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A RETROSPECTIVE ANALYSIS OF TREATMENT OUTCOME IN MULTI DRUG RESISTANT TUBERCULOSIS PATIENTS ON BEDAQUILINE IN A TERTIARY CARE CENTRE OF JHARKHAND

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Abstract

Introduction- Tuberculosis is a significant health challenge for India due to its high incidence and mortality among the cases. India has committed to eliminate Tuberculosis by 2025 and taken many steps towards achieving the goal. However, the increase in Multi Drug-resistant Tuberculosis(MDR-TB) cases is cause for growing concern. The introduction of Bedaquiline in National Tuberculosis Elimination Program(NTEP) has helped to shorten the treatment regimen for Drug-resistant cases. Hence in this context the study was under taken to analyse the treatment outcome of patients on bedaquiline based multiple drug regimen and its effectiveness.

Materials and Methods- MDR-TB patients enrolled for Bedaquiline based regimen from 2018 to 2021 at a DR-TB Centre in a tertiary care health centre were included in the study. A retrospective analysis of treatment outcome was done using the data available in NIKSHAY portal. Cured or treatment completed were grouped as favourable outcome, whereas the dead, lost to follow-up, not evaluated or treatment regimen changed were considered to be unfavourable outcome.

Result- A total of 156 patients were initiated on Bedaquiline based regimen between 2018 and 2021.Altogether 95 (60.9%) patients had favourable outcome. None of the examined variable (age, gender and year of treatment) was found to have statistically significant association with outcome ($p<0.05$).

Conclusion- The study highlights the importance of treating MDR-TB patients with bedaquiline based regimen for favourable outcome. Bedaquiline is well tolerated drug and is relatively effective for treatment of MDR-TB patients.

Keywords- Tuberculosis, Multi Drug-Resistant Tuberculosis, Bedaquiline, Treatment Outcome, Nikshay

Introduction

Tuberculosis(TB) caused by *Mycobacterium tuberculosis* is one of the oldest disease and most common infectious cause of mortality globally. [1,2] Inspite of significant advancement in medical

field, TB still remains a significant global health challenge, particularly in India which has very high incidence and mortality among TB cases. [3,4] It alone is responsible for estimated 26 lakh people contracting the disease and about 4 lakh people dying from it annually. The economic burden of TB in terms of loss of lives, income and workdays is also substantial, usually affecting the most economically productive age group of society resulting in a significant loss of working days and pushing TB patients further into the vortex of poverty. [2]

TB has always been in the developmental agenda as part of 'Stop TB strategy' under Millennium Development Goals and 'End TB Strategy' under Sustainable Development Goals.[1] India, as a signatory of the United Nations Sustainable Development Goals (UN-SDGs), has committed to the achievement of the 'End TB' targets by 2025, five years ahead of the SDG timeline of 2030.[5] To combat the problem, post-COVID-19 pandemic, India embarked on a journey towards accelerating tuberculosis (TB) elimination, guided by the National Strategic Plan (NSP) 2017–25 implemented by Ministry of Health and Family Welfare (MoHFW) with the goal to achieve SDG End TB targets by 2025.[2,5-6] Providing integrated, patient-centred care for all patients with TB is one of the components of END TB Strategy. Diagnosis, notification and timely initiation of treatment is an important cornerstone for the elimination of TB. [1]

For this purpose, Government of India has taken many steps. One of them was launch of NIKSHAY portal which helps in monitoring collection and collation of patient wise data.[5] It is a case-based, web-based real time patient management TB notification portal for digitalizing and tracking the patients with TB along with referral and feedback mechanism since 2018.[1,5] One of the key features of 'Nikshay' is the generation of a unique Nikshay ID for each TB patient at the site of diagnosis, which can help in tracking the patient from diagnosis till treatment outcome.[1] It captures all the components of service delivery from curative to preventive services.[5]

From 2020 the Revised National Tuberculosis Control Program(RNTCP) has been replaced by National Tuberculosis Elimination Program(NTEP). [3] Many new initiatives have been undertaken to achieve the goal of TB elimination under NTEP. With the effort of Government and the world commitment to End TB, the burden has been greatly reduced in line with Government plan to eliminate it by 2025.India's efforts to ensure early detection and treatment initiation, along with a host of community engagement efforts has resulted in a decline of 16% in TB incidence (new cases emerging each year) and a 18% reduction in mortality due to TB, since 2015. The incidence rate in India had fallen from 237 per lakh population in 2015 to 199 per lakh population in 2022 and mortality rate had declined from 28 per lakh population in 2015 to 23 per lakh population in 2022 as per the Global TB Report 2023 released by World Health Organization (WHO). [5]

Drug-resistant bacterial infections are on the rise globally, which has placed sharp focus on drug-resistant tuberculosis(DR-TB), its diagnosis and treatment.[7] Although overall TB rates are on the decline, the prevalence of multidrug-resistant TB (MDR-TB) and, more recently, extensively drug-resistant TB (XDR-TB) is increasing and spreading at an alarming rate, which is a cause of concern.[8] Over the past 20 years, it has become apparent that the widespread dissemination of drug-resistant TB will continue to challenge global efforts to cure patients and meet the ambitious targets of the End TB Strategy and the Sustainable Development Goals.[7]

The existence DR-TB has been confirmed since the development of anti-TB chemotherapy. [4] DR-TB continues to be a public health problem, taking a heavy toll on patients, their families, communities and health-care systems. Compared to the treatment for drug susceptible TB (DS-TB), DR-TB regimens require a longer course, higher pill burden and higher toxicity profile, resulting in lower adherence and poorer treatment outcomes, including deaths. [6] A total of 63939 cases of MDR-TB were diagnosed in India as per Global TB report 2023. [5] The global effort to successfully fight TB is being threatened by DR-TB. [4]

MDR-TB is defined as TB resistant to both rifampicin and isoniazid. In addition, extensively drug-resistant TB (XDR-TB), is defined as MDR with additional resistance to any fluoroquinolone and to second-line injectable agents.[9] Over the past few decades, treatment of multidrug-resistant (MDR)/extensively drug resistant (XDR) tuberculosis (TB) has been challenging for patients,

healthcare workers and healthcare services because of its prolonged duration (up to 20– 24 months), toxicity, costs and sub-optimal outcomes.[10] Improving treatment outcomes in multidrug-resistant tuberculosis (MDR-TB) is partly hampered by inadequate effective anti-tubercular agents.[9]

The introduction of novel drugs and the prioritization of repurposed drugs has led to substantial changes in drug selection for the treatment of drug-resistant tuberculosis (DR-TB) over the last few years. [11] Development of bedaquiline and delamanid has potentially changed the treatment landscape for MDR-TB. [9,10]

Bedaquiline(BDQ) deserves particular attention because it is the first anti-tubercular agent approved by the U.S. Food and Drug Administration (FDA) in 2012 since the late 1970s.[8-12] Bedaquiline is a diarylquinoline antimycobacterial drug that is a key component of several novel regimens in clinical development for drug-susceptible and drug-resistant TB.[6,8-9,12-13] It works by inhibiting the mycobacterial ATP synthase and consequently depleting the cellular energy stores.[6,8-9,11-12] It has stronger bactericidal activity than the existing anti-TB drugs.[12] The recommended dosage is 400 mg once daily for 2 weeks followed by 200 mg three times per week for 22 weeks.[13]

Updated WHO guidelines, published in June 2020, recommend a shorter treatment regimen for patients with MDR/RR-TB not resistant to fluoroquinolones (of 9–11 months), with the inclusion of bedaquiline instead of an injectable agent, making the regimen all oral. [7,10] This is to maximize treatment outcomes and minimize the toxicity associated with injectable agents. [12]

NTEP provides simplified shorter oral bedaquiline containing MDR/RR-TB regimen.[3,6] Shorter oral bedaquiline-containing MDR/RR-TB regimen is recommended for those MDR/ RR-TB patients in whom resistance to the component drugs has been excluded or those who have not been previously treated for more than one month with second-line drugs used in shorter oral bedaquiline-containing MDR/RR-TB regimen and have no other exclusion criteria.[6] For screening eligible patients elaborate guidelines has been prepared by Ministry of Health and Family Welfare (Guidelines for Programmatic Management of Drug Resistant Tuberculosis in India 2021).[6]

BDQ has shown significant benefits in improving the time to culture conversion in MDR-TB patients. [6,8-10] It shows strong bactericidal and sterilizing activities against *Mycobacterium tuberculosis*. The drug has a high volume of distribution, with extensive tissue distribution, highly bound to plasma proteins and is metabolized in liver. The drug has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping BDQ. [6,9-10]

Despite the outstanding advantages of BDQ as a very promising anti-TB drug, there is a black box warning relating to the drug's effectiveness and safety.[8] It has the potential risk of prolonging the QT interval.[8-10,12] The most commonly reported side effects of BDQ include headache, dizziness, vomiting and arthralgia.[8] Even with the use of these newer drugs, successful outcomes and treatment options are limited in patients with fluoroquinolone-resistant and extensively drug-resistant TB (XDR)-TB.[14]

Hence this study was undertaken to assess the treatment outcome of bedaquiline based regimen in MDR-TB patients of India, thus determining its effectiveness.

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Materials and Methods

All the patients enrolled for bedaquiline based regimen as per the PMDT guidelines from 2018 to 2021 at DR-TB Centre, RIMS Ranchi were included in the study. Nikshay portal was utilized to access information about sociodemographic profile, diagnostics and treatment received and outcomes of the patients.

Operational definitions: [4,6]

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response and no evidence of treatment failed.

Treatment completed: A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failed

Treatment failed: A patient whose treatment regimen needs to be terminated or permanently change of at least two or more anti-Tb drugs to a new regimen option or treatment strategy.
Died: A patient who died before starting or during the course of treatment.
Lost to follow-up: A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated: A patient for whom no treatment outcome was assigned.
Treatment regimen changed: A patient whose treatment regimen has a change of at least one or more anti-TB drugs before being declared as failed.
All the patients who were either cured or had treatment completed were grouped as having favourable outcome whereas patients who died or were lost to follow-up or were not evaluated or had their treatment regimen changed were considered to show unfavourable outcome.
All the data was entered into MS-Excel sheet and SPSS software was used for data analysis. Frequency, mean, standard deviation and time trends were determined using descriptive analysis. Chi-square test was used for determining difference in proportions.

Results

A total of 156 MDR-TB patients were started on bedaquiline based regimen between 2018 and 2021 comprising 143 (91.7%) pulmonary and 13 (8.3%) extra pulmonary MDR-TB cases. There were 91(58.33%) male and 65 (41.67%) female patients. There has been an increase in number of patients since the start in 2018 as seen in Figure 1.

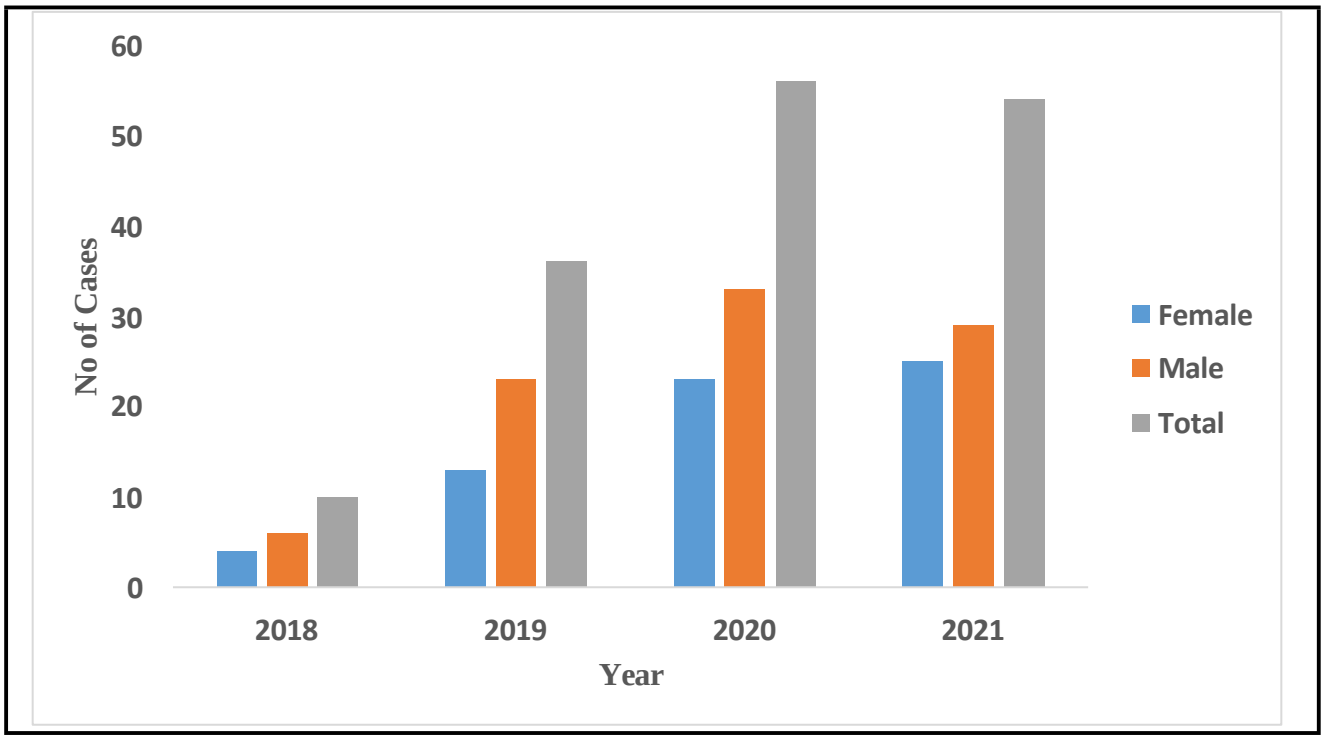

Figure 1: Year wise distribution of MDR-TB cases on Bedaquiline

The age distribution of patients ranged from 5 – 75 years with 53.2% of all patients belonging to the age group 18-30 years followed by 36.5% patients in the age group of 31-59 years. The mean age of all the patients is 31.9 years with a standard deviation of 12.95 years. The mean age of males at 33.51 years is slightly higher than that of female patients at 29.66 years. The year-wise age and gender distribution of all the patients is shown in Table 1.

Table 1: Sociodemographic profile

	Year wise distribution of the study population				
Variable	2018(n=10)	2019(n=36)	2020(n=56)	2021(n=54)	Total(n=156)
Age group (Percentage)					
<18	1 (10)	2 (5.6)	2 (3.6)	2 (3.7)	7 (4.5)
18-30	5 (50)	20 (55.66)	29 (51.8)	29 (53.7)	83 (53.2)
31-59	3 (30)	13 (36.1)	20 (35.7)	21 (38.9)	57 (36.5)
>=60	1 (10)	1 (2.8)	5 (8.9)	2 (3.7)	9 (5.8)
Gender (Mean Age, SD)					
Female	4 (30.75,23.07)	13 (25.54,7.5)	23 (29.87,13.95)	25 (31.44,14.15)	65 (29.66,13.49)
Male	6 (33.67, 10.23)	23 (32.87,12.16)	33 (34.61,12.99)	29 (32.72,12.72)	91 (33.51,12.36)

Figure 2 shows the year-wise treatment outcome of the MDR-TB patients. 95 (60.9%) patients showed a favourable outcome consisting of 30 (19.2%) cured and 65 (41.7%) treatment completed patients. During the course of treatment 16 (10.3%) patients died and 27 (17.3%) were lost to follow-up. There was need to change treatment regimen for 17 (10.9%) patients and 1 patient could not be evaluated for outcome. There were nil cases of treatment failure.

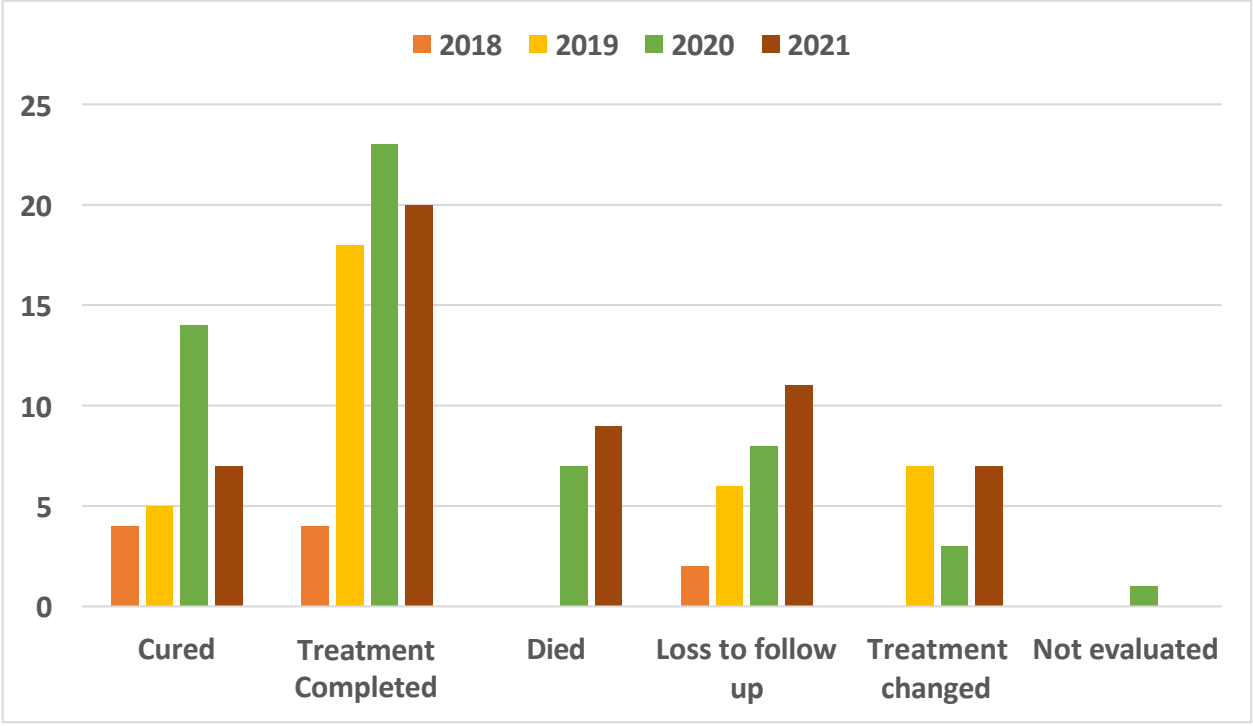

Figure 2: Treatment outcome among patients of MDR-TB (n=156)

There has been no statistically significant association ($p<0.05$) between sociodemographic factors (age, gender and year of treatment) and treatment outcome as evident from Table 2. All patients were tested for HIV and only one patient was found to be reactive and result for three patients were unknown. Diabetes mellitus testing was done on 133 patients, with 12 being diabetic and results for 2 were unknown.

Table 2: Association of sociodemographic factors with the treatment outcome

Variable	Favourable Treatment Outcome (n=95)	Unfavourable Treatment Outcome (n=61)	p value
Age-Group			0.6
<18	5(71.4)	2(28.6)	
18-30	53(63.9)	30(36.1)	
31-59	33(57.9)	24(42.1)	
>=60	4(44.9)	5(55.6)	
Gender			0.42
Female	42(64.6)	23(35.4)	
Male	53(58.2)	38(41.8)	
Year wise			0.17
2018	8(80)	2(20)	
2019	23(63.9)	13(36.1)	
2020	37(66.1)	19(33.9)	
2021	27(50)	27(50)	

Discussion

India has a high burden of TB and Government efforts have led to improvement in the situation, however DR-TB cases are cause for concern due to rapid increase in numbers. Various initiatives have been taken under NTEP to address this issue, one of them being introduction of bedaquiline based multi drug treatment regimens. Most of the patients have pulmonary MDR-TB in the study as it is more common. In patients with extra pulmonary MDR-TB, lymph nodes were the most affected sites. Bedaquiline based regimen has shown favourable outcome as shown by this study. This is in line with similar results obtained in studies by Li J et al and Gao et al. [12] Females in the present study have more favourable treatment outcome than males. Geriatric patients have poor outcome compared to rest of the patients which may be related to presence of other co-morbid factors. However, there was no statistically significant association with either age group, gender or year of treatment. The unfavourable outcomes could be due to adverse effects, migration of patients and lack of awareness among patients. [4,12] HIV testing is being done for all the MDR-TB patients, leading to early identification and vastly improving outcome in immunocompromised patients. However screening for diabetes needs to be increased. This study conducted had its own limitations as MDR-TB patients were enrolled from a single DR-TB centre. Since data available in Nikshay portal was used for analysis, other comorbidities (e.g COPD, hypertension, cardiomyopathies and liver diseases) which may be associated with treatment outcome could not be analyzed. [4]

Conclusion

The present study affirmed the relative effectiveness of bedaquiline for MDR-TB patients. Our study data suggests that bedaquiline is well tolerated and is effective in MDR-TB patients based on the favourable outcomes. There is need to have drug susceptibility testing to identify resistant strains to bedaquiline at the earliest. Also a surveillance system is required for the evaluation of adverse effects and mechanisms of resistance and co-resistance with other anti-TB drugs. The treatment with bedaquiline is challenging due to the safety and financial concerns, hence the patients should have timely access and adhere to the treatment. Further research with patients from all over India and long term follow-up is recommended for better understanding of effectiveness and safety profile of bedaquiline.

Conflict of Interest: None
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