reported for follow up. All these 129 patients were cases of pulmonary MDR- TB and constituted final study population.

75.1% (n=97) were in the age group of 16-45 years. The overall male to female ratio was 3.96:1 and mean age was 38.5± 2.248 years (range 15-70). Majority of patients that attended follow up were male (n=103,79.8%) and females were 26 in number (20.1%). Sixty one patients (47.2%) were illiterate, 34.1% (n=44) patients were educated upto secondary level followed by primary level literacy (16.2%). Only 1.5% patients were graduate and 0.7% were postgraduates.

During follow up of 3rd to 7th month sputum culture reports, total 109 (84.4%) patients were reported as culture converted while 6 (4.6%) failed to do so. In 14 (10.8%) patients, the follow up sputum culture reports were either not available or status was unknown (table 1). The culture conversions rates at different months are provided in table 2.

116 (89.9%) patients has clinical improvement while 13 (10%) patients reported no clinical improvement (table 1).

Radiological regression was observed in 81 (62.7%) of patients. Radiological progression was noticed on chest radiographs of 19 (14.7%) patients and in 29 (22.4%) of patients, the lesions were stationary (table 1). Thus overall radiological improvement was seen in 81 (62.7%) and no radiological improvement in 48 (37.2%) patients.

Clinical and radiological variables which may affect bacteriological outcomes at end of IP were studied for any association. Clinical improvement at end of IP (two tailed P value 0.05954,) and radiological improvement at end of IP (two tailed P value 0.9597) failed for any positive relation with culture conversions at end of IP (table 3).

Discussion

In our study 109 (84.4%) patients were converted to negative culture during follow up period at the end of IP. In most of patients (n=94, 72.8%) culture conversion occurred at the end of 3 months while at 6 months, 109 (84.4%) were culture converted to negative. These data are similar to study conducted by Singla et al in which 100 (79%) patients achieved sputum culture conversion within 8 months.[10] 82% and 98% of those 100 patient became culture negative within 3 and 6 months of treatment respectively.[10] Joseph et al, also reported similar results with 84% (32/38) culture conversion rates at 3 months and 87% (33/38) at 6 months.[11] In a Nigerian study[12], 138 (85%) patient were culture negative at the end of intensive phase again similar to our findings. In study by Jain et al, 89 (68%) patient were culture converted within 9 months and among these patients, 73 (82%) and 84 (94%) patients achieved culture conversion within 3 and 6 months respectively.[13] In a South African study[14] 89% (40/45) patients were culture converted with in initial six months and median time for culture conversion was reported to be 62 days. In our study, since 72.8% of patient achieved culture conversion at the end of 3 months, gives insight that a standardized ambulatory based regimen is highly effective in earlier culture conversions and can rapidly control, transmission of disease in community.

Sputum culture conversion has been used as a very important tool for assessing treatment outcomes. Yew et al found that negative sputum culture at 3 months was predictive of eventual cure in 100% of patients.[15] In their study, the predictive value for failure of positive sputum culture at 3 months was 84.6% .Overall after 6 months, predictive value for failure and success of negative and positive sputum culture reached 100 % .[15] They concluded that during first 6 months, monthly close follow up of sputum culture for AFB adds in predicting final treatment outcome.[15]

Kurbatova et al[16], found that the 6-month Sputum culture conversion in comparison to without 6-month Sputum culture conversion were associated with higher proportion of successful treatment outcome at end of treatment. In their study, the sensitivity and specificity were found to be 91.8% and 57.8% , respectively for Sputum culture conversion by the end of 6 months of treatment for predicting success in comparison to death and failure and positive predictive value was found to be 76.5%.[16]

US Food and Drug Administration (FDA) reviewed various studies across the globe , most of studies showed a median time of 2 months for sputum culture conversion with varying conversion rates from 56%-95% and also found that higher relapse rates were associated with the lowest sputum culture conversion rates.[17] The FDA concluded that in MDR-TB patients "Sputum culture conversion can be used to predict the long-term clinical outcome of cure/ relapse with a reasonable degree of confidence".[17] So, sputum culture conversion during or at the end of intensive phase can help in getting what could be our final outcome of treatment and can help in taking appropriate measure, finding out what could be the possible cause with more vigilant and strict monitoring including adherence with possible earlier need to go for second line *drug-susceptibility testing* during intensive phase for non-conversion of sputum cultures.

In our study radiological improvement was noticed in 81(62.7%) patients while no radiological improvement was seen in 48 (37.2%) patients. In an Tanzanian study[18] , there was also overall significant improvement in chest radiographs at the end of 6 months. In study conducted by Dhingra et al[7], radiological improvement was noticed in 67% of cases. They conclude that radiological improvement was associated with favourable final outcome.[7] Although only 12 (44.4%) patients out of 27 were having radiological extensive disease in their study while in our study 106 (82.1%) had extensive disease at initiation of Category IV regimen. Also Jain et al reported radiological improvement in all patients with successful final treatment outcome and was statistically significant.[13] However we could not find any significant association between radiological improvement and culture conversion at end of IP(two tailed P value = 0.9597, Risk ratio 1.001).

In our study, subjective clinical improvement was seen in 116 (89.9%) of patients while no improvement was seen in 13 (10.0%) of patients. We could not find any study which directly correlates clinical subjective criteria for treatment outcomes or impact on culture conversion rates. However in our study 103 (88.7%) patients had culture conversion among group of clinical improvement (n=116) while with in group with no clinical improvement (n=13) only 6(46.1%) patients achieved culture conversion (Risk ratio 1.283, confidence limits 0.8588, 1.918) but this correlation was statistically insignificant (two tailed P value 0.05954). The interpersonal variability of perception of improvement or no improvement may vary considerably between subjects, thus further studies are warranted in interpretation of results.

Limitations

There are few limitations to our study. Firstly, we have reported only interim outcomes at end of intensive phase rather than final treatment outcome. Since available literature at the end of intensive phase is limited, we have no option other than to use studies with final outcomes for comparisons. However we still believe that these data will help in adding to literature particularly in Indian scenario from this vary part of country.

Table 1
Outcome at end of intensive phase

1.	Bacteriological Outcome	No.of Patients(n=129)	Percentage
a.	Culture converted	109	84.4%
b.	Culture not converted	6	4.6%

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c.	Data not available/Status Unknown	14	10.8%
2.	Clinical (subjective) Outcome		
a.	Improvement	116	89.9%
b.	No improvement	13	10.0%
3.	Radiological Outcome		
a.	Regression	81	62.7%
b.	Progression	19	14.7%
c.	Stationary	29	22.4%

Table 2 Culture conversion rates at 3rd,4th ,5th and 6th months during follow up period

Culture conversion month	3rd	4th	5th	6th
Cumulative number of patient and percentage	94(72.8%)	97(75.1%)	105(81.3%)	109(84.4%)

Table 3
Correlation between clinical and radiological variables with culture conversion (bacteriological outcome) at end of IP

	Culture conversion	Culture non conversion	2 tailed P value (Mid-P exact test)	Risk ratio (confidence limits: lower and upper)
Clinical Improvement(n=116)	103	4	0.05954	1.283 (0.8588, 1.918)
No Clinical Improvement (n=13)	6	2		
Radiological Improvement (n=81)	73	4	0.9597	1.001 (0.9133,1.096)
No Radiological Improvement (n=48)	36	2		

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