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Study of sputum culture conversion at the end of intensive phase (I.P) in Bedaquiline versus non bedaquiline containing antitubercular regimen at NDR-TB Centre

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Abstract
Background: Bedaquiline and delamanid offer the possibility of more effective and less toxic treatment for multidrug-resistant (MDR) tuberculosis (TB). With this treatment, however, some patients remain at high risk for an unfavorable treatment outcome. The present study was undertaken to compare sputum culture conversion rate at the end of 24 weeks (I.P.) of bedaquiline containing antitubercular regimen with bedaquiline not containing antitubercular regimen. **Method:** Total 57 patients of MDR-TB and XDR-TB who were started on antitubercular regimen in the period between 2018 to 2020 were enrolled in the study. Patients were divided into bedaquiline containing antitubercular regimen and nonbedaquiline antitubercular regimen. Follow up sputum culture were done on 3rd, 4th, 5th, 6th month of treatment. Sputum sample is collected and send for culture in RNTCP accredited lab. Sputum culture conversion rate of bedaquiline regimen was compared with nonbedaquiline regimen. **Results:** Patients with bedaquiline (BDQ) containing regimen were 40 (70.18%) and 17 (29.82%) patients were seen on without BDQ containing regimen. Out of 57, 24 (60%) male patients were on bedaquiline (BDQ) and 12 (70.58%) were on without bedaquiline regimen, 16(40%) female patients were on BDQ and without BDQ there were only 5 (29%). Out of 40 patients who were started on BDQ containing regimen, 39 patients came negative at the end of 6th month, culture conversion rate was 97.5%. Whereas out of 17 patients who were started on without BDQ containing regimen, 13 patients came negative at the end of 6th month, culture conversion rate was 76.47%**. Conclusion:** BDQ containing regimen has significantly more culture conversion rate at the end of 24 weeks (Intensive phase) as compared to non BDQ containing regimen.
Keywords: Bedaquiline; Multidrug-resistant; Tuberculosis; Sputum culture; Antitubercular regimen

Introduction

Tuberculosis is an infectious disease usually caused by Mycobacterium tuberculosis (MTB) bacteria.[1] The emergence of drug-resistant strains of Mycobacterium tuberculosis has become a significant public health problem and has led to a setback in efforts to end TB in many countries. According to new PMDT guideline 2019 -5.58 lakhs cases of MDR/RR-TB estimated globaly and 1.35 lakhs cases estimated in India. Three countries accounted for approximately half of the world's cases of MDR/RR-TB: India (24%), China (13%) and the Russian Federation (10%).Also, the treatment success of MDR-TB remains low globally, at 55%, which further reduces to 40% in the presence of additional drug resistance to fluoroquinolones or /and second line injectable (MDRFQ/MDRSLI) (extensively drug-resistant TB) with 8% failure or relapse, 15% death and 23% default.[3][4]

In order to close the gap between diagnosis and treatment of drug resistant TB (DR-TB) and to increase the treatment success rate, we require newer diagnostics, higher coverage of drug susceptibility testing, easy access to appropriate treatment, and new medicines/treatment regimens that have higher efficacy and better safety.

Bedaquiline (BDQ) is a diarylquinolone, developed as TMC207 (Sirturo), is the first drug in a novel class approved for the treatment of TB since rifampin was approved in 1971.[5] Bedaquiline has shown bactericidal activity in vitro,in murine models of tuberculosis.[2] Bedaquiline was approved for medical use in the United States in 2012.[6]WHO also released interim policy guidance on the inclusion of BDQ in combination therapy for treating MDR-TB patients.[7] Considering the increasing number of DR-TB cases reported in India and as there was only limited experience available globally on the safety and efficacy of BDQ used under programmatic conditions, this drug was introduced under conditional access program (BDQ-CAP) in the country in line with the recommendations from the drug regulatory authority of India.[7]

The Apex Committee under Ministry of health and family welfare, Government of India approved the use of BDQ-CAP in November 2015.

Mechanism of action: Bedaquiline kills both dormant and actively replicating mycobacteria by inhibiting mycobacterial adenosine triphosphate (ATP) synthase, an essential membrane-bound enzyme, interfering with energy production and disrupting intracellular metabolism.[8][9]

Dose: 400 mg daily from 0-2 weeks

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200 mg thrice a week from 3-24 weeks

Pharmacokietics: Bedaquiline is well absorbed in human, reaching a peak concentration in 5 h, and subsequently the concentration declines in a triexponential fashion.[8][10] It has high volume of distribution, with extensive tissue distribution.

BDQ is highly protein bound (>99.9%).[11] It undergoes N-methylation primarily via hepatic CYP3A4 with contributions from CYP2C8 and CYP2C19 and it is primarily excreted fecally.[12] It has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping BDQ.It is given to adults & children aged 5 years to less than 18 yrs of age and weighing at least 15 kg, controlled stable arrythmia, pregnancy & lactating women.[13]

Side effects of BDQ: QT prolongation, nausea, vomiting, headache, etc.

AIMS & OBJECTIVES

- To estimate rate of the sputum culture conversion of at the end of 24 weeks (I.P.) of bedaquiline containing antitubercular regimen.
- To estimate rate of sputum culture conversion at the end of 24 weeks (I.P.) of bedaquiline not containing antitubercular regimen.
- To compare sputum culture conversion rate at the end of 24 weeks (I.P.) of bedaquiline containing antitubercular regimen with bedaquiline not containing antitubercular regimen

Materials and Methods

The study design was an analytical study conducted in Nodal DR-TB centre in Maharashtra. Total 57 MDR-TB & XDR-TB patients were included in the study during a period from 1Jan 2021 to 31Dec 2021. Convenience sampling method used for selection of patients.

Inclusion criteria- 1) Tuberculosis patients, with resistant to rifampicin and isoniazide with or without resistance to other first line drugs (MDR-TB) in RNTCP accrediated lab 2) A MDR-TB patient, with additionally resistant to a fluroquinolone and second line injectable aminoglycosides (XDR-TB) in RNTCP accrediated lab 3) Patients of age >18 years

Exclusion criteria- 1) Pregnancy and lactating mother 2) Patients age <18 yrs 3) Loss to follow up patients.

Methodology-

Systematic analysis of routinely collected programmatic data under Revisced National Tuberculosis Control Programme (RNTCP)/National tuberculosis elimination programme (NTEP). Patients of MDR-TB and XDR-TB who were started on antitubercular regimen in the period between 2018 to 2020 were included in the study. Patient's data was collected and divided into bedaquiline containing antitubercular regimen and nonbedaquiline antitubercular regimen. Patients follow up data on sputum culture was collected. Follow up sputum culture should be done on 3rd, 4th, 5th, 6th month of treatment. Sputum sample was collected and send for culture in RNTCP accrediated lab. Sputum culture conversion rate of bedaquiline regimen was compared with nonbedaquiline regimen.

Results & Discussion

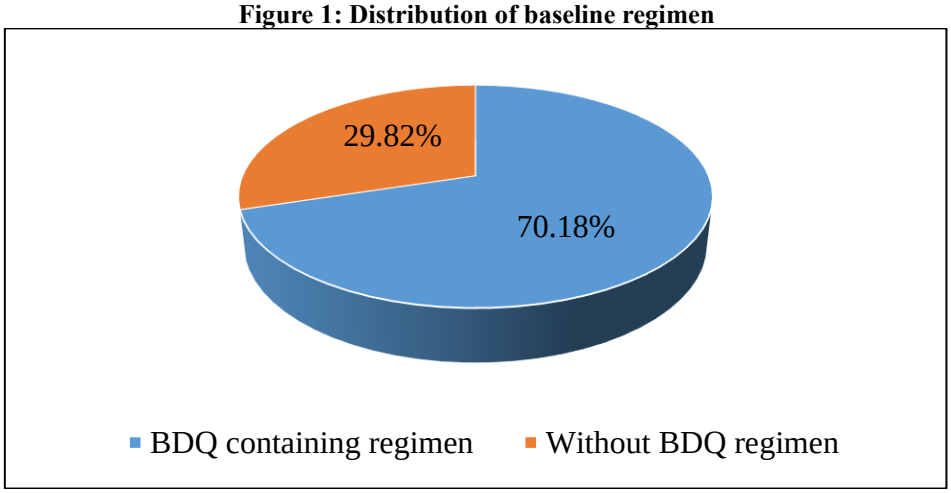
Out of 57, 24 (60%) male patients were on bedaquiline (BDQ) and 12 (70.58%) were on without bedaquiline regimen whereas 16(40%) female patients were on BDQ and without BDQ there were only 5 (29%), (Table 1).

Table 1: Demographic data presentation

Demographic data	With BDQ	Without BDQ
Male	24 (60%)	12 (70.58%)
Female	16 (40%)	05 (29%)
Total	40	17

In the following (figure1) study patients with bedaquiline (BDQ) containing regimen were 40 (70.18%) and 17 (29.82%) patients were seen on without BDQ containing regimen.

Figure 1: Distribution of baseline regimen



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Out of 40 patients who were strated on BDQ containing regimen, 39 patients came negative at the end of 6th month, culture conversion rate was 97.5%.

Out of 17 patients who were strated on without BDQ containing regimen, 13 patients came negative at the end of 6th month, culture conversion rate was 76.47%, (Table 2).

Table 2: Distribution of baseline regimen.

Baseline regimen	Culture type	On 6th Culture
BDQ containing regimen	Positive	01 (2.5%)
	Negative	39 (97.5%)
Without BDQ containing regimen	Positive	4 (23.52%)
	Negative	13 (76.47%)

CONCLUSION

BDQ containing regimen has significantly more culture conversion rate at the end of 24 weeks (Intensive phase) as compared to non BDQ containing regimen.

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