IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 2 Ser.8 (February. 2020), PP 33-38
www.iosrjournals.org

Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant –Tuberculosis

Dr BabuSatesh Kumar Seelam[1], Dr P Hima Sanjana[2], Dr D Sudheer[3], Dr J Triveni[4], Dr Ch R N Bushan Rao[5], Dr Sudeena[6]

[1](Postgraduate, Department of Pulmonary medicine, Guntur Medical College, Guntur),
[2](Intern, Guntur Medical College, Guntur)
[3](Assistant Professor, Department of Pulmonary medicine, Guntur Medical College, Guntur),
[4](Medical officer, Nodal DR-TB Center, Guntur Medical College, Guntur)
[5](Professor & HOD, Department of Pulmonary medicine, Guntur Medical College, Guntur)
[6](Associate Professor, Department of Pulmonary medicine, Guntur Medical College, Guntur)
Corresponding Author: Dr P Hima Sanjana[2] (Intern, Guntur Medical College, Guntur) D/o Dr P Srinivasa Rao, 12-19-100, Head Post Office Road, Kothapet, Guntur, 522001

Abstract
Background: *Drug-resistant tuberculosis (DR-TB) is a global health problem with notoriously tricky and challenging treatment. In 2012, the Food and Drug Administration approved the use of bedaquiline fumarate as part of combination therapy for multidrug-resistant tuberculosis (MDR TB). The use of bedaquiline in MDR and XDR TB treatment regimens appears to be effective and safe across different settings, although the certainty of the evidence assessed was very low.*
Aim: *To determine outcomes of bedaquiline Treatment in Patients with Drug-Resistant Tuberculosis*
Materials and methods: *It is a prospective study conducted in Nodal DR-TB center, Department of Pulmonary Medicine, Guntur Medical College, Guntur. 60 cases of pre-XDR and XDR TB are treated with bedaquiline for 6 months as part of an anti-TB regimen constructed according to WHO guidelines and follow up done up to 12 months (monthly for 6 months and quarterly till 12th month) after initiation of treatment. The outcome of interest considered in this dataset was sputum conversion rate, mortality, treatment success rate, and serious adverse events experienced by patients during treatment.*
Results*: A total of 60 confirmed pre-XDR TB and XDR TB cases included in the study. Sputum conversion to negative in 49 cases at the end of 3rd month, 6 in 4th month, 1 in 5th and 6th month each. Among the complications reported, 16.66% are gastrointestinal, followed by 10% cardiovascular, 5% neurological, 5% hematological, and 1% psychiatric illness. Most of these complications are the first 6 months. Only 11.66% of mortality reported.*
Conclusion: *Faster sputum conversion, better tolerability, better response with Bedaquiline combining regimen.*
Keywords: *Bedaquiline, pre-XDR TB, XDR TB, CBNAAT, LPA, Lost to follow up after treatment, outcome, safety, adverse effects.*

Date of Submission: 30-01-2020 Date of Acceptance: 15-02-2020

I. Introduction

The emergence of drug-resistant tuberculosis (DR-TB) is a major global problem to control TB. In 2013, the World Health Organization (WHO) estimated that 4,80, 000 people developed multidrug-resistant TB (MDR-TB), of which 2,10, 000 died *(***1***).* MDR-TB is a form of TB caused by a Mycobacterium tuberculosis (MTB*)* strain resistant to at least Rifampicin and Isoniazid. Resistance with Fluroquinalones and Aminoglycosides are called XDR-TB, Resistance to either aminoglycosides or fluoroquinolones are called pre-XDR-TB.

In the 2010 cohort of detected cases, only 48% were successfully treated, as a result of a high frequency of death (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors. Ninety-two countries have reported at least one case of extensively drug-resistant TB (XDR-TB), a form of MDR-TB with additional resistance to fluoroquinolones and second-line injectable drugs.

Current treatment regimens for MDR-TB patients are far from satisfactory. These usually require at least 20 months of treatment with a combination of second-line drugs that are more toxic and less effective than the drugs used to treat drug-susceptible TB. The treatment success rates were 64% with individualized regimens

and 54% with standardized treatment *(***2,3***)*. On average, an estimated 9.6% of MDR-TB cases have XDR-TB. Treatment options for XDR-TB patients are even more limited, and with lower cure rates compared to MDR-TB.

Second-line drugs may have significant interactions with other drugs used to treat comorbidities often associated with TB, such as antiretroviral treatment for human immunodeficiency virus (HIV) co-infected subjects. These drug interactions may be responsible for limited drug efficacy, or increased organ toxicity, and side-effects, thus posing an additional challenge to treatment completion in co-infected patients (**4-8**). For all these reasons, new TB drugs and novel regimens needed to enable faster, safer, less toxic, and more effective treatment for persons with drug-resistant TB.

Bedaquiline is a new anti-TB drug to be introduced into the market in almost 50 years. The drug belongs to the diarylquioline family and has a novel mechanism of action against *M. tuberculosis (***9***)*. The drug is given daily for two weeks and then thrice weekly for a total of six months *(***10***)*. It has a long half-life of almost five-and-a-half months. The drug was approved under an accelerated procedure by the USFDA in December 2012 *(***11***)* and conditionally approved by the EMA in February 2014 *(***12***)*. World Health Organization recommends Bedaquiline for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB).

II. Methodology

***Study design*:**

It is a prospective study conducted among 60 subjects of confirmed pre-XDR-TB, XDR TB patients for 1 year. Patients treated with bedaquiline from October 2018 to September 2019 and hospitalized in DR-TB nodal center, Department of Pulmonary Medicine, Guntur Medical College, Guntur, A.P included. CBNAAT and LPA positive for MTB and resistant to at least Isoniazid (INH) and Rifampin (RIF) , Fluroquinalone or/and Aminoglycoside resistant cases are taken. Standard definitions of MDR-TB and XDR-TB and treatment outcomes assigned according to WHO definitions [**13**].

Ethics:

Local Institutional ethics committees approved the protocol at all study sites approval no: GMC/IEC/226/2019. The study conducted following the principles of the Declaration of Good Clinical Practice, and all patients (or their representatives) provided written informed consent.

***Objectives*:**

Assessment of the Effectiveness, Safety, and Survival performance indicators from the cohorts of pre-XDR-TB and XDR TB patients who receive treatment with bedaquiline.

a. Effectiveness - through the evaluation of treatment outcomes in cohorts of patients treated with bedaquiline in addition to (optimized) background regimen,

b. Safety - through the evaluation of the type, frequency, severity, and seriousness of adverse events related to the use of bedaquiline;

c. Survival - through evaluation of the mortality rates when receiving bedaquiline (and related causes of death).

Patients and treatment

Inclusion criteria: Pre XDR-TB, XDR-TB cases and age >18 years patients (one patient < 18 years included as there was no delamanid treatment at that time)

Exclusion criteria: MDR‑TB cases, age less than 18 years, pregnancy, and concurrent major medical or psychiatric illness.

Standardized regimen provided under supervision. Intensive phase (IP) with six drugs - KM, OFX or LFX, ETO, CS, PZA, EMB. Continuation phase (CP) with four drugs - OFX, ETO, CS, and EMB. Duration of IP for a minimum of 6 months extended up to 9 months in patients in case culture positive at the 4th month of treatment followed by CP for a minimum of 18 months, leading to a total duration of 24-27 months of treatment. Dosage according to weight band: Patients weighing<45 kg - KM (500 mg), ETO (500 mg), CS (500 mg), OFX (600 mg) or LFX (500 mg), PZA (1250 mg), and EMB (800 mg) and patients weighing ≥45 kg - KM (750 mg), ETO (750 mg), CS (750 mg), OFX (800 mg) or LFX (750 mg), PZA (1500 mg), and EMB (1200 mg). Drugs provided free of cost to the patients every month.

All Patients were followed up for cultures monthly for 6 months and quarterly for the next 6 months. All TB cases were CBNAAT positive. Standard definitions for MDR-TB and XDR-TB, sputum conversion, adherence to the treatment, and treatment outcomes up to 12th month were assigned according to WHO definitions [**14**].

Treatment Outcome:

Death: Patient died for any reason during MDR‑TB treatment Still on treatment: When for any reason, was receiving the treatment at the time of preparation of treatment outcome report

Lost to follow‑up or default: When initiated on a prescribed regimen but did not turn up for follow‑up during any stage of the
study

Smear conversion: Two negative consecutive sputum smears after treatment initiation

Culture conversion: Two consecutive negative cultures after treatment initiation

Diagnosis:

Pretreatment investigations included CBNAAT and LPA for MTB and drug sensitivity to first and second-line drugs, complete haemogram, chest X‑ray, renal and liver function tests, and thyroid profile, ECG, and human immunodeficiency virus (HIV) infection before the initiation of treatment. CBNAAT has done at Nodal DR-TB center, Guntur, with the GXIV-4-D processing unit, procured from Cepheid, USA. LPA by reference center, Vizag through GT-Blot 48 Hain life science GmbH, Nehren, Germany. ECG by Philips ECG Machine TC20, Top 12 channel and reviewed by a cardiologist from the department of cardiology, Guntur medical college, Guntur.

III. Results

After a complete evaluation, 60 cases of confirmed pre XDR TB and XDR TB cases by CBNAAT and LPA included, and Bedaquiline started along with other MDR TB drugs. Among 60 cases, 4 cases are HIV positive, 2 are male, and 2 are female patients. 42(70%) male and 18(30%) are female patients with median weight of 40kg, most of them are 31 to 50 years of age(no.32) followed by 21 to 30 years(no.12), 51 to 60 (no.7), 61 to 70(no.5) and 71 to 80. 30% from urban areas, 70% are from rural areas. Only one patient is in the pediatric age, i.e.,13 yrs female and, she is XDR-TB case.

Sputum converted to negative 49 cases in 3 months, 6 are in 4^{th} month, 1 in 5^{th} and 1 in 6^{th} month.

Among the complications, 16.66% gastrointestinal, followed by 10% cardiovascular, 5% neurological, 5% hematological, and 1% psychiatric problems. Most of these complications are within 6 months. 10 cases died during the treatment, and all are HIV nonreactive, 6 patients had smoking and alcohol history, 3 are diabetic.

Table:1

Baseline patient demographic and clinical characteristics	
Characteristics	***n* (%)**
Age distribution (years)	
≤20	3 (5)
21-30	12 (20)
31-40	16(26.6)
41-50	16(26.6)
≥ 51	13(13.6)
Sex distribution of patients	
Male	42(70)
Female	18 (30)
Geographical distribution	
Urban	44 (73.3)
Rural	16 (26.6)
Weight (kg)	
≤30	6 (10)
31-40	17(28.3)
41-50	18 (30)
51-60	12 (20)
≥61	8 (13.3)
BMI (Kg/m^2)	21.28 ± 10.17
Type of DR TB pattern	
Pre XDR TB	
Male	28(46.6)
Female	15(25)
XDR TB	
Male	4(6.6)
Female	3(5)
Risk factors	
Alcoholism	18 (30)
Diabetes mellitus	7(11.66)
Smoking	23(38.3)
HIV Status	4(6.6)

Diagram.1: Pie diagram showing duration of sputum conversion after initiation of treatment.

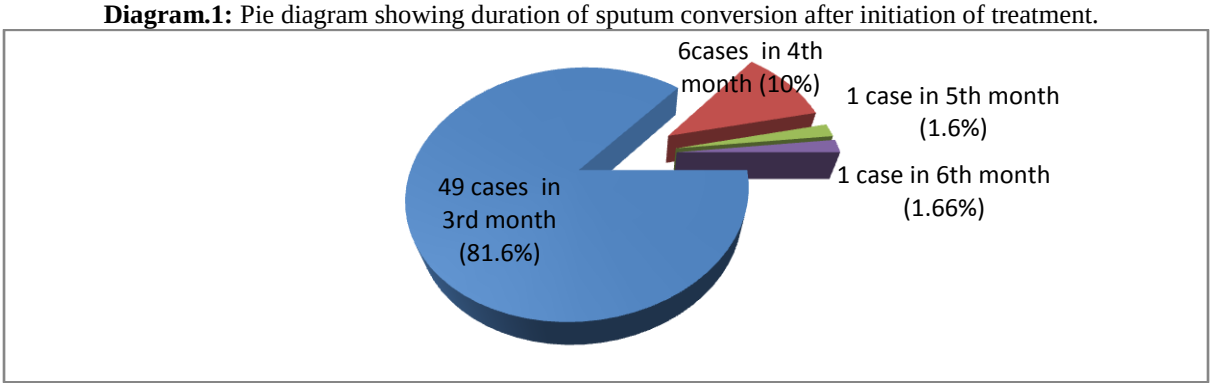
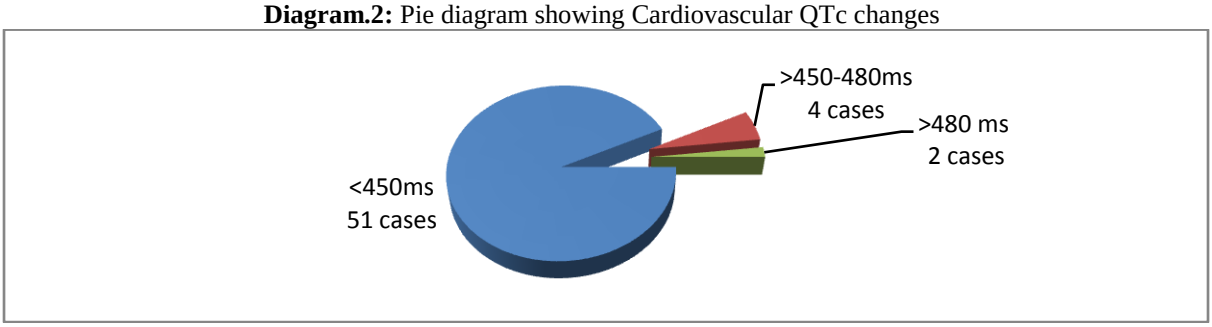


Table.2. Incidence of treatment-emergent adverse events.

s.no	Type of system involved	0– 6 months	7–12 months
1	Anemia	3 (5%)	-
2	Gastrointestinal	9 (15%)	1 (1.66%)
3	Psychiatric problems	1(1.66%)	-
4	Cardiovascular QTc changes	4 (6.66%)	2 (3.33%)
	< 450	51 (85%)	
	>450 -480	3 (5%)	1(1.66%)
	>480	1 (1.66%)	1 (1.66%)

Diagram.2: Pie diagram showing Cardiovascular QTc changes



The patients having no culture conversion, as well as those who died or who discontinued before the considered time point, were termed as lost to follow-up in the current study. Total cases dead were 10. Deaths in 0-6 months during the treatment period were 8 (13.33%), while 7-12 months after treatment were 2 (3.33%). 3 deaths reported without sputum conversion.

IV. Discussion

The emergence of drug-resistant tuberculosis (TB) is a significant threat to global TB care and control. On average, an estimated 9.6% of MDR-TB cases have XDR-TB. Treatment options for XDR-TB patients are even more limited, and with lower cure rates compared to MDR-TB. In a subset of 200 XDR-TB patients in 14 countries, treatment success was achieved in only 33% while 26% of the patients died ***(*3,4,15*)***

To assist countries preparing for introduction of new drugs or treatment regimens under programmatic conditions, the WHO initiated a process in 2012 to (i) develop ad hoc policy recommendations for TB treatment with new drugs; and (ii) assist countries to prepare for safe and effective uptake of these new drugs or regimens under programmatic conditions ***(*5*)***. It also aims to complement existing and new policy guidance on the use of new drugs for the treatment of TB or MDR-TB.

Out 0f 60 cases 73.3% are male, 26.6% are female patients respectively. Most of them are middle-aged groups between 30 to 50 years, 75% are from rural areas, 25% are from an urban area with an average body weight between 31 to 50 kg. Most of the cases in our study are from rural areas between 21 -30 years (table.1). The increasing cases from rural areas may be due to social stigma, lost-to-followup, lack of understanding of the disease, and duration of medication.

Patients treated with bedaquiline containing regimen are 88.33% pre-XDR TB, 11.66% XDR TB type of drug resistance pattern. Among these cohorts, 93.33% are resistant to fluoroquinolone, 6.33% are resistant to second-line injectable drugs. The successful outcome reported in our study is 83.33%. 5% are lost to follow up, and 11.33% died among remaining the remaining 16.33% cases.

Bedaquiline started in 60 confirmed cases of pre-XDR and XDR TB, treated for 24 weeks, and we followed up sputum conversion up to 54 weeks. 81.66% had sputum conversion in the 3rd month, 10% in the 4th month, and 1.66% in the 5th and 6th months each. The end sees 81.66% of the sputum conversion rate of 3rd month and 95% by the end of 24 weeks, whereas unknown (Lost to follow up after treatment) is 5%. In Andreas H. Diacon et al. study, the median time to sputum-culture conversion was faster in the bedaquiline group than in the placebo group (83 days vs. 125 days), culture conversion at both 24 and 120 weeks (**9**). Our study concludes sputum conversion in 81.66% of patients less than 90days. It confirmed the sputum conversion is faster in Bedaquiline containing regimen than without Bedaquiline containing regimen.

16.66% of cases had gastrointestinal system complications of which diarrhea was shared, followed by nausea and vomiting. Cardiovascular system complications are 2nd most common with QTc prolongation seen in 10% of cases followed by anemia, neurological, and psychiatric illness. Most of the complications reported within 6 months. No severe hepatotoxicity or renal dysfunction reported. Among 60 cases, QTc prolongation between 450-480ms reported in 4 cases, >480ms in 2 cases. One patient died in 2nd month, and 2 patients died within 1 month of the treatment due to the severity of the illness, but not due to QTc prolongation. Median increases in the QTc interval were small or non-existent in the group as a whole and resolved without changing the treatment regimen. Andreas H. Diacon et al. study The most frequent adverse events were nausea, arthralgia, and vomiting; our study is correlating with this study (**9**).

Our study adds some information about the use of bedaquiline in persons living with HIV on ART therapy, showing favorable outcomes without serious adverse events and nil mortality, concluding that the safety and culture conversion outcomes for HIV patients on ART with pre-XDR- and XDR-TB, suggest that BDQ maybe both efficacious and safe.

Table: 3.

Summary of the characteristics and evolution of patients who died or experienced adverse events.

s/n	Death after initiation of BDQ (In month)	Type of DR TB	Sputum conversion in months after initiation of BDQ	Age & Gender	Associated risk factors					**Cause of death estimated after Death audit (Verbal autopsy and Medical Autopsy)**
					HIV	DM	Smoking	Alcohol	COPD	
1	5th	Pre XDR	4th	30 - M	NR	-	+	+	+	COPD with Type 2 Respiratory failure
2	11th	Pre XDR	3rd	19 - F	NR	-	-	-	-	Severe Anaemia and Malnutrition
3	3rd	Pre XDR	3rd	54 - M	NR	+	+	-	-	Death after post CABG while under BDQ treatment
4	5th	Pre XDR	4th	35 - M	NR	-	-	+	-	Alcoholic cirrhosis and Ascites
5	6th	Pre XDR	3rd	34 - M	NR	+	+	+	-	Cardiac – Prolonged QTc
6	9th	XDR	3rd	47 - M	NR	-	+	+	-	Cardiac - prolonged QTc
7	2nd	Pre XDR	-	35 - F	NR	-	-	-	-	Extensive disease
8	0	Pre XDR	-	63 - M	NR	-	-	-	-	Massive Hemoptysis
9	4th	Pre XDR	3rd	40 - M	NR	-	+	+	+	COPD with Type 2 Respiratory failure
10	0	Pre XDR	-	45 - M	NR	+	+	+	-	Extensive disease
					0	3	6	6	2	

Mortality was 11.66%, which was high in the first 6 months. 3.33% died within one month and 1.66% in 2nd month of the treatment due to extensive lung lesions, 3.33% died due to QTc prolongation, rest of them died probably due to associated risk factors. Andreas H. Diacon et al. study, there is a risk of increased QTc prolongation for bedaquiline in combination with other QT-interval–prolonging drugs, such as fluoroquinolones (**9**). There is a risk with Bedaquiline, but it is not significant, Regular cardiac evaluation and follow up should be done in elderly and patients with associated cardiovascular risk factors.

The limitations of our study are that the follow up not extended up to treatment completion, no comparison group with regimen without bedaquiline, and finally small study population.

V. Conclusion

Our results show promising outcomes in the reassuring safety profile of combining bedaquiline to pre-XDR and XDR TB regimen, results in faster sputum conversion, well-tolerated, with modest QTc prolongation. Therefore not only effective, safe, and better survival, but also achieving reduced risk of evolution to a more resistant subtype and reducing the period of person-to-person transmission of MDR-TB, which considered to be considerable hurdles to the ambitious goal of elimination of TB by 2025.

References:

[1]. World Health Organization. Global Tuberculosis Report 2015. Geneva, World Health Organization, 2015.
[2]. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009; 9: 153–161.
[3]. Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. Int J Tuberc Lung Dis 2016; 20: 177–186.
[4]. 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.
[5]. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J.2017; 49:1700387.
[6]. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017;49:1602308.
[7]. World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis 2018 update. 2018 [cited 2019 Jan 15].
[8]. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis. 2004;8:1382–4.
[9]. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014; 371: 723–732.
[10]. Pym AS, Diacon AH, Tang S-J, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2016; 47: 564–574.
[11]. Lu X, Smare C, Kambili C, El Khoury AC, Wolfson LJ. Health outcomes of bedaquiline in the treatment of multidrug-resistant tuberculosis in selected high burden countries. BMC Health Serv Res. 2017;17:87.
[12]. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. 2013 [cited 2018 Mar 19].
[13]. World Health Organization. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva, World Health Organization, 2014.
[14]. Weiss P, Chen W, Cook VJ, Johnston JC. Treatment outcomes from community‐based drug-resistant tuberculosis treatment programs: A systematic review and meta‐analysis. BMC Infect Dis 2014;14:333.
[15]. Van Deun A, Salim MA, Das AP, Bastian I, Portaels F. Results of a standardized regimen for multidrug‐resistant tuberculosis in Bangladesh. Int J Tuberc Lung Dis 2004;8:560‐7.

Dr P Hima Sanjana. "Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant – Tuberculosis." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(2), 2020, pp. 33-38.