

Factors Affecting Outcome of Bedaquiline Containing Regimen in Treatment of Rifampicin Resistant, Multi Drug Resistant and Pre Extensively Drug Resistant Pulmonary Tuberculosis

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Conflict of interest: Nil

Abstract:

Background: The latest anti-tubercular drug resistance surveillance data show that 3.5% of new and 18% of previously treated tuberculosis cases in the world are estimated to have multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). India accounts for about one-fourth of the global burden of MDR-TB. Emergence of drug resistant has been a serious threat to eliminate tuberculosis, End TB 2025. The estimated number of MDR/RR - TB cases in India is 124000 (9.1/lakh population). A total of 109 countries are using all - oral longer regimens for the treatment of MDR/RR - TB.

Objective: To assess the effectiveness of the Bedaquiline containing regimen. To analyse the factors affecting treatment outcomes of rifampicin resistant, multi drug resistant pulmonary tuberculosis patients treated with Bedaquiline containing regimens.

Methods: We studied cases of rifampicin and multidrug resistant tuberculosis registered at drug resistant tuberculosis centre, Mysore. During the time period of January 2021 to March 2022. (14months) Patients were treated according to programmatic management of drug resistant tuberculosis guidelines. (PMDT) followed up with NIKSHAY mobile application.

Results: 115 cases were studied, out of which 104 were drug resistant pulmonary tuberculosis. Based on line probe assay (LPA), drug susceptibility (DST) reports 50.96% RR -TB 31.7% MDR TB, 17.30% Pre XDR. 31 cases were treated with shorter Bedaquiline regimen, 73 cases were treated with all oral longer regimen. 86% patients had past history of treatment with first line antitubercular treatment under national programme. 4 cases were co-infected with tuberculosis and human immune deficiency virus. 53 cases cured, 20 cases treatment complete, 8 lost follow up, 3 failure, 20 died. Cure rate of Bedaquiline containing regimen in RRTB-50.9%, MDRTB-54.5%, Pre XDRTB-44.4%. Most common comorbidity associated was diabetes, most common adverse reaction was associated with linezolid-anaemia, bicytopenia; Cycloserine - psychiatry issues, clofazimine -hyperpigmentation. In 4 cases regimen was changed from shorter to AOLR regimen based on LPA, DST reports. In 6 cases AOLR regimen was modified due to adverse events.

Conclusion: In our present study treatment cure rate was 50.96%. Patients treated with Bedaquiline regimen for DRTB showed lower mortality, and fewer manageable adverse events, indicating improved tolerance and compliance compared to previous treatments.

Keywords: Rifampicin, Multidrug Resistant Tuberculosis, Programmatic Management Of Drug Resistant Tuberculosis, Bedaquiline, Line Probe Assay.

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Introduction

In Global TB report 2022, India reported the MDR/RR-TB prevalence rate of 316 per 1 lakh

population and incidence rate of 8.5 per 1 lakh population. The proportion of bacteriologically

confirmed TB cases tested for rifampicin resistance among new cases (pulmonary) was 76% and for the previously treated was 73%. [1] India accounts for about one-fourth of the global burden of MDR-TB.

There are five categories of drug - resistant TB used by the national health programs at present: isoniazid (INH) -resistant TB, RR - TB, and MDR - TB (RR and INH resistant), pre - extensively drug - resistant TB (pre -XDRTB) and XDR - TB. Pre - XDR - TB is TB that is resistant to rifampicin (MDR/RR - TB) and any fluoroquinolone (a class of second - line anti - TB drugs). XDR - TB is TB that is resistant to rifampicin (MDR/RR -TB), plus any fluoroquinolone, plus additional resistance of one of the drugs of Group A either Bedaquiline or Linezolid. [2]

In India, current guidelines for DR-TB management (PMDT) are aligned with WHO recommendations and include U-DST (Xpert MTB/RIF and second-line LPA) for all presumptive cases and short-term MDR-TB regimens of 9-12 months AOLR regimen of 18 months. [3]

The global outcomes of drug-resistant tuberculosis treatment are poor, with low cure rates and high mortality. Treatment is long and many medications have poor tolerability. Side effects and adverse events are common, making treatment more complicated. Managing these cases is also expensive and burdensome. The present study emphasis on factors affecting treatment outcome of drug resistant tuberculosis.

Materials and Method

The study was conducted by the Department of Pulmonary Medicine in the Princess Krishnajamanni Tuberculosis and Chest Diseases (PK TB & CD) hospital, Drug resistance TB centre (DR TB) and Mysore Medical College and Research institute.

It was a retrospective single centre based descriptive study. Patient who were enrolled and initiated on treatment with shorter Bedaquiline or all oral longer regimen during the time period of January 2021 to march 2022. (14 months) were analysed, followed up with NIKSHAY application

Inclusion Criteria: Patients of age 18 years or older diagnosed case of rifampicin, multidrug-resistant pulmonary tuberculosis based on CBNAAT, culture, and LPA reports.

Exclusion Criteria:

1. Extra pulmonary tuberculosis.

2. Severe hepatic and renal disease.

3. Patients with cardiac abnormalities like uncontrolled arrhythmias, marked prolongation of QT/QTc interval.

Data was collected from medical records of DR TB centre after getting permission from District tuberculosis officer, institutional ethical committee.

Results

Among the cohort of 104 eligible DRTB patients, 68 were males and 36 were females. The mean age of study participants was 43.4 years. The mean BMI was 17.53 kg/cm² majority were undernourished.

The most common presenting symptom among the study population was cough expectoration and fever found in 75%. 20% presented with haemoptysis. Anorexia, breathlessness were other presenting symptoms.

Among 104 patients, on chest ray PA view 73 were having bilateral cavitory lung disease, and 31 patients were having less than 50% lung involvement.

Based on LPA, Culture DST reports 50.96% RR - TB, 31.7% MDR TB, 17.30% Pre XDR. 31 cases were treated with shorter Bedaquiline regimen, 73 cases were treated with all oral longer regimen.

82.60% patients had past history of treatment with first line antitubercular treatment under national programme. 4 cases were co-infected with tuberculosis and human immune deficiency virus.

In 56 of study population personal habits such as tobacco consumption, alcohol consumption, and smoking were present. Most common co - morbidities were hypertension 10 patients, diabetes 14 patients, thyroid dysfunction 4 patients, diabetes was most common.

The most common body systems showing Adverse Events were hematological- anemia, and bicytopenia (42%) associated with Linezolid followed by gastrointestinal -hepatitis, nausea and vomiting (28%), and dermatological - hyperpigmentation (14%) associated with clofazimine, psychiatry -mood disorder associated with cycloserine. In 4 cases regimen was changed from shorter to AOLR regimen based on SLLPA, DST reports. In 6 cases AOLR regimen was modified due to adverse events. Treatment outcome 50.96% cases cured, 19.2% cases treatment complete, 7.6 % lost follow up 2.8% failure, 19% died.

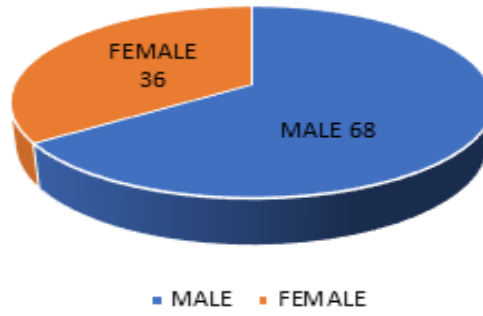


Figure 1

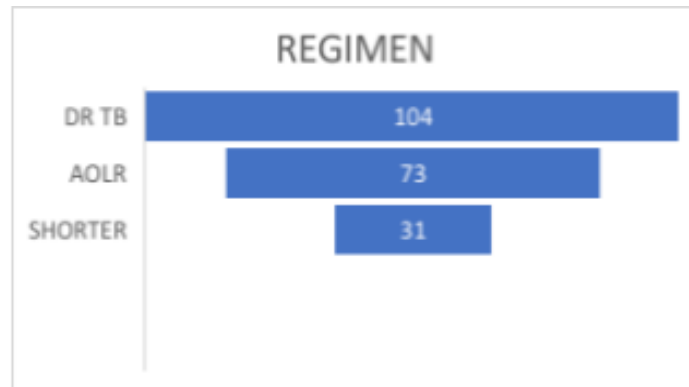


Figure 2

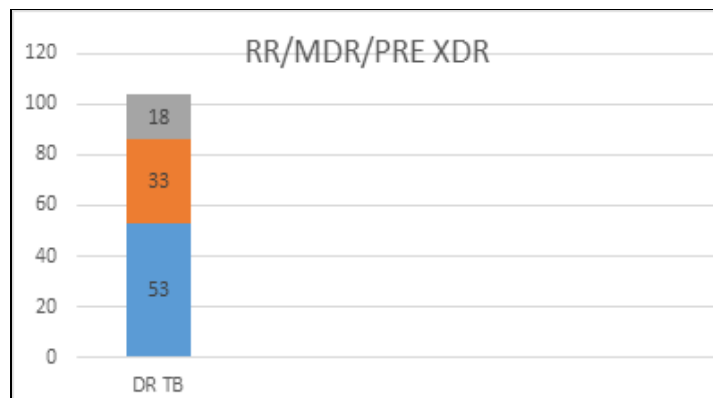


Figure 3

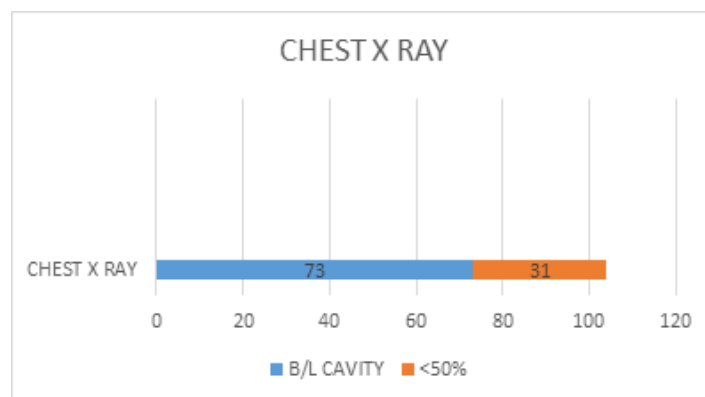


Figure 4

SYSTEM	MILD	MODERATE	SEVERE	LIFE THREATENING	TOTAL
GASTROINTESTINAL	3	-	-	-	4 (28%)
RENAL	-	-	-	-	-
RESPIRATORY	-	-	-	-	-
OPHTHAMOLOGICAL	1	-	-	-	1(7%)
DERMATOLOGICAL	-	2	-	-	2(14%)
HAEMATOLOGICAL	-	2	4	-	6(42%)
PYSCHIATRY	-	1	-	-	1(7%)

Figure 5

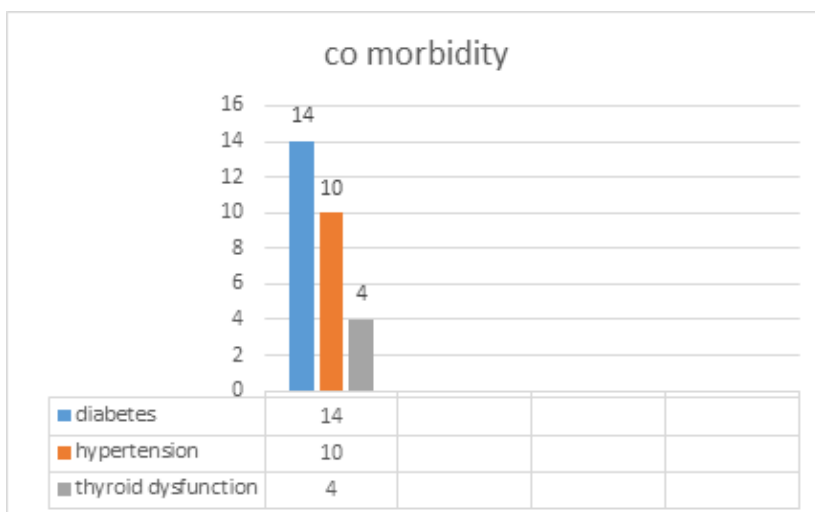


Figure 1

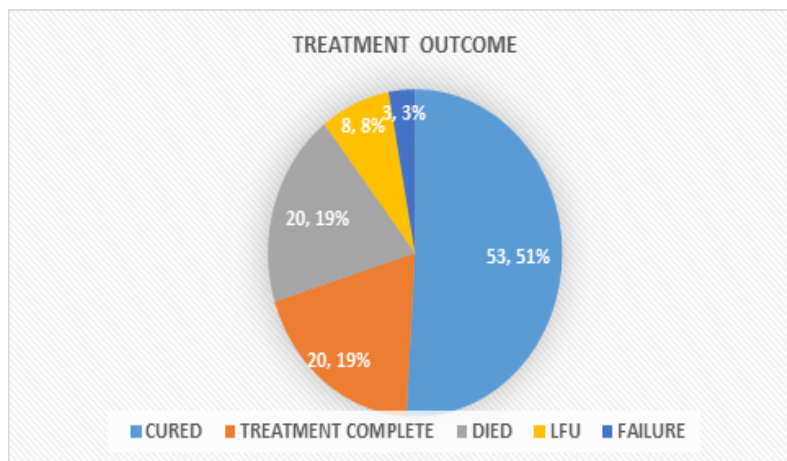


Figure 2

Table 1: Statistical analysis fisher s exact test

Factors	Outcome		P value
	Favourable	Unfavourable	
Male	33	35	0.541
Female	20	16	
Age <45	30	21	0.123
Age >45	23	30	
BMI <17.5	31	30	1
BMI >17.5	22	21	
B/L Cavity	34	39	0.702
<50% lung	19	12	
Co morbidity -yes	10	4	0.150
Co morbidity -no	43	47	
RR/MDR	45	41	0.490
Pre XDR	8	10	

Table 2: Treatment outcome

	RR TB	MDR TB	PRE-XDR TB
CURED	27	18	8
TREATMENT COMPLETE	6	7	7
DIED	14	5	1
LFU	5	2	1
FAILURE	1	1	1
	53	33	18

Discussion

In a meta-analysis published in Lancet, the results of 12,030 patients from 25 countries across 50 studies were analyzed. Among them, 7346 (61%) experienced treatment success, 1017 (8%) faced failure or relapse, and 1729 (14%) unfortunately passed away. [4]

In a study conducted by Koirala et al. involving 383 patients treated with bedaquiline but not delamanid, 284 (74.2%) achieved treatment success. On the other hand, 25 (6.5%) patients died, 11 (2.9%) failed, and 63 (16.5%) were lost to follow-up. Our study demonstrated lower cure rates compared to the meta-analysis findings. [5]

In a research carried out by Sandip V et al., the majority of the participants were young (under 30 years old), had a low body mass index (below 18.5 kg/m²), and had received prior treatment with anti-TB medications. [6]

In a study involving 290 subjects, 53% were male and 47% were female, with the male-to-female ratio increasing with age, a trend that was consistent with our own findings. [7]

In a research conducted by Sergey and colleagues, the percentage of HIV co-infected patients was 22.1%. [8] In a study led by Manoj Kumar Pippal [9] and team, HIV co-infection was detected in 5% of the study participants, whereas it was 3.8% in our own study.

Overall, cases of MDR-TB generally exhibited more extensive disease and were more likely to be bilateral. Recent studies indicate that a radiological sign that could provide good specificity for diagnosing pulmonary MDR-TB is the presence of thick-walled multiple cavities, especially if the number of cavities is three or more. In adult patients, new cases of MDR-TB seem to have a similar prevalence of cavity lesions, estimated to be around 70%, compared to previously treated MDR-TB cases, which showed similar results in our study. [10]

According to a study conducted by Sandip V. Barvaliya et al., 54% of the study population exhibited personal habits such as tobacco consumption, alcohol consumption, and smoking. Which was similar in our study. [6]

A large proportion of patients, specifically 82.6%, had previous experience with anti-tubercular medications, exceeding the findings of the research carried out by Alena Skrahina, HennadzHurevich et al. This suggests the progressive emergence of drug-resistant strains as a result of repeated exposure to inadequate treatment. [11]

In our study, we observed a lower number of adverse events compared to previous studies conducted by V. S. Salhotra et al and Sandip V Barvaliya et al. The most frequent adverse events affecting various body systems were hematological, specifically anemia and bi-cytopenia (42%) linked to Linezolid. This was followed by gastrointestinal issues such as hepatitis, nausea, and vomiting

(28%), as well as dermatological problems like hyperpigmentation (14%) associated with clofazimine. Additionally, psychiatry-related adverse events included mood disorders associated with cycloserine. [6]

Conclusion

In our study, the treatment regimen containing Bedaquiline resulted in a cure rate of 50.96%. We conducted an analysis on various factors that influenced the effectiveness of this regimen. Factors such as elderly age, severity of chest x-ray involvement, diabetes, and treatment interruptions were found to be associated with poor or unfavorable outcomes. The study emphasizes the significance of considering both demographic and clinical characteristics of patients when developing and executing treatment plans for tuberculosis. It is essential to take into consideration variables like age, BMI, previous treatment history, gender, socioeconomic status, and comorbidities to deliver personalized and efficient care for individuals affected by this disease. Interventions such as education on smoking/alcoholism, diabetes management, ensuring treatment adherence, regular follow-ups, nutritional support, and digital patient monitoring may enhance the effectiveness of the Bedaquiline-containing regimen.

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