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ORIGINAL RESEARCH

Outcomes of Treatment in Multi Drug Resistant TB patients on MDR regimen including Bedaquiline in Amritsar: Retrospective record study

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ABSTRACT
Drug-resistant TB (DR-TB) strains are more difficult to treat than drug-susceptible strains, endangering worldwide progress toward the goals established by the WHO's End TB Strategy. Evidence-based policy recommendations for the care and treatment of DR-TB patients are therefore desperately needed. **Methods:** 139 Patients of Rifampicin-resistant TB on all oral longer MDR regimen (AOLMR) were enrolled under NTEP from 2020 to 2022 were selected retrospectively. **Results:** Out of 139 enrolled patients, 50 (35%) were cured, 38(27%) completed treatment,19 (13%) were lost to follow up, 28 (20%) died and 4 (0.02%) failed treatment.Out of 90 reported ADRs, QTc prolongation {N=30 (33%)} and peripheral neuropathy {N=17 (18%)} were majority of the side effects. **Conclusion:** Patients with MDR TB had poor treatment outcomes from the standardized regimen. One of the biggest obstacles to a successful outcome is the length of therapy and defaulters.
Keywords: MDR-TB, Standardized regimen, treatment outcomes, AOLMR, Rifampicin Resistance, WHO, Bedaquiline

INTRODUCTION

MDR-TB (multidrug-resistant tuberculosis), is one of a major global public health issue in developing countries like India. MDR TB is associated with high morbidity and mortality. In 2017, approximately 230,000 fatalities were reported. [1] The high death rate among MDR and Extensive drug resistant (XDR) TB is due to lack of safe, affordable, and easily transportable medications for drug resistant TB. [2].The estimated incidence of MDR/RR-TB in India was 119,000 (with a range of 93,000 to 145,000) in 2021, according to the Global TB Report 2022. [3]There was a noticeable decrease in the total number of DR-TB cases detected under the program compared to 2019 during the COVID-19 pandemic.There were steady improvements in TB treatment coverage between 2010 and 2019: from 51% in 2010 to 57% in 2015 and then 70% in 2019, globally. Disruptions caused by the COVID-19 pandemic then resulted in a sharp reversal of progress in 2020, only 58% of patients received treatment, returning to 2015 levels. [3]The need for newer, more potent, and better-tolerated anti-TB drugs is highlighted by the fact that the traditional treatment for MDR-TB is linked to serious side effects, greater rates of treatment default, and lower cure rates than drug-sensitive TB. In 2019, the WHO recommended an all-oral MDR-TB regimen, which includes fluoroquinolones, linezolid, and the newer antimycobacterial drug bedaquiline as the primary components of treatment. Bedaquiline (BDQ), a novel diarylquinoline, has a minimum inhibitory concentration (MIC) that ranges from 0.002 to 0.013 µg/mL which exhibits strong in vitro activity against both drug-sensitive and drug-resistant strains of Mycobacterium tuberculosis (Mtb).[4]The mechanism of action of BDQ is to inhibit ATP synthesis, a process which is essential for the growth and survival of strains of mycobacterium tuberculosis, even in its dormant state.5Nevertheless, BDQ has certain pharmacological and toxicological issues in spite of its efficacy. Its high lipophilicity (cLogP = 7.25) causes tissue buildup through phospholipidosis, which results in a lengthy terminal half-life (T1/2 = 5.5

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months). [6]Therefore, we aim to analyse the outcomes of treatment in MDR-TB patients who are on all oral longer MDR regimen including BDQ.

MATERIAL AND METHODS

All patients registered and started on DR-TB treatment between January 2020 and December 2022—serving eight districts for MDR treatment in the state of Punjab, including Amritsar, Gurdaspur, Pathankot, TaranTaran, Kapurthala, Jalandhar, Hoshiarpur, and Nawashaher—were the subjects of a retrospective record-based study. For diagnosis, treatment, and additional follow-up, patients from the aforementioned districts were sent to our hospital.Patient treatment cards, TB registers, and culture and drug susceptibility laboratory registers kept at the centers were among the documents viewed. Cure or completion of treatment were considered favorable treatment outcomes, whereas death, failure of treatment, loss to follow-up, termination of treatment due to adverse reaction, and switching to an XDR-TB regimen were considered unfavorable treatment outcomes.This study had been conducted after approval from the ethical committee.

INCLUSION CRITERIA

- Patients who were diagnosed with rifampicin resistant TB.
- Rifampicin resistant/MDR-TB patients receiving all-oral longer MDR regimen including BDQ from January 2020 to December 2022.

EXCLUSION CRITERIA

- Patients on shorter injectable MDR regimen.
- Patients who were transferred out.

STUDY POPULATION AND CHARACTERISTICS

Out of the 139 patients enrolled in this study, 70 (50.3%) were female and 69 (49.6%) were male. The majority of patients were between the age group of 17 and 26. Three patients out of 139 were HIV reactive. Out of the 139 patients, 15 were diagnosed with extrapulmonary MDR TB and 124 with pulmonary MDR TB. The average weight of patients were 44.4 ± 10.60 kg.

RESULTS

While 51 (36%) cases had unfavorable results {dead cases 28 (20%), lost to follow up cases 19 (13%), treatment failed 4 (0.028)}, 88 (63%) patients had favorable outcomes {cured cases 72 (51%), treatment completed cases 16 (11%)}. QTc prolongation accounted for 33% of the 90 recorded adverse drug reactions, whereas peripheral neuropathy accounted for 18%. In 17% and 16% of cases, respectively, hepatitis and electrolyte imbalance were observed. Haematological ADR was present in 10% of individuals, while ocular and ENT manifestations occurred in 5% and 4% of instances, respectively.

TABLE 1- DEMOGRAPHICS AND CLINICAL PROFILE

	NUMBER OF CASES (%)
DEMOGRAPHICS	
Sex (male/female)	**69/70 (49%/50%)**
Age (male/female)	
7-16 years	**07/03**
17-26 years	**34/21**
27-36 years	**14/13**
37-46 years	**05/12**
47-56 years	**05/13**
57-66 years	**04/03**
67-76 years	**01/03**
77-86 years	**00/01**
Site of disease	
Extrapulmonary	**15**
Pulmonary	**124**
Hiv status	
Non-reactive	**136**
Reactive	**03**

TABLE 2 – TREATMENT OUTCOME

ROW LABELS	**TREATMENT OUTCOME**
TC	25
T FAILED	4
LTFU	19
DIED	28
CURED	63
Grand Total	**139**

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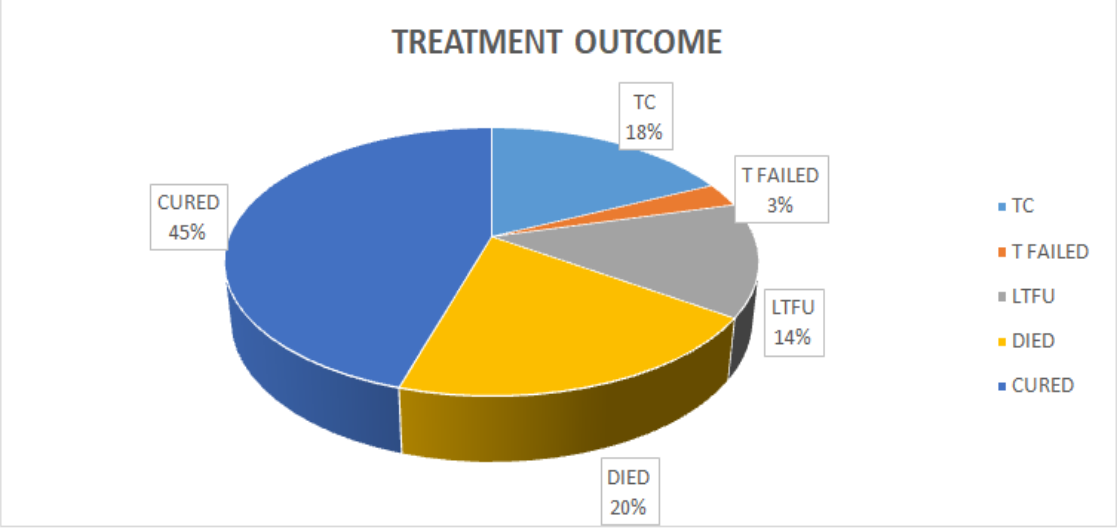
TC- Treatment completed, T FAILED- Treatment Failed, LTFU- Lost To Follow Up



TC- TREATMENT COMPLETED, T FAILED- TREATMENT FAILED, LTFU- LOST TO FOLLOW UP

TABLE 3 – PERCENTAGE OF REPORTED ADVERSE DRUG REACTIONS

ADRs	Reported ADRs(N=90)
QTc prolongation	30 (33%)
Peripheral neuropathy	17 (18%)
Hepatitis	16 (17%)
Electrolyte imbalance	15 (16%)
Haematological abnormalities	10 (11%)
Ophthalmic	5 (5%)
ENT	4 (4%)

MINOR	MILD	13 (14.4%)
	MODERATE	31 (34.4%)
SERIOUS	MEDICALLY SIGNIFICANT	39 (43.5%)
	LIFE THREATENING	5 (5.5%)
	DEATH	2 (2.2%)
	TOTAL NUMBER OF CASES N=90	

DISCUSSION

In numerous countries, efforts to eliminate tuberculosis (TB) have been challenged by the emergence of strains of drug-resistant Mycobacterium tuberculosis, exacerbating the public health crisis. Three countries make up nearly half of the global MDR/RR-TB cases: India (24%), China (13%), and the Russian Federation (10%).[7]According to WHO estimates, there were 10 million cases of tuberculosis in 2020, 1,400,000 deaths (including 208,000 deaths among those living with HIV), and 465,000 cases of drug-resistant tuberculosis.(8)Over the past 20 years, the global epidemiology of mycobacterial drug resistance has gotten worse due to the emergence of extensively drug-resistant tuberculosis (XDR-TB) and multidrug-resistant tuberculosis (MDR-TB). Only about 50% of patients with MDR-TB respond well to treatment, which is still a low success rate. [8] One major factor in treatment failure across many regions is the shortage of effective medications to combat MDR-TB and XDR-TB. Additionally, MDR-TB treatment tends to be lengthy and costly. Numerous efforts have aimed at reducing treatment duration and creating more effective drugs. Consequently, several new medications, such as linezolid, as well as innovative drugs like bedaquiline and delamanid, have been tested for MDR-TB treatment due to their unique mechanisms of action.[9]

Our retrospective study aimed to evaluate the outcomes of treatment in drug resistant TB patients on all oral longer regimen including bedaquiline.In our study, there was no gender bias as the number of males {N=69;49%} was almost equal to females {N=70;50%}.This result is consistent with a research conducted in Karachi by CF McQuaid that found no gender preference.10. According to this study, a sizable percentage of patients experienced cure or treatment success, demonstrating the potential efficacy of these regimens. The results of a 2023 study conducted at GMC Patiala on the treatment outcomes of MDR-TB patients treated with bedaquiline under programmatic management at a

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tertiary care facility in Punjab, India, are in line with our study's 51% cure rate (N=72). This result is consistent with a research conducted in Karachi by CF McQuaid that found no gender preference.10. According to this study, a sizable percentage of patients experienced cure or treatment success, demonstrating the potential efficacy of these regimens. The results of a 2023 study conducted at GMC Patiala on the treatment outcomes of MDR-TB patients treated with bedaquiline under programmatic management at a tertiary care facility in Punjab, India, are in line with our study's 51% cure rate (N=72). [11] Additionally, our findings are consistent with a multicenter study conducted in 2017 by Sergey et al. that comprised 247 MDR-TB cases with culture confirmation. While 71.3% of participants in that study were successfully cured with 9% completing treatment, 13.4% dead, 7.3% defaulted, and 7.7% had treatment failure. [12] In contrast, 40% of drug resistant TB patients in the study conducted by DumitroChesov and colleagues were cured. This may be the result of drug withdrawal brought on by related side effects, missed follow-up appointments, or fatalities. [13]

Safety and Tolerability

Although longer oral regimens show promise in terms of effectiveness, our investigation also revealed a number of safety issues. 90 admitted cases in our study reported adverse effects. 30 patients (33%) had ADR of QTc prolongation, 17 cases (18%) had neurological problems, and 15 cases (16%) had electrolyte imbalance. Haematological and GIT abnormalities were found in 10 cases (11%) and in 16 cases (17%), respectively. Five (5%) and four (4%) individuals, respectively, experienced ocular and ENT side effects. This is in line with a 2022 study conducted at NITRD Delhi [14], which highlighted the possibility of adverse consequences from long-term use of several anti-TB medications, requiring close monitoring and care.

The incidence of serious adverse events in our cohort was 46%, which is comparable to or slightly higher than that reported in similar studies. [4]This emphasizes how crucial it is to maintain constant watchfulness and provide supportive care during the course of therapy in order to reduce these adverse drug reactions.

Limitations

There are various restrictions on this study. Due to its retrospective nature, it is prone to intrinsic biases including missing data and differences in treatment approaches. Furthermore, the particular patient group and healthcare environment from which the data were gathered may limit the generalizability of our findings. To validate our findings and get over these restrictions, more prospective research is required.

Conflict of Interest

The authors confirm that they have no active or potential conflicts of interest of any kind

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None

CONCLUSION

In conclusion, longer oral regimens for MDR pulmonary tuberculosis demonstrate promising effectiveness with a manageable safety profile. However, attention to adverse effects and patient-specific factors is crucial. Our study contributes to the growing body of evidence supporting the use of oral regimens and highlights areas for future research to optimize treatment strategies for MDR-TB.

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