Treatment Outcomes of Short Course Regimens for Multidrug-Resistant Tuberculosis patients in Peshawar

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Author Contributions

MAK SMN UU AJ conceived idea, MAK UU NU drafted the study, MAK SMN collected data, MAK SMN AA FJ did statistical analysis and interpretation of data, MAK AA FJ UU AJ critical review manuscript, All approved final version to be published.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Abstract

Background: Tuberculosis (TB) still remain a global public health problem. TB is deadly disease caused by a bacterium named Mycobacterium tuberculosis (MTB). Now a day TB is resurgence in the form of drug resistant TB (DR-TB). In order to improve adherence to anti-TB treatment, the World Health Organization (WHO) promotes the use of directly observed therapy (DOT), in which patients undertake medications under the direct observation of a health care provider.

Objectives: The present study was conducted with the aim to find out treatment outcome of 11 months STR treatment for MDR-TB patients at PMDT-LRH.

Results: This study was conducted from July 2017 to March 2020. In this study only those patients were enrolled who were eligible for newly assigned 11 months short treatment of MDR-TB. All those patients who were achieved final outcomes at time of this final draft were included in this study. The numbers of such patients were 109. Mean age of study cases was 19.544 with standard deviation ±15.947. Majority of study cases (56.0%) were females. For study purpose, study cases were divided into four different groups, of which most of the cases belonged to the age group form 45 years to 64 years of age. About 77.1% of these cases achieved successful treatment outcome and remaining 22.9% of study cases achieved unsuccessful treatment outcome.

Conclusion: The findings of the current study have several clear implications for TB control efforts. In light of these findings, it could be concluded that to reduce DR-TB transmission in the community, improvement of treatment outcomes, via ensuring adherence, paying special attention to poor and patient having very far residency form the treatment site. Treatment adherence made better by offering a short, highly effective treatment regimen for MDR-TB because of the main challenge in achieving the successful treatment outcome is the large number of pills that patients must ingest every day. This study also concluded that with the experience and dedicated team it is very easy to achieve best success rate for any type of treatment.

Keywords: TB; MDR-TB; Treatment Adherence; STR; Peshawar; Pakistan

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Introduction

Tuberculosis (TB) still remain a global public health problem. TB is deadly disease caused by a bacterium named Mycobacterium tuberculosis (MTB). Through continuous efforts TB is somewhat control in few areas of the country but still remain exist in many countries of the world. Now a day TB is resurgence in the form of drug resistant TB (DR-TB). The most terrible form of DR-TB is Multidrug-resistant tuberculosis (MDR-TB). MDR-TB is defined as form of TB resistant to at least two most powerful drugs named rifampicin (RMP) and isoniazid (INH).[1] It is an emerging public health crisis now a day. Treatment of DR-TB is somewhat difficult as compared to DS-TB. However, despite all the possible measures to fight against TB, its global burden remains alarming.

According to the World Health Organization (WHO), around 480,000 people develop MDR-TB and 190,000 people die from the disease each year.[2] Currently recommended (conventional) regimens for MDR-TB treatment are complex, long (at least 20 months), expensive, and poorly tolerated and have a modest global treatment success rate of 52%.[3-6] In order to improve adherence to anti-TB treatment, the World Health Organization (WHO) promotes the use of directly observed therapy (DOT), in which patients undertake medications under the direct observation of a health care provider. However, DOT is difficult and costly to implement in resource-scarce settings where health infrastructure is poor and access to health care is limited. The prolonged duration of conventional regimens of MDR-TB makes the implementation of DOT even more challenging. Strategies aimed at reducing the duration of MDR-TB treatment and the frequency of dosing administration while improving efficacy and safety profiles are therefore desirable.[6,7]

The choice of an effective, efficient and appropriate treatment regimen is challenging, as the most commonly proposed regimens are lengthy, complex, poorly tolerated, expensive and of only moderate effectiveness. To resolve this issue WHO and other partners tried to initiate different types of treatment for MDR-TB. One of the most promising treatment type is short treatment regimen also known as Bangladesh regimen which declared high success rate compared to conventional type of treatment. Following this short treatment, different countries also started projects of STR in their respected countries to achieve better treatment outcome. Now a day in most of the countries different types of STR type treatment have been started with different types of drugs.

Pakistan is one of the top listed countries ranking fourth among the top 22 MDR-TB countries. Based on 4.2% primary resistance and 19% resistance in re-treatment cases, the WHO has an estimated annual incidence of approximately 15000 MDR-TB cases in Pakistan.[2] The increasing rate of MDR and XDR-TB in Pakistan underscores the importance of effective treatment programs of DR-TB. There is an urgent need for extensive research to elaborate efficient diagnosis, treatment, and control of MDR-TB as poor implementation of treatment protocols leads to further resistance, which emerge in the form of XDR-TB. Understanding the risk factors responsible for poor treatment outcomes among MDR-TB, patients is necessary to improve the treatment outcomes. So here in this country, STR treatment of MDR-TB is also initiated in the year 2017. National Tuberculosis Programme (NTP) of Pakistan initiated STR for MDR-TB in different hospitals of the country. In Khyber Pakhtunkhwa, STR was first initiated at Programmatic Management of drug resistant TB (PMDT) unit, Lady Reading Hospital Peshawar. LRH is one of the oldest and best ever centre for treatment of MDR-TB. Initially here in this centre, STR treatment with 4-6/11 months of duration was initiate. To know about the efficacy of this treatment, this study was conducted with the objective to know the treatment outcome of 4-6/11 months STR treatment at this unit.

Methodology

Study design: This was a retrospective cohort institutional base study conducted at PMDT – LRH included patients with bacteriologically confirmed MDR-TB. Duration of study was from December 2017 to March 2020. All study cases must follow the inclusion and exclusion criteria of study. Here in this centre all treatment was provided free of charge. Treatment at the present centre following the guidelines of WHO and NTP Pakistan. Patients received counseling to maximize adherence, nutritional support, and transportation reimbursement for their ambulatory visits.

Treatment Scheme: Study patients were to receive a

Table 1. Gender wise distribution of study cases

Gender	Frequency	Percentage (%)
Male	48	44.0
Female	61	56.0
Total	109	100.0

Table 2. Age distribution of study cases

Age Group (Years)	Frequency	Percentage (%)
15 - 24	07	6.4
25 - 44	23	21.1
45 - 64	79	72.5
Total	109	100.0

11-months treatment regimen, with all drugs given daily throughout. An intensive phase of a minimum duration of 4-6 months with Amikacin (AM) 10–15 mg/kg, Moxifloxacin 400 mg, Ethionamide (ETH) 15–20 mg/kg, Clofazimine 100 mg, INH (High dose) 5 mg/kg, EMB 25 mg/kg and Pyrazinamide 30–40 mg/kg was followed by a fixed-duration continuation phase of 5 months with the same drugs, but omitting INH and AM and Eto 4-6 Am, Z, E, Mfx, Eto, Cfz, INH (High Dose) / 5 Z, E, Mfx, Cfz. The continuation phase was started if two consecutive sputum smears of early morning specimens at the end of the fourth month were negative. If either specimen was positive, the intensive phase was prolonged up to a maximum of 2 months, guided by the monthly sputum smear examination result.

Sputum smear, culture, and chest radiographs (CXR) were obtained at the time of enrollment, and then monthly during the intensive phase of treatment, whereas the continuation phase was accompanied by monthly smear and bimonthly culture and chest radiograph. Patients' compliance and medication adherence was closely monitored by trained treatment supporters and directly observed therapy facilitators. All patients were psychologically assessed, and personalized counseling was provided on monthly follow up visits.

Data management and analysis: All required data were double-entered and through this process first entered into Microsoft excel sheet and then transferred into SPSS version 23 for further analysis. Percentage and cross tabulation was used for analysis purposes. Final outcomes were divided into two main heading i.e. successful treatment outcome and unsuccessful treatment outcome (Died, Loss to follow up and failure).

Results

This study was conducted from July 2017 to Dec 2018. In this study only those patients were enrolled who were eligible for newly assigned 11 months short treatment of MDR-TB. All those patients who were achieved final outcomes at time of this final draft were included in this study. The numbers of such patients were 109. Mean age of study cases was 19.544 with standard deviation ±15.947. Majority of study cases (56.0%) were females (Table 1). For study purpose, study cases were divided into four different groups, of which most of the cases belonged to the age group form 45 years to 64 years of age (Table 2).

Body Mass index (BMI) is also one of the important indicator in the treatment of MDR-TB. Here in this study all study cases were divided into two groups i.e. one group consists of all those individuals whom BMI was lower than 25 Kg/m^2 and the other group consists of all those individuals whom BMI is equal or more than 25Kg/m^2. Among the study cases most of the cases were with BMI lower than 25Kg/m^2 (Table 3).

Table 3. Distribution of study cases on the basis of their body mass index (BMI)

Body Mass Index (Kg/m^2)	Frequency	Percentage (%)
< 25	89	81.7
≥ 25	20	18.3
	109	100.0

Table 4. Cross tabulation of body mass index vs gender

	BMI (Kg/m^2)		
Gender	<25 Kg/m^2 (%)	≥25 Kg/m^2 (%)	Total
Female	50 (45.8)	11 (10.1)	61
Male	39 (35.8)	9 (8.3)	48
Total	89 (81.6)	20 (18.4)	109

Table 5. Cross tabulation of body mass index vs age groups

	BMI		
Age Group	<25 Kg/m^2 (%)	≥25 Kg/m^2 (%)	Total
15 - 24	07 (6.4)	00 (0.0)	07 (6.4)
25 - 44	21 (19.3)	02 (1.8)	22 (21.1)
45 - 64	61 (55.9)	18 (16.6)	79 (72.5)
Total	89 (81.6)	20 (18.4)	109 (100.0)

In this study cross tabulation of BMI with age and gender was also studied and results were presented in table 4 and 5. Table 4 showed that majority of study cases belonged to BMI lower than 25Kg/m^2, of which 45.8% were in female gender. Similarly cases with BMI more than 25Kg/m^2 were also more in female as compared to male gender. Similarly cases in both BMIs groups were from higher age group having age of 45 to 64 years of age (Table 5).

Previously treatment and its outcome along with resistance pattern also play important role in newly design short treatment courses. Among the present study, 63 (%) of study cases took previously TB treatment with first line anti TB drugs (FLDs). Among these cases 55.5% patients achieved successful treatment outcomes (Table 6 & 7).

Table 6. Distribution of study cases according to their previously TB treatment

Registration Group	Frequency	Percentage (%)
New	46	42.2
Previously Treated after Failure	20	18.3
Previously treated after Relapse	09	08.3
Other Previously Treated	34	31.2
Total	109	100.0

Table 7. Outcomes of Previously TB treatment of study cases (n=63)

Treatment Outcomes	Frequency	Percent
Complete	02	3.2
Cured	33	52.3
Failed	26	41.3
Loss to Follow up	02	3.2
Total	63	100.0

All study cases enrolled for treatment here in PMDT LRH were completed full course of their treatment with newly design short treatment courses. At the time of study these patients achieved final outcome and about 77.1% of these cases achieved successful treatment outcome and remaining 22.9% of study cases achieved unsuccessful treatment outcome.

Table 8. Final Treatment Outcomes of study cases

Treatment Outcomes	Frequency	Percent
Cured	84	77.1
Failed	01	0.9
Died	15	13.8
Lost to Follow up	09	8.3
Total	109	100.0

Discussion

For all health authorities, DR-TB is a serious public health concern. Accurate diagnosis and effective treatment of DR-TB is essential to face this problem. Effective management of DR-TB is important not only for cure of the effected population, but most importantly to prevent further transmission of resistant strains. For treatment of MDR-TB, the routine longer treatment of MDR-TB is not satisfactory outcome so need some other type of treatment. So in order to improve the adherence and successful outcomes of MDR-TB patients, WHO has recently recommended a new shorter treatment regimen which was initiated in Bangladesh and also known as Bangladesh regimen. Time duration of this new STR treatment comprised of 4–6 months intensive phase followed by 5 months of continuation phase of treatment. Programmatic Management of Drug Resistant TB Unit, Lady Reading hospital Peshawar initiated treatment for DR-TB patients from the year 2008 and followed treatment role of PMDTs in the year 2012. PMDT LRH is one of the best treatment site of the country. Treatment outcomes of the enrolled

patients at present site are not bad but still need improvement. So for better result newly STR treatment was also initiated in the year 2017. For finding the outcomes of this first cohort patients starting their treatment in the year 2017 this study was conducted. The present study is the first ever study from this area covering first cohort of patients enrolled for newly short treatment at PMDT LRH Peshawar Pakistan. This study was designed to know the final outcomes of this first cohort at PMDT LRH.

The demographic profile of patients in the present study was similar to some other studies conducted by Turett et al, Khan et al and Park et al.[1,8,9] Majority of the study cases were of female gender patients in the economically productive age group.

Among study cases, 84 (77.1%) patients achieved successful outcome, which is close to the target set by the Global Plan to stop TB. This percentage is somewhat lower than the achievement of the study from Bangladesh (85.0%), 89.0% from Cameron and 89.0% from a study conducted in Niger.[10-12] On the other side this result is comparatively better compared with longer WHO-recommended regimens studies such as 49% in a study conducted in south Africa, 54.9% from a study conducted in Shanghai, 64% in New York, and 48.2% in South Korean report.[13-16]

One of the most important treatment indicator of MDR-TB is treatment failure (TF) which was 0.9% in the present study which is much less than internationally reported pooled rates of 11% (10-12%) for the longer MDR-TB regimen excluding XDR-TB.[17]

If we compared the results of the present study with another study conducted in the year 2015 in the same PMDT unit. Study cases of the previous study were on longer treatment regimens (LTR) whereas study cases of the present study was on newly short treatment. Base line treatment regimen for previous study consists of 8 Am, Cs, Eto, Lfx, Z, PAS/16 Cs, Eto, Lfx, Z, PAS+B6 whereas the present study with STR treatment consists of 4-6 Am, Z, E, Mfx, Eto, Cfz, INH (High Dose) / 5 Z, E, Mfx, Cfz. First basic difference between two types of treatment was duration of treatment and other difference was choice of drugs. LTR consists of Cycloserine, Levofloxacin and PAS which were absent in STR whereas in STR for this drugs Ethambutol, Isoniazid, Cfz and Moxifloxacine were added. In both types of treatment, injectables Amikacin, PZA, Ethionamide were present. Interesting findings were concluded from both this studies. Rate of successful outcome in LTR treatment in the year 2015 was 74.3% of study cases where this rate in the present study with STR treatment was 77.1%. Treatment failure with LTR was 5.6% whereas with STR treatment it was 0.9%. Death rate in LTR treatment was 19% whereas this rate within STR was 13.8%. Loss to follow up (LTFU) in LTR treatment was 1.1% which was 8.3% in STR treatment. If we look at these results STR is looking better than LTR and if the LTFU rate in STR remain lower as in the LTR treatment then the achievement of successful outcome reach upto 90% which is very promising and best result and comparable with the fining of other international level studies. Total of 9 (8.3%) of the patients during this treatment was declared as LTFU. Among these 9 patients 2 patients are Afghan nationality and due to change of their addresses they were declared as LTFU. Among these 4 patients were from very far areas and they were unable to pay for their routine visits from their village to PMDT unit at Peshawar. One more patient also change his residence from Khyber Pakhtunkhwa to Islamabad area and according to that patient he took treatment form Islamabad but due to unavailability of his record he declared as LTFU. Two patients in this LTFU lists face severe side effects after initiation of these drugs so there treatment stop for more then 2 months and hence declared them as LTFU. If we are able to resolve such issues like adverse drugs reactions, enhance and regular social support and facilitate poor patients then it is very easy to achieve success rate of more than 80%. In both types of treatments, successful outcomes of the present PMDT unit is better than many centers of the country as well as other country. There are different possible reasons for this achievement present. Whole treatment for each patient in the PMDT LRH is under programmatic management system. Here in this center patients were facilitated through ambulatory care treatment. Every patient visited PMDT unit along his/her treatment supporter for routine checkup and drugs for one month. Sputum smear, culture, and chest radiographs (CXR) were obtained at the time of enrollment, and then monthly during the intensive phase of treatment, whereas the continuation phase was accompanied by monthly smear and bimonthly culture and chest radiograph. All patients were tested at baseline for HIV, and blood investigations were performed at baseline, and at every month as per national DR-TB guidelines. Patients' compliance and medication adherence was closely monitored by trained treatment supporters and directly observed therapy facilitators. All patients were psychologically assessed, and personalized counseling was provided on monthly follow up visits. Home visits were arranged for individual patient for contact screening, infection control measures at home and to create a liaison with the regional district TB officer. Adverse events if any, associated with second line drugs were monitored and managed promptly, utilizing multiple approaches of counselling, administering ancillary

drugs and in rare cases, permanent removal of any culprit drug from the treatment regimen as a last resort. Patients received counseling to maximize adherence with treatment. World health organization recently made some changes with this STR treatment and has announced changes in treatment regimens for drug resistant tuberculosis. According to this new announcement STR treatment regimens now consists of all oral, bedaquiline-containing regimens in place of the injectable-containing standardised shorter regimen.[18] In the primary analysis on which the WHO guidelines decision was based, treatment success rates for the all-oral bedaquiline containing regimen was 73% versus 60% in the standardised shorter regimen.[19] This new change in the regimen will help patients and free them the most terrible part of DR-TB regimen which was injectable drugs. Besides treatment regimen programmatic implementation of shorter regimens requires close attention to the management of side effects, and infrastructure to support patient adherence. As already discussed this is the first ever study conducted with the aims to find out outcomes of newly STR treatment, hence this study is of great importance having a number of strengths. One of the most important strength of this study was that this study was performed under PMDT therefore reflects accurate consequences and its results are likely to be generalizable to programs in other similar settings of the country. Secondly, there was careful attention to monitoring and starting treatment to all patients on the basis of their baseline DST results to rule out any possible wrong selection of drugs. Finally, the study has been able to provide important findings for newly STR treatment and its impact on treatment of MDR-TB.

Conclusion

The findings of the current study have several clear implications for TB control efforts. In light of these findings, it could be concluded that to reduce DR-TB transmission in the community, improvement of treatment outcomes, via ensuring adherence, paying special attention to poor and patient having very far residency from the treatment site. Treatment adherence made better by offering a short, highly effective treatment regimen for MDR-TB because of the main challenge in achieving the successful treatment outcome is the large number of pills that patients must ingest every day. This study also concluded that with the experience and dedicated team it is very easy to achieve best success rate for any type of treatment.

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