Original Article

Prospective study on outcome of MDR-TB using the shorter regimen during COVID-19 pandemic

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Abstract

Background: According to Indian TB report 2020, 66,225 MDR/RR-TB cases were detected in India, 56,569 (85%) were put on treatment, and 40,397 (75%) were initiated on shorter drug regimens at the time of diagnosis. In the absence of an effective vaccine, there is an urgent need for new treatment regimens, drugs, and diagnostics to slow the evolution of drug resistance and limit transmission of resistant variants, as well as to ameliorate the treatment outcome of patients infected with MDR/XDR M. tuberculosis strains. **Aim:** To evaluate the efficacy of a shorter drug regimen in MDR-PTB and estimate the adverse effects of drugs used in the regimen. **Methods:** This is an institution-based prospective study which included 135 confirmed MDR-PTB patients. Patients with extra-pulmonary MDR-TB and use of SLI for more than one month were excluded. **Results:** The success rate using a shorter regimen was 65.2% which is respectable, given the COVID-19 pandemic considered during the study period. Minor adverse events such as nausea (39.3%) and vomiting (34.8%) were reported. Rare adverse effects such as hearing loss (8.9%) and hypothyroidism (0.2%) were also seen in the study population. **Conclusion:** Overall treatment success was similar when compared to other studies done previously. A shorter drug regimen was associated with minor adverse effects such as gastrointestinal adverse effects such as vomiting and hearing loss observed in elderly patients. Baseline unknown drug resistance and lower BMI were associated with unsuccessful outcomes. Measures should be taken to improve nutrition. Our results argue the need for improving baseline DST at peripheral areas in order to effectively evaluate resistance to other drugs, especially in settings with high levels of first and second-line drug resistance.

Keywords: COVID-19, multidrug-resistant tuberculosis, second line injectables, shorter regimen, success rate, World Health Organization

Introduction

Tuberculosis is one of the most detrimental diseases known to mankind. In 1993, the World Health Organization (WHO) issued a press release announcing that tuberculosis (TB) was a global emergency, making it the first infectious disease to be declared as such. Although progress has been made, no country has eliminated TB and there are three million missed TB diagnosis each year.[1] A total of 1.5 million people died from TB in 2020 (including 214,000 people with HIV).[2]

Multidrug-resistant TB (MDR TB) is defined as when a patient's biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs.[3] A global total of 206,030 people with MDR/RR-TB were detected and notified in 2019, a 10% increase from 2018. Globally, only about one in three people with DR-TB accessed treatment in 2020. The Theme of World TB Day 2022—"Invest to End TB. Save Lives"—conveys

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Received: 29-08-2022 **Revised:** 08-12-2022
Accepted: 12-01-2023 **Published:** 30-06-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1723_22

How to cite this article: Kumar GS, Sameena P, Karthik V, Ghanate N. Prospective study on outcome of MDR-TB using the shorter regimen during COVID-19 pandemic. J Family Med Prim Care 2023;12:1087-91.

the urgent need to invest resources to ramp up the fight against TB and achieve the commitments to end TB made by global leaders.[4] Elimination of TB by 2035 will only be possible if countries address the emergence of drug-resistant (DR) strains of Mycobacterium tuberculosis effectively.[5] This is especially critical in the context of the COVID-19 pandemic that has put End TB progress at risk. Thus, there is a need for a regimen that is shorter, yet effective is essential.

Since 2016, WHO guidelines have included options for treating MDR/RR-TB with a standard regimen of 9 to 11 months duration (the "shorter regimen") rather than a longer individual regimen of at least 20 months.[6] Treatment of MDR-TB using shorter regimens in different studies ranges from 43 to 77.1%.[7-9] Given this varied range of success rates, our study aimed to identify the success rate and factors associated with the outcome of shorter regimens in MDR-TB patients in India which is one of the highest burdened countries with TB.

Methods

Ethical approval

This study was approved by the Institutional Ethical Committee of Osmania Medical College, Telangana, in September 2019.

Material and Methods

This is a prospective observational study that was conducted on 135 patients with confirmed MDR-PTB visiting (outpatient and inpatient) the Department of Pulmonary Medicine, Government General and Chest Hospital, Hyderabad. Patients with rifampicin-resistant pulmonary TB cases without or with resistance to isoniazid were included. Patients with resistance to FQ or SLI, Z, presence of InhA mutation were excluded. Pregnancy, any extrapulmonary disease in PLHIV, disseminated, meningeal, or central nervous system TB were other exclusion criteria. Pre-treatment evaluation clinical evaluation by a physician included history and physical examination, height/weight, chest X-ray, HIV testing, complete blood count, RFT, LFT, TFT, ECG, UPT, ophthalmological opinion, and audiometry as shown in Tables 1 and 2. The patients were selected after obtaining prior informed and written consent. They were treated with the following regimen (4–6) months of the intensive phase of Mfxh Km/Am Eto Cfz Z Hh E, and (5) months of Mfxh Cfz Z E was given. Sputum for smear and cultures was sent every month after three months of treatment. After completion of the treatment, patients were assigned outcomes, such as cured, treatment completed, treatment failure, lost to follow-up, expired, and any adverse events experienced during the treatment were noted.

Data analysis

Microsoft Excel and SPSS were used for statistical analysis. Discrete variables were presented such as frequency and percentages. Discrete variables were presented as frequency and percentages. A value of $P < 0.05$ was considered statistically significant.

Results

There were 135 patients in the present study. There were 64 (47.4%) females, with slightly higher male patients (52.6%). The mean age among the study population was 37.7 years. The mean age among females and males is 34.5 years, 40.6 years, respectively. There were 56 (41%) patients in the 18–30 years age group, showing there was a greater incidence of MDR-TB among the young population. There was significantly higher urban population of 108 (80%), and 27 (20%) patients from rural areas. The mean BMI was 19.8 kg/m^2. Thirty-eight (28.1%) patients had BMI less than 18. Ninety-seven (71.8%) patients had normal BMI.

Seventy-one (52.6%) patients were diagnosed with primary MDR-TB. Past history of tuberculosis was observed in 64 patients (47.4%). Out of which 54 patients had one episode of TB, ten patients had more than one episode of TB. Twenty-five patients (39%) completed their six months of ATT. Twenty-one (15.6%) patients had contact with DR-TB patients. Cavities in the radiograph were seen in 50 (37%) patients. Anemia was present in 64 (42.2%) patients. Diabetes mellitus was seen in 23 (17%) patients, and smoking was seen in 30 patients. Twenty-three patients were alcoholics.

The treatment outcomes were observed as follows; eighty-five patients (63%) were declared cured as shown in [Table 3]. Cured rates observed among males and females were (48.3% and 52.3%), respectively. Three patients (2.2%) completed treatment. Thirteen patients (9.6%) were changed to other regimen as two patients experienced adverse effects and could not continue the regimen and 11 patients showed resistance to either FQ/SLI as LPA reports were obtained later. Seven patients (5%) were lost to follow-up. Three patients (2.2%) were considered treatment failures. Twenty-four patients (17.8%) had expired during the study period. There were 14 male patients, and 10 females among those who expired.

Figure 1 shows that nausea was the most common adverse effect seen in 53 patients (39.3%) followed by vomiting which was seen in 48 patients (34.8%). Twelve patients (8.9%) had hearing loss. Rash was seen in eight patients (5.9%). Vertigo was

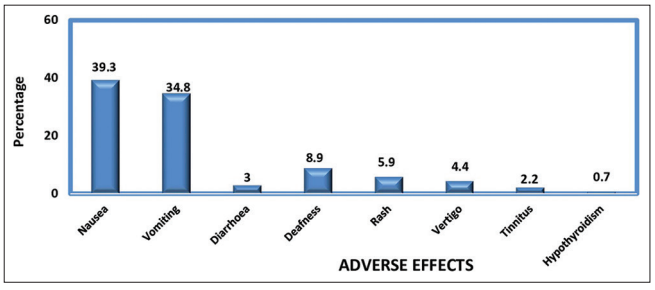

Figure 1: Showing adverse effects experienced during the shorter MDR-TB regimen

Table 1: Baseline parameters of pre-treatment evaluation

Pre-treatment biochemical investigations	Mean value
Hb	10.1±1.5
Platlets	3.73±1.5
RBS (mg/dl)	132±20
S.Bilirubin (mg/dl)	0.62±0.21
S.Creatinine (mg/dl)	0.81±0.27
PTA (db)	26.33±8
TSH	2.23±0.25
QT-interval msec	394±24

Table 2: Mean values of biochemical investigations

Variable	Number/percentage
Age	
18-30 years	56 (41%)
31-40 years	38 (28%)
>40 years	41 (30%)
Females	64 (47.4%)
Males	71 (52.6%)
Urban	108 (80%)
Rural	27 (20%)
BMI <18	38 (28.1%)
BMI >18	97 (71.8%)
Anemia	67 (42.2%)
Radiographic presentation	
Cavitary disease	50 (37%)
Non-cavitary disease	85 (63%)
New MDR-TB	71
Previous PTB	64
Completed treatment	25 (39%)
Cured	19 (30%)
Lost to follow-up	20 (31%)
1 episode	54 (40%)
>1 episode	10 (7.4%)
Other factors	
DM	23 (17%)
Smokers	30 (22%)
Alcoholism	23 (17%)

reported by six patients (4.4%). Tinnitus was reported in three patients (2.2%). One patient had reported hypothyroidism as an adverse event.

Discussion

Treatment for people with rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) is longer, and requires drugs that are more expensive and more toxic.

The mean age in this study was 37.7 years, which is similar to most of the studies conducted 79 by Aung *et al.*,[10] Kuaban *et al.*,[11] Piubello *et al.*,[12] and Trebucq *et al.*[13] There were a total of 135 patients in the present study, i.e., 52.6% were males and 47.4% were females which is similar to the study conducted by Nunn *et al.*[14] In the present study, the percentage of patients with BMI <18 was 28.1% which is similar to the study conducted by Trébucq *et al.*[13]

Sixty-four patients (47.4%) had a past history of PTB. Moreover, there were 71 patients (52.6%) who presented with MDR-PTB without any history previously, the increased incidence of primary drug-resistant tuberculosis could be attributed due to increased incidence of drug-resistant tuberculosis and also the easy availability of use of genotypic methods to find out drug-resistant strains of mycobacterium tuberculosis which is incorporated into the treatment and operative guidelines for the treatment of TB. Chest radiographs revealed the presence of cavities in 37% of the patients, which is similar to the study conducted by Piubello *et al.*[12] There were 23 (17%) patients who had diabetes mellitus as a risk factor which was similar to the study conducted by Soeroto *et al.*[8]

Eighty-five (63.2%) patients were declared cured in the present study. This was higher than the study conducted by Philipp du Cros *et al.*[6] and Soeroto *et al.*[8] Treatment was completed in two patients (2.2%). Treatment failure was seen in 02 (2.2%) patients, which was less than the study conducted by Das *et al.*[7] The lost to follow-up was 5.2% similar to the study conducted by Trébucq *et al.*,[13] where 4.8% of the patients were lost to follow-up.

Mortality rate in the present study was (n = 24) 17.8%, less than the study conducted by Soeroto *et al.*[8] The mean age among this group was 41 years. Eighteen out of 24 patients had a previous history of Tuberculosis. The mean BMI of these patients was 17.8 kg/m^2 which was slightly lower than normal. Fifteen patients had the radiologically severe disease at the time of presentation.

Nausea and vomiting were the most common side effects observed in all the groups. Aminoglycosides may cause ototoxicity and nephrotoxicity. Hearing loss observed in the present study was similar to the study conducted by Nunn *et al.*[14] The incidence of hearing loss in the present study is 8.9% which is lesser than the study conducted by Piubello *et al.*,[12] hearing loss was 20% and Trébucq *et al.*,[13] hearing loss was 14.4%. There were 12 patients who had complaints of hearing loss; there were 11 females and one male patient. Eight out of 12 patients were elderly patients with a mean age of 45 years. The dosing frequency of KM was reduced to three times a week for patients with ototoxicity. The baseline PTA was normal among these subjects. PTA was done after the patients complained about hearing loss.

Skin pigmentation caused by clofazimine which was seen in two patients (1.4%) in the present study compared to the study conducted by Philipp du Cros *et al.*[6] skin pigmentation was seen in two patients (3.1%). Hypothyroidism was seen in one patient in the present study which was similar compared to the study conducted by Philipp du Cros *et al.*[6] Majority of the adverse effects were mild; treatment interruption was not seen due to adverse events in any of the patients. Gastrointestinal adverse events were managed symptomatically. Patients were counseled about the change in skin discoloration after stopping the drug (clofazimine). Hypothyroidism was treated with a thyroid supplement.

The treatment outcomes were divided into favorable (cured and treatment completed groups) and unfavorable (lost to follow-up, treatment failed, expired). In this study, patients with history of contact with DR-TB and lower BMI were associated with the unfavorable outcome as shown in Table 4.

Conclusions

The success rate of this regimen was above when compared to the latest data reported to WHO showing a treatment success rate for MDR-TB of 57% globally and also, other studies.[7,8] Shorter drug regimen was associated with minor adverse effects such as gastrointestinal adverse effects such as vomiting and hearing loss observed in elderly patients. Baseline unknown drug resistance and lower BMI were associated with unsuccessful outcomes. This was one of the handful of studies conducted on MDR-TB during the COVID-19 pandemic. There is also a need for further studies to establish the efficacy of shorter regimen which has been showing various success rates in different countries across the world.

Table 3: Treatment outcome among the study population

Outcome	Number (%)
Favorable outcome	85 (65.2%)
Completed	03
9 months	-
>9 months	03
Cured	82 (63%)
9 months	63
10 months (1 month extended IP)	09
11 months (2 months extended IP)	10
Unfavorable outcome	
Lost to follow-up	07 (5.2%)
<6 months	01
>6 months	06
Treatment failure	03 (2.2%)
After IP	01
After CP (reversion)	02
Death	24 (17.8%)
<1 month	03
1-3 months	14
3-6 months	06
>6 months	01
Changed to another regimen	13 (9.6%)
Adverse effects	02
Resistance pattern	11
FQ alone	08
AG alone	02
FQ + AG	01

Table 4: Characteristics of favorable and unfavorable outcomes

Variable observed	Favorable outcome	Unfavorable outcome	P
Age (mean)	37.76 years	37.70 years	0.98
BMI (mean)	20.31	19.03	0.03*
Males	42 (47.7%)	25 (53.2%)	0.43
Females	46 (52.3%)	22 (46.8%)	0.52
Alcoholism	13 (14.8%)	10 (21.3%)	0.33
Diabetes	16 (18.2%)	07 (14.9%)	0.43
Single cavity	13 (44.8%)	05 (23.8%)	0.15
Multiple cavities	16 (55.2%)	16 (76.2%)	0.24
History of contact DR-TB	10 (11.4%)	11 (23.4%)	0.04*
Past h/o tuberculosis			
One episode	34 (38.6%)	20 (42.6%)	0.22
>1 episode	04 (4.5%)	04 (6.5%)	0.60

*P <0.05

Limitations

As per the recently concluded drug resistance survey data in India (2014–2016),[15] MDR-TB among new cases is estimated at 2.84% and among re-treatment cases at 11.6%. There is a need for improving baseline DST at peripheral areas in order to effectively evaluate resistance to other drugs, especially in settings with high levels of first and second-line drug resistance. Audiometry was performed in elderly patients when they had complaints of decreased hearing. Few patients who were enrolled in the study had an interruption in the supply of anti-TB drugs due to the pandemic contributing to slightly higher rates of loss to follow-up, death, and treatment non-adherence.

Financial support and sponsorship

Supported by the operational research committee which was developed and run by the State TB cell, Hyderabad, Telangana.

Conflicts of interest

There are no conflicts of interest.

References

1. Nakajima H. Editorial: Tuberculosis: A global emergency. World Health 1993;46:3.
2. Tuberculosis (TB) World Health Organization. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis. [Last accessed 2022 Dec 08].
3. Guidelines for programmatic management of drug resistant tuberculosis in India 2021. Available from: https://tbcindia.gov.in/showfile.php?lid=3590. [Last accessed 2022 Dec 08].
4. Petersen E, Al-Abri S, Chakaya J, Goletti D, Parolina L, Wejse C, *et al.* World TB Day 2022: Revamping and reshaping global TB control programs by advancing lessons learnt from the COVID-19 pandemic. Int J Infect Dis 2022;124(Suppl 1) S1–3.
5. Abidi S, Achar J, Neino MM, Bang D, Benedetti A, Brode S, *et al.* Standardised shorter regimens versus individualised longer regimens for rifampin-or multidrug-resistant tuberculosis. Eur Respir J 2020;55:1901467.
6. du Cros P, Khamraev A, Tigay Z, Abdrasuliev T, Greig J, Cooke G, *et al.* Outcomes with a shorter multidrug-resistant tuberculosis regimen from Karakalpakstan, Uzbekistan. ERJ Open Res 2021;7:00537–2020. doi: 10.1183/23120541.00537-2020.
7. Das PK, Ganguly SB. Effectiveness of the shorter MDR regimen in the management of tuberculosis: Shortfall in the outcome of disease a multidimensional approach and evaluation for a better alternative. Biomed Biotechnol Res J 2020;4:143–7.

8. Soeroto AY, Nurhayati RD, Purwiga A, Lestari BW, Pratiwi C, Santoso P, *et al.* Factors associated with treatment outcome of MDR/RR-TB patients treated with shorter injectable based regimen in West Java Indonesia. PLoS One 2022;17:e0263304.
9. Khan MA, Aziz A, Ullah U, Ullah N, Jan F, Nasir SM, *et al.* Treatment outcomes of short course regimens for multidrug-resistant tuberculosis patients in Peshawar. Pak J Chest Med 2020;26:210–6.
10. Aung KJ, Van Deun A, Declercq E, Sarker 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;18:1180–7.
11. Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis 2015;19:517–24.
12. Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M, *et al.* High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: No relapses. Int J Tuberc Lung Dis 2014;18:1188–94.
13. Trébucq A, Schwoebel V, Kuaban C, Kashongwe Munogolo Z, Fikouma V, Bakayoko A. Expanding shortened MDR-TB treatment: The West African experience. Int J Tuberc Lung Dis 2014;(Suppl 1):S15.
14. Nunn AJ, Phillips PP, Meredith SK, Chiang CY, Conradie F, Dalai D, *et al.* A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med 2019;380:1201–13.
15. Mishra GP, Mulani JD. First national anti-tuberculosis drug resistance survey (NDRS) from India-An eye opener. J Infectiol Epidemiol 2018;1:26–9.