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The study of Bedaquiline implementation under the National TB Programme at NITRD, central India

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Background: Bedaquiline (BDQ) was approved for treatment of drug-resistant TB (DR-TB) under the Conditional Access Programme (CAP) of the Revised National Tuberculosis Control Programme (RNTCP). We present early efficacy and safety of BDQ-containing regimens for DR-TB. **Aim and Objective:** To ascertain the early efficacy and safety of bedaquline-containing regimens in the treatment of DR-TB. **Methods:** BDQ-containing regimens along with other drugs were designed as per WHO recommendations for DR-TB patients. They were followed up for sputum smear and culture conversion, adverse events during the treatment. **Results:** A cohort of 69 DR-TB patients (mean age: 30.22) were initiated on BDQ-containing regimens. Of the available sputum results, smear conversion was seen in 46.4% and 89.85% of patients at the end of the 1st week and 3rd month, respectively. Similarly, 92.54% and 95.45% of patients had culture conversion at the end of the 3rd and 6th months, respectively. 69 adverse events (AE), including 10 deaths. **Conclusion:** Bedaquiline, along with an optimized background regimen, has shown early sputum conversion in a larger number of difficult-to-treat patients having additional resistance to second-line drugs along with INH and Rifampicin. The regimen is feasible in programmatic conditions and is relatively safe.

Keywords: Bedaquiline, Tuberculosis, **NITRD**

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. It can affect any part of the body and any age group. Drug-resistant TB (DRTB) is a continuing threat. Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS). Millions of people continue to fall sick with TB each year [1]. According to the Global TB Report 2019, an estimated 10.0 million (range, 9.0–11.1 million) people fell ill with TB in 2018, a number that has been relatively stable in recent years. Globally, there were 1.2 million (range, 1.1–1.3 million) TB deaths among HIV-negative people in 2018 (a 27% reduction from 1.7 million in 2000) and an additional 2,51,000 deaths (range, 2,23,000–2,81,000) among HIV-positive people (a 60% reduction from 6,20,000 in 2000). Since 2007, TB has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1]

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India has the dubious distinction of being one of the high-burden countries for TB, TB-HIV, and MDR-TB as per WHO classification. There are an estimated 79,000 multidrug-resistant TB patients among the notified cases of pulmonary TB each year. Drug-resistant TB can be of various types. Multidrug-resistant tuberculosis (MDR TB) is defined as TB resistant to rifampicin and isoniazid. Pre-XDR TB is MDR TB with resistance to either fluroquinolone or a second-line injectable drug, and extensively drug-resistant TB (XDR-TB) is defined as MDR with additional resistance to a fluroquinolone and second-line injectable agents. In view of the poor treatment outcomes in MDR-TB patients [2], newer drugs (bedaquiline [3-4] and delamanid [3]) are being tried along with other agents (repurposed drugs [5-7] linezolid and clofazamine) in order to have better success rates. WHO recommends the use of bedaquiline for a maximum duration of 24 weeks. Nausea and hepatitis are the most common side effects associated with this drug. The Revised National TB Control Programme (RNTCP) recommended use of Bedaquiline in 2016 under the Conditional Access Programme (CAP). The National Institute of TB and Respiratory Diseases (NITRD) was one of the initial implementing sites under the CAP. The experiences of the Institute in respect of effectiveness and feasibility of Bedaquiline implementation under field conditions and the ADRs and their management are being shared.

Material and Methods

Study Design: It was an Observational Retrospective and Prospective longitudinal study.

Study Site: The study was conducted at the Department of Respiratory Diseases & Tuberculosis,Rajan Babu Institute for Pulmonary Medicine and Tuberculosis (RBIPMT), North Delhi Municipal Corporation, GTB Nagar, Kingsway Camp, Delhi-110009

Study period: Intake period started from 1st October 2018 to 30th April 2019. Every patient wasfollowed up at 3 months and 6 months of treatment; the last date of follow-up was31st October 2019.

Study Population: It was a hospital OPD and indoor-based study. All patients who had MDR failure, pre-XDR, and XDR PTB at the DRTB center of RBIPMT and who met our inclusion and exclusion criteria were taken up as a study group. The enrolment was done both through the outpatient department (OPD) and indoor patients.

Consent & ethical considerations

The study was carried out after obtaining approval from the Institutional Human Ethical Committee. An informed written consent was obtained from all the patients. Patients who showed voluntariness were enrolled in the study. All patients had the freedom of opting out of study at any point in time during study.

Patient inclusion criteria

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- All MDR Failure, Pre-XDR, and XDR TB patients registered for a fully oral bedaquiline-containing individualized treatment regimen under PMDT at the DR TB Center of RBIPMT under RNTCP.
- All patients who give written consent and are willing to pursue regular follow-up sputum culture for AFB and admission and further investigations if desired.

Patient exclusion criteria

- Extra pulmonary TB patients.
- Patients are not providing a sputum sample.
- Children less than 18 years of age
- Patients unfit for bedaquiline as per RNTCP criteria for biochemical tests and ECG

Sampling Technique: Every consecutive patient fulfilling inclusion and exclusioncriteria was enrolled to complete the sample size.

Data collection techniques and tools

Patients were identified from the PMDT register at the RBIPMT DR-TB Centre. Informed, written consent was taken from the patient who fulfilled the inclusion criteria for their inclusion in the study. Study subjects were enrolled, and proforma was filled as per Annexure 3 by the personal interview method. The socioeconomic status was determined by a modified Kuppuswamy scale. The X-rays were read as per the guidelines of the National Tuberculosis Association of the USA. Relevant investigations mentioned below will be performed. Patients were followed up at 3rd and 6th months. The results of expanded DST, 3rd, and 6th month cultures were obtained from the New Delhi TB Centre.

Statistical analysis

Descriptive statistics will be analyzed with SPSS version 18.0 software. Continuous variables will be presented as mean (SD) or median if the data is skewed. Categorical variables will be expressed as frequencies and percentages. Continuous variables will be analyzed using student t-tests as appropriate. Nominal categorical data between the groups will be compared using the chi-squared test. For all statistical tests, a p- value less than 0.05 will be taken to indicate a significant difference.

Results and Interpretation

The study was conducted at Rajan Babu Institute of Pulmonary Medicine & Tuberculosis Hospital and attached Kingsway chest OPD. A total of 69 patients were enrolled. A total of 5 patients died during the study, out of which 1 patient died before the 3rd month follow-up and 4 patients died between the 3rd and 6th month follow-up. Groups studied are given below.

Table 1: Demographic characteristics of the study population.

Patient characteristics	N	%

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Male	44	63.77
Female	25	36.23
Age (year)	30.22	
BMI (mean)	21.84	
HIV positive	1	1.15

Among the 69 study subjects, 63.77% were male and 36.23% were female, with a mean age of 30.22 years and a mean BMI of 21.84 kg/m2. The male-female ratio increased with age.

Table 2: Drug sensitivity profile of the study population.

Classification	**N**	**%**
PRE-XDR	62	89.86
XDR (FQ + SLI)	59	85.5
MDR-TB (failure)	3	4.34

Nearly 89.86% of the patients were pre-XDR (228/290). The individual drug sensitivity pattern showed 85.5% (59/69) were fluroquinolone resistant, and 4.34% (3/69) were second-line injectable resistant. In addition, the DST profile from amongst the available reports also indicated a high level of ethionamide resistance of 84.1% (58/69) and over 76.81% pyrazinamide resistance (53/69). Resistance to other second-line drugs was less than 2%. Most of the patients received high-dose Moxifloxacin (around 40%), second-line injectables (73%), linezolid (90%), Clofazamine (86%), Ethionamide (58%), and Cycloserine (60%). Some patients required in addition other WHO group D3 (currently group C) drugs. Among the available smear results, more than 50.7% (35/69) were smear negative at the end of the first week, 90.9% were negative by the 12th week, and 95.65% (66/69) by the 24th week. Among the available culture results, 94.2% by the 3rd month and 97.1% were culture negative at the end of 6 months.

The number of adverse events reported among the study subjects was 69 episodes in 25 patients. 36.2% of episodes were mild, 28.98% were moderate, and 37.68% were severe adverse events. recting the electrolytes (magnesium, potassium, calcium). The other notable ADRs like neuropathy, eye changes, and bone mQTc prolongation were reported in 21.7% (15 patients). QTc orrecting the electrolytes (magnesium, potassium, calcium). The other notable ADRs like neuropathy, eye changes, and bone marrow suppression were related to linezolid. There were significant coordination issues during treatment in the field conditions in the context of follow-up investigations (ECG, sputum examination, and blood tests) and reporting and management of ADRs.

Table 3: Smear and culture conversion of the study population after initiation of treatment.

Period	**Smear**		**Culture**	
	Positive	**Negative**	**Positive**	**Negative**
Week 1	32(46.4)	33(47.8)	35	26

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Month 3	28(40.6)	62(89.85)	10(14.71%)	58(85.29%)
Month 4	3(4.3)	48(69.6)	5(7.46%)	62(92.54%)
Month 5	2(2.9)	45(65.2)	3(4.54%)	63(95.45%)
Month 6	1(1.4)	46(66.7)	66(100%)	64(100%)

Table 4: Frequency of adverse drug events grouped by body system.

Reported AE by body system	**N**	**%**
Gastrointestinal	4	5.8
Respiratory	1	1.4
Hepatotoxicity	1	1.4
Peripheral neuropathy	10	14.5
QT prolongation	18	26.1
Neurological disorder/headache	6	8.7
Cardiac event (includes hypotension)	2	2.9
Ototoxicity	4	5.8
Others	1	1.4
Dermatological	7	10.1
Nephrotoxicity	0	0
Haematological	7	10.1
Musculoskeletal	1	1.4
Ophthalmologic	5	7.24

Discussion

The study was carried out at Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, a tertiary care institute for respiratory diseases and tuberculosis under the North Delhi Municipal Corporation. RBIPMT was one of the six institutes where BDQ under CAP was started in 2016. WHO, in a rapid communication in 2018, moved towards a BDQ-containing fully oral longer regimen. BDQ-containing regimens are in use throughout the country as per PMDT 2017 guidelines. RBIPMT is the first institute to roll out a fully oral BDQ-containing longer regimen.

The majority were in the younger age group, and the male-female ratio increased with age. Only one patient was HIV reactive among the study subjects. Resistance to Pyrazinamide was much higher at 83% as compared to other studies (3-42%). [8] This is important in the context of designing the OBR. The OBR of individual patients was designed by the DR-TB Review Committee based on the patient's previous treatment history, exposure to previous anti-TB drugs, drug sensitivity pattern, and pre-treatment evaluation reports. The regimen was designed based on national guidelines for programmatic management of drug-resistant tuberculosis. Similar results were observed with culture. Similar observations have also been reported in other studies. [9]

The interim analysis of this cohort of MDR-TB patients receiving bedaquiline shows a culture conversion rate of 96% at 6 months. This was comparable with other patient cohorts. [9-10] The loss to follow up is only around 7.2% (5/69) which is much less than other studies wherein it has been reported as above 20%. [1, 11-12] The reported adverse events were 69 episodes, with 37.7% serious adverse events. The main safety concern of Bedaquiline is cardiotoxicity. Bedaquiline has been shown to prolong the QT interval, and the association with other drugs such as clofazamine or moxifloxacin can enhance this effect. The QTc prolongation was detected through routine monitoring with regular electrocardiography. In most cases, it was found to be related to electrolyte disturbances, however, it did not result in permanent discontinuation of bedaquiline. It was temporarily withheld, and once the electrolytes were corrected, the bedaquiline and other QTc-prolonging drugs could be reintroduced.

It was permanently discontinued in only four patients. This is important because most patients received at least one other QT-prolonging drug (clofazamine or high-dose moxifloxacin) in addition to Bedaquline. The management of cardiotoxicity needed timely ECG, electrolyte testing, and correction of electrolytes. Linezolid was also found to lead to a large number of adverse events like anemia, thrombocytopenia, and peripheral and optic neuritis. The same has also been reported by other researchers. [13-14] Training the treatment supporters in recognizing the commonly occurring adverse reactions and referring the patient to an appropriate treatment facility providing timely action can lead to greater adherence to treatment and a reduction in loss to follow-up. There are 5 deaths reported in the study; most of these were due to poor general condition at the onset of treatment. This was comparable to the 13% deaths reported by Diacon et al. [15] Most deaths (53%) happened in the first three months of the treatment. More than 2/3rd of all deaths were culture converted before dying, reducing the risk of spread of pre-XDR/XDR TB. Regular training for all levels of health personnel, including treatment supporters, is important in the management of MDR and XDR TB.

Conclusion

This study concluded that regimens containing Bedaquiline are effective as they lead to early smear and culture conversion. Adverse reactions do occur with these regimens but are manageable. Implementation in the field is feasible; however, it requires strengthening of infrastructure in terms of training the peripheral staff for early identification and management of common adverse drug reactions and making ECG and electrolyte testing available. Also needed is developing coordination and linkage mechanisms for timely referral and management of adverse drug reactions.

Reference

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019.
2. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug-resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9. e1001300.
3. World Health Organization. The Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis Interim Policy Guidance. Geneva, Switzerland: WHO; 2013. WHO/HTM/TB/2013.6.

4. European Medical Agency. Bedaquiline (Sirturo): Summary of Product Characteristics London. UK: EMA; 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002614/WC500163209.pdf. Accessed January 2019.
5. Gualano G, Capone S, Matteelli A, Palmieri F. New antituberculosis drugs: from clinical trial to programmatic use. Infect Dis Rep. 2016;8(2):6569. https://doi.org/10.4081/idr.2016.6569. Published 2016 Jun 24.
6. Sharma D, Dhuriya YK, Deo N, Bisht D. Repurposing and revival of the drugs: a new approach to combat the drug-resistant tuberculosis. Front Microbiol. 2017;8:2452. https://doi.org/10.3389/fmicb.2017.02452.
7. Silva DR, Dalcolmo M, Tiberi S, et al. New and repurposed drugs to treat multidrug- and extensively drug-resistant tuberculosis. J Bras Pneumol. 2018;44(2):153e
8. Zignol M, Dean AS, Alikhanova N, et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. Lancet Infect Dis. 2016;16:1185e https://doi.org/10.1016/S1473-3099(16) 30190-6.
9. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drugresistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis. 2015;19:979e
10. Guglielmetti L, Le Duˆ D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis. 2015;60:188e
11. World Health Organization. Global Tuberculosis Report, 2016. Geneva, Switzerland: WHO; 2016. WHO/HTM/TB. 2016.
12. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicenter study. Eur Respir J. 2017;49:1700387. https://doi.org/10.1183/13993003.00387-2017.
13. Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety, and tolerability of linezolid-containing regimens in treating MDRTB and XDR-TB: systematic review and meta-analysis. Eur Respir J. 2012;40:1430e
14. About the endTB Project. Geneva, Switzerland: endTB; 2017. http://www.endtb.org/about. Accessed January 19.
15. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009;360:2397e