Assessment of Reasons and Pattern of Treatment Interruption during Intensive Phase of MDR-TB Treatment

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Abstract

Treatment interruptions are not uncommon during treatment of multidrug resistant tuberculosis (MDR-TB). Identification and management of factors contributing to treatment interruptions may leads to better treatment adherence and outcomes. Study was conducted with aim to assess overall causes of treatment interruption and to identify its pattern during intensive phase (IP) of standardized MDR TB regimen under programme conditions at Drug Resistant Tuberculosis Centre (DR-TB) Ajmer (Rajasthan) India. All eligible patients were followed at end of IP for exploring treatment interruption and its associated reasons. Data related to MDR-TB treatment were reviewed and extracted retrospectively from treatment cards and master cards maintained at DR-TB centre. Total 126 patients were followed at the end of intensive phase. There were 100 (79.3%) males and 26 (20.6%) females in study group. The mean age of cohort was 38.1 years. A total 31(24.6%) patients interrupted the treatment during intensive phase for variable periods. Most commonly, 13 patients (41.9%) interrupted the treatment for duration between 8-30 days, followed by 12 patients (38.7%) that missed the doses for duration of ≤ 7days. On assessment of overall cause of treatment interruption, the most common reason emerged was moving out of area (29%), followed by adverse drug reactions (19.3%). In conclusion, close supervision and training of DOT provider and management of adverse drug reactions are desirable for better treatment adherence and ultimately outcome.

Key words: MDR TB, Treatment interruption, outcome.

Introduction

Multi drug resistant tuberculosis (MDR TB) is a man made problem associated with poor treatment adherence, improper treatment apart from poor quality drugs contributing to its development [1].

MDR TB is defined **as** resistance to at-least rifampicin and isoniazid [1]. Global TB Report 2017, estimated 6,01,000 new cases of MDRTB/RR in world with contribution of estimated 147000 cases from India in 2016[2]. Recently, In India, rate of MDR among newly diagnosed and previously treated TB cases are reported 2.84% and 11.60% respectively[2].

MDR TB treatment is prolong and involves several drugs with many adverse effects. Default and treatment interruption are not uncommon during treatment and because of these factors, the completion of treatment becomes challenging in many patients [1]. In addition, certain patient, clinical and programme related factors also contribute to treatment interruptions in MDR TB patients [3-5]. Identifying and managing these contributing factors during the therapy can help patients

towards better adherence to therapy with subsequent fruitful outcomes.

This study was planned to assess overall causes of treatment interruption and to identify its pattern during Intensive Phase (IP) of standardized MDR TB regimen under programme conditions.

Material And Method

This was a hospital based cross sectional type of observational study after approval by institutional ethical committee. All confirmed Multidrug resistant pulmonary tuberculosis patients under Revised National Tuberculosis Control Programme (RNTCP) criteria [1] admitted at our DR-TB (Drug Resistant Tuberculosis) Centre in year 2012 were included in this study and were followed up at the end of IP for exploring treatment interruption and its associated reasons. Those patients who were unwilling to come for follow up, not traceable, lost, died during IP, defaulted from treatment and transferred out to other unit and with incomplete records were excluded. Also transferred in patients from other units were also excluded. Informed written consent was taken from every patient. Baseline socioeconomic, demographic and clinical information were collected through medical records maintained at DR TB centre. Data related to MDR-TB treatment were also reviewed and extracted retrospectively from treatment cards and master cards maintained at DR-TB centre. Treatment interruption was defined as missing treatment dose for at least 1 day but for period less than 2 consecutive months [1, 3]. Total number of missed days of treatment were divided in four groups i.e. (A) ≤ 7 days (B) 8-30 days (C) 31-60 days and (D) > 60 days.

Patients were followed up at the end of IP for assessing overall cause of treatment interruption that included both the patient as well as programme related factors. Causes of interruption were categorized in to: (A) Adverse drug reactions; (B) Number of pills; (C) Approach and availability of DOT provider; (D) defaulter habits; (E) Alcohol /Drug addiction and (F) Any other factors. Combinations of these factors if any were also analysed in subsequent category i.e. (G), (H) etc. All information to accomplish objectives was collected by personal interview of study subjects at DR-TB centre using pre-designed proforma and questionnaire.

Under programmatic conditions [1], drugs were given under direct observation as single daily dosage by a DOT (directly observed treatment) provider. Drugs were supervised on six days of week but on Sunday, the oral drugs were administered without supervision and the injection kanamycin was omitted [1]. The DOT provider visit to patients home on same day if patient fail to attend his DOT appointment so as to investigate why patient did not came for DOT and to work with the patient and the family to identify and solve any specific problem in this regard and ensure further continuation of the treatment [1].

Statistical Analysis

Data collected were entered in Microsoft excel 2010 worksheet in the form of master chart. Categorical variables were expressed in absolute numbers or percentages and continuous variables were expressed as mean±SD. The statistical analysis was performed using MaxStat Lite version (Version 3.60).

Results

Total 126 patients were followed at the end of intensive phase and thus constituted our final study population. There were 100 (79.3%) males and 26 (20.6%) females in this cohort. The mean age of cohort was 38.1 years. Mean pre-treatment BMI was 15.79 (with C.I. (95%) of mean ± 0.406).

95(75.3%) patients did not miss any dose during intensive phase as evident on treatment cards review and on

personal interview regarding any interruption of treatment during intensive phase. A total 31(24.6%) patients interrupted the treatment during intensive phase for variable periods on review of treatment cards. Most commonly, 13 patients (41.9%) interrupted the treatment for duration between 8-30 days, followed by 12 patients (38.7%) that missed the doses for duration of ≤ 7days. Only one patient (3.2%) interrupted the treatment for cumulative total of greater than 60 days (table 1).

On assessment of overall cause of treatment interruption, the most common reason emerged was moving out of area (29%), followed by adverse drug reactions (19.3%). In four patients (12.9%), shortage of drugs at public health institutions was the sole reason for treatment interruption. In three patients (9.6%), approach and availability of DOT provider was the reason behind the missing doses while in another 3 patients (9.6%); both approach and availability of DOT provider along with adverse drug reaction contributed towards the treatment interruption (table 2).

Table 1: **Total duration of treatment Interruption and its distribution**

S.No.	Total days of missed doses(interruption)	No.of patients(n=31)	Percentage
1	≤ 7 days	12	38.7%
2	8-30	13	41.9%
3	31-60	5	16.1%
4	>60	1	3.2%

Table 2:Reason for treatment Interruptions

Reason for Interruption	No.of patients (n=31)	Percentage
A. Adverse drug reactions.	6	19.3%
B. Number of pills	1	3.2%
C. Approach and availability of DOT provider.	3	9.6%
D. Habitual Defaulter.	0	0%
E. Alcohol /Drug addiction.	0	0%
F. Any other	16	51.6%
1.Moved out of area	9	29.0%
2.Long duration of Treatment	0	0%
3.Shortage of drugs at public health institution level	4	12.9%
4. Employed at work	2	6.4%
5.Forgot to go DOT centre	1	3.2%
G. Adverse drug reactions & Approach and availability of DOT provider.	3	9.6%
H. Approach and availability of DOT provider& Shortage of drugs at public health institution level	1	3.2%
I. Number of pills& Long duration of Treatment	1	3.2%

Discussion

Causes of MDR TB treatment interruption are many and complex in nature [3]. In our study a total of 31(24.6%) patients interrupted treatment during intensive phase. 12(38.7%) patients interrupted for period ≤ 7 days and 13(41.9%) patients for duration between 8 to 30 days.

In a study conducted at Philippines [3] studying pattern of treatment interruption, the median age of cohort having 583 MDR TB patients was 37.5 years with majority of patients being male (60.2%), and the data were similar to our study.

In their study, during initial 6 months, 70.8% (n=413) patient interrupted the treatment, however; they found no significant association between treatment interruption pattern during initial 6 months of MDR TB treatment with failure to convert to negative sputum culture at 6 months.

In another study conducted at China [4]; among MDR TB patient who have had at least 6 months of therapy, 68%(n=75/110) patients interrupted treatment with median of three interruptions and median duration of severe interruption was found to be 30 days.

Another study conducted in West Asia [5] investigating the effects of treatment interruption pattern on outcome of MDR TB patients, a total 393 patients were included and median age of cohort was 38 years with male predominance.

In their study, 323 (82.1%) patients interrupted treatment and median duration of interruption was 3 days for patient with successful outcome and 4 days in unsuccessful outcome group. On multivariate analysis, a pattern of long duration of interruption and short gaps between interruptions was associated with unsuccessful outcome [5].

Treatment interruptions may affect therapeutic drug levels that are desired to treat MDR TB [3]. Patients who miss ≥ 10 % doses of treatment during first 6 months of MDR TB treatment periods are at risk for sputum culture non conversion at 6 month follow up [3]. Also treatment adherence below 80% may be another strong predictor for unsuccessful outcome [5].

In our study, the main causes of treatment interruption were moving out of area (29%) and adverse drug reactions (19.3%). In a Chinese study [4], chief reasons of interruptions were adverse drug reactions (37%) and forgotten to take medicine (27%). In another study [5], treatment refusal and patient absence followed by side effects were main causes of interrupting the treatment. Moving out of area (n=9, 29%) was found as most common reason for interruption in our study.

Treatment of MDR TB is relatively prolong and complex [1]. Patient may travel outside the treatment area for vocational or social reasons and it may be difficult to hold them to defined region for longer period of time and this has emerged as one important reason for interruption of treatment.

Six (19.3%) patients pointed towards adverse drug reactions as the main reason for interrupting regimen. Adverse drug reactions are more common with second line drugs and prompt management of side effects are necessary for compliance towards MDR TB treatment [1]. Our study also highlights the side effects to second line anti TB drugs as an important reason for treatment interruption.

Shortage of drugs at public health institutions was the reasons in 4(12.9%) patients. Procurement of drugs must be in time and in advance as well its supply to Peripheral health facilities should be uninterrupted so that patient get his/her medication daily without any interruption.

Approach and availability of DOT provider was another reasons in 3 (9.6%) patients. Patients poorly adhere to treatment when their TB care provider are untrained and work unsupervised [6]. Bad attitude of DOT provider and unavailability of daily TB care in health institutions may be reasons for missing doses [6].

Numbers of pills was mentioned by 1(3.2%) patient as a cause for interruptions. Daily intake of such a large

number of drugs was found unsatisfactory by this patient leading to interruption of treatment.

In 2(6.45%) patients, employed at work with tight schedule was reason for treatment interruption as they could not leave their workplace to receive medicines under direct observation. Podewils *et al* [3] suggested that employment may lead to variable and longer MDR TB treatment interruption.Work place DOT may be an alternative strategy for employed patients [3].

While only 1(3.2%) patient missed doses due to forget to go DOT centre for drug intake, while 3(9.6%) patients reported combined adverse drug reactions and approach and availability of DOT provider as a reason for interruption.

Patient with history of alcohol addiction are more likely to miss doses during MDR TB treatment [3]. In none of the patients, alcohol/drug addictions and previous defaulter habits were reason for interruptions in our study.

About a quarter of patients interrupted treatment during intensive phase in our study. This highlights, the need of close supervision and training of DOT provider and management of adverse drug reactions for better treatment adherence and subsequent outcomes.

Our study has many limitations. The data on treatment interruptions in MDR TB were analysed in a small group and more so only during the intensive phase. We analysed and compared our results with other studies having treatment completion.

We assessed patient and programme related factors retrospectively and thus biased for recall problems. But despite these limitations our study explores important factors responsible for treatment interruption that needs to be addressed for better treatment outcomes in MDR TB.

Conclusion

Close supervision and training of DOT provider and management of adverse drug reactions are desirable for better treatment adherence and ultimately outcome.

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