Outcomes of bedaquiline-containing regimen in the treatment of adults with drug-resistant tuberculosis in a tertiary care center in Rajasthan

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Abstract

The emergence of drug-resistant strains of *Mycobacterium tuberculosis* has become a significant public health problem and has led to a setback in the efforts to end tuberculosis (TB) worldwide. The longer duration, heavier pill load, and higher toxicity profile of drug-resistant TB regimens compared to those for drug-susceptible TB lead to reduced adherence and worse treatment results, including mortality. This study was conducted to estimate treatment outcomes and adverse effects in patients with drug-resistant TB on a bedaquiline-containing regimen. Patients after the pre-treatment evaluation were enrolled in a bedaquiline-containing regimen. These patients were followed up for 18 months, and the final outcome was assessed along with the adverse effects. It was found that 49 (84.4%) patients achieved culture conversion by 3 months, 54 (93.1%) achieved culture conversion by 6 months, 52 (83.81%) had favorable outcomes (cured, treatment completed), and 10 had unfavorable outcomes (died, lost to follow-up, failed). Coupled with gradually increasing trends in success rates since 2012, lesser failure rates and fewer concerns regarding grave adverse effects are a silver lining in the cloud of increasing burden and widening resistance patterns. More funding has to be directed towards ensuring adherence and finding high-risk individuals to expedite the achievement of sustainable development goals.

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Introduction

Tuberculosis (TB) is a communicable disease that is a major cause of morbidity, one of the top 10 causes of mortality, and the leading cause of death from a single infectious agent [1]. The World Health Organization (WHO) estimates that up to half a million new cases of multidrug-resistant TB (MDR-TB) occur each year globally, of which India (24%), China (13%), and the Russian Federation (10%) account for approximately half of the world's total [1]. Globally, between 2015 and 2020, the newly diagnosed MDR-TB rates were relatively stable, but they rose in 2021. This increase as a blow in the face of sustainable development goals is considered to be a consequence of the COVID-19 pandemic on TB detection [2]. Advanced resistance patterns, especially resistance to second-line injectable drugs, have been found to be a significant predictor of poor long-term survival in some studies [3]. In light of this, the WHO issued a conditional recommendation for bedaquiline use in adult MDR-TB patients in 2015, which was scaled up to fully oral regimens by 2022.

Materials and Methods

In collaboration with the district TB Center of Kota, a prospective observational study was conducted on patients registered through the programmatic management of drug-resistant TB (PMDT) between July 2020 and July 2021. In consideration of the decentralization of MDR-TB care, other districts coming under the catchment area of the nodal center of Kota were also included

in this research study. All patients chosen to be started on bedaquiline and who underwent pre-treatment evaluation within the last month were admitted and were started on bedaquiline. For each patient, apart from baseline physical, radiological, and biochemical parameters, to look for associated risk factors, additional data on previous anti-tuberculosis treatment, comorbidities, education, and contact history were also collected *via* patient interview. After the pre-treatment evaluation, patients were started on all longer oral regimens containing bedaquiline, levofloxacin/moxifloxacin, linezolid, clofazimine, and cycloserine, along with pyridoxine (100 mg). The primary outcome measures were considered as per the PMDT guidelines, as follows: cured/treatment completed/loss to follow-up/died. Patients who have completed the treatment and for whom final culture reports are awaited were categorized as having completed the treatment. Sputum conversion rates and radiological and clinical improvement were considered to determine the final outcome of the patients. Apart from this, adverse drug reactions were noted and categorized.

All the demographic and clinical data collected during pre-treatment evaluation and follow-up was recorded in proformas, which were later entered into Microsoft Excel (Microsoft Inc., Redmond, WA, USA). After ensuring the completeness of the data, descriptive analysis was done. Measures of association were computed based on the type of variables. Categorical variables were compared using the Chi-square (c^2 test), and continuous variables were recorded as medians and interquartile ranges. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) software version 29.0 (IBM, Armonk, NY, USA).

Ethical approval was obtained from the Institutional Ethical Committee (No. F.3/Acad/Ethical clearance/2021/51 dated 3.05.2021). Access to patient data from registers and the online Nik Shay portal was given by the department head and corresponding district TB officer. For follow-up, verbal consent from the caregivers of the patient was also obtained.

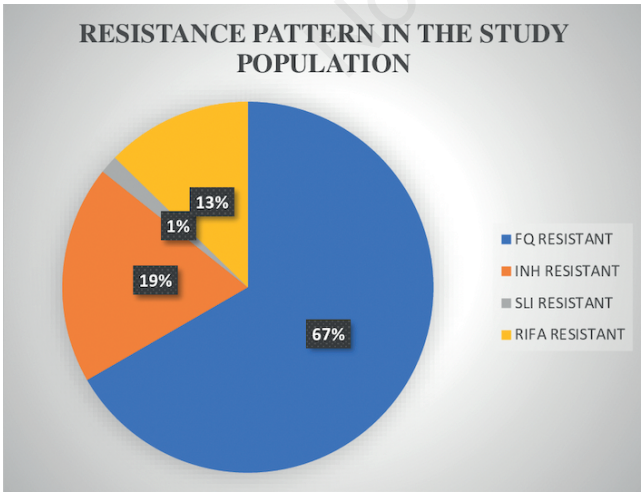

Figure 1. Pie chart showing resistance pattern in the study population. FQ, fluoroquinolone; INH, isoniazid; SLI, second line injectables; RIFA, rifampicin.

Results

Patient demographics

We enrolled about 62 patients during the aforementioned study period, among whom 44 (71%) were males and 18 (29%) were females. The sample's mean age was 37.58±15.196. The demographic and clinical details of the study population have been summarized in Table 1 and Figure 1. The resistance pattern has been summarized in Figure 2. First-line and second-line probe assay (LPA) were used for drug susceptibility testing (DST), but LPA reports were not available for all patients due to insufficient facilities during the COVID-19 pandemic. Among these 62 patients, bedaquiline was substituted for SLI in 39 patients, of whom 7 had failed on a shorter regimen with second-line injectables. The remaining 32 patients were started on a bedaquiline-containing regimen based on the DST reports.

Adverse effects

During the treatment of the enrolled participants, 57 of them, which accounts for about 91.9%, reported at least one adverse event (Table 2). Among these, two events were considered unrelated to the treatment, as no causation could be attributed to any drugs. 55 of these events required treatment in one form or another, but not all events led to hospitalization. The most common adverse effects observed were electrolyte imbalance (40.3%), gastrointestinal (38.59%), elevated transaminases (17.54%), cardiac (15.78%), and musculoskeletal (12.28%). The most common electrolyte imbalance observed was hypokalemia, which was corrected before discharge following the initiation of bedaquiline. Peripheral neuropathy and seizures were the neurological side effects encountered, among which 9 patients had peripheral neuropathy and one

Table 1. Patient demographics.

Variables	Number	%
Gender		
Male	44	71
Female	18	29
Age		
18-25 years	16	25.8
26-50 years	31	50
>50 years	13	20.96
Sputum smear-positive	40	64.51
Sputum CBNAAT positive	59	95.16
Extrapulmonary TB	3	4.83
BMI		
<18.5 kg/m^2	30	48.3
>18.5 kg/m^2	32	51.61
HIV co-infection	0	0
Anaemia	37	59.6
Diabetes	11	17.74
Hypertension	7	11.2
Previous history of anti-tuberculosis therapy	45	72.5
Malignancy	1	1.6
Cerebrovascular accident	1	1.6

CBNAAT, Cartridge based nucleic acid amplification test; BMI, body mass index; TB, tuberculosis.

had seizures, none of which warranted discontinuation of any drug. Though cardiac adverse effects were a major concern in bedaquiline under a conditional access program, the frequency was minimal in our study but had major implications. The median corrected QT interval (QTc) during the pre-treatment evaluation was found to be 380 ms (±39.215) with an average fluctuation of 53.71 ms during the first 14 days of treatment.

Table 3 and Figure 2 summarize the fluctuations in QTc. QTc prolongation (adjusted for gender) was found in 7 patients, along with 2 cases of arrhythmia following the initiation of a bedaquiline-containing regimen. Bedaquiline had to be stopped in one patient due to QT prolongation. Psychiatric side effects in the form of depression were observed in one patient (1.75%) and compulsive behavior in another patient. Cycloserine had to be stopped in the depressed patient, whereas the regimen was continued along with psychiatric medications in the other. No recurrence of symptoms was observed after the completion of the treatment.

Optic neuropathy was observed in 2 patients for whom linezolid was discontinued after ruling out other causes for the presentation. The symptoms reversed after the cessation of the drug, and linezolid was replaced with other drugs as per the replacement sequence. Arthralgia was another common adverse effect encountered in about 7 (12.28%) patients who were managed with nonsteroidal anti-inflammatory drugs, along with monitoring of uric acid levels without discontinuing any drug. Hyperpigmentation was observed in 5 (8.77%) patients, more towards the end of treatment, which was found to be irreversible after completion of treatment in all of them. Two patients presented with severe anemia, which was microcytic in nature, and linezolid was temporarily stopped. One patient was restarted on lower doses of linezolid, whereas the drug had to be discontinued and replaced with other drugs in the other. Deep vein thrombosis and hearing loss were observed in one patient each, which was concluded to be unrelated to the current regimen.

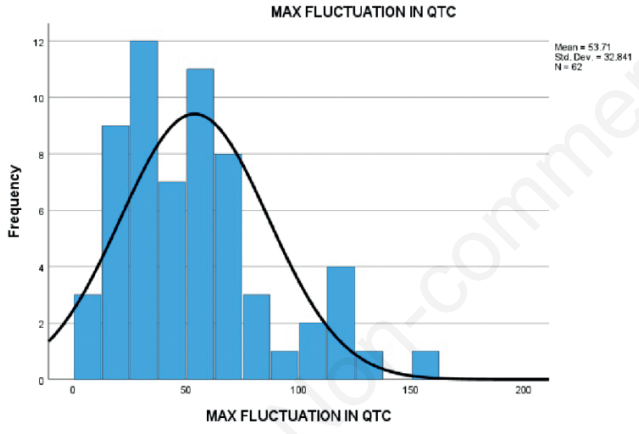

Figure 2. Distribution of fluctuations in corrected QT interval (QTc) from baseline which shows right skewness of data with more participants having fluctuations <50 ms with an outlier towards 150 ms. Std. Dev., standard deviation.

Outcomes

Interim outcomes

Out of the 61 patients successfully treated with bedaquiline, 49 (84.4%) and 54 (93.1%) attained sputum conversion by 3 and 6

Table 2. Adverse reactions among study participants.

Variable	Frequency	%
Adverse effect - none	5	8.06
Any	57	91.9
Events related to treatment	55	88.70
Events leading to discontinuation of treatment	8	12.90
Bedaquiline stopped due to adverse events	1	1.75
Gastrointestinal	22	38.59
Hepatic	10	17.54
Electrolyte imbalance	23	40.3
Cardiac	9	15.78
Nervous system	10	17.54
Musculoskeletal	7	12.28
Dermatologic	5	8.77
Psychiatric	2	3.50
Ocular	2	3.50
Anaemia	2	3.50
Ear, nose and throat	1	1.75
Hemoptysis	2	3.50
Deep vein thrombosis	1	1.75

Table 3. Corrected QT interval changes after the treatment initiation.

Variable	Number
Highest QTc<450	44
Highest QTc=450-480	9
Highest QTc=480-500	0
Highest QTc>500	1
Increase from baseline 0-30	18
Increase from baseline >30-60	21
Increase from baseline >60	23

QTc, corrected QT interval.

months, respectively. Among the patients who achieved sputum conversion, 3 patients had culture reversion by 6 months, and the median time to sputum conversion was found to be 90 days (±80.378). By the end of 90 days, 4 patients had died and 5 had been lost to follow-up.

Final outcome

Out of the 62 study participants, the treatment regimen failed in one patient who had a sputum reversion by the end of 18 months, and bedaquiline had to be discontinued in one patient due to the persisting adverse effects, which are categorized under failure. The outcomes are summarized in Tables 4 and 5.

Discussion

We evaluated the treatment outcomes of drug-resistant TB patients for whom bedaquiline was included in their regimen, along with the adverse effects. The socio-demographic data of our study population were compared with the previous studies, and it was found that there was a male predominance (71%), with the mean age being 37.58±15.196. The maximum number of patients diagnosed and started on bedaquiline was among the reproductive age group of 26-50 years. The regimen was well tolerated, considering only a few untoward occurrences and discontinuations of drugs owing to it. Electrolyte imbalance was observed to be the most prevalent (40%) followed by gastric intolerance (38%), hepatic derangement (17%), cardiac (15%), and neurologic (15%), which is almost similar to the study findings of Salhotra *et al*. [4]. The overall incidence of adverse effects (92%) is similar to multiple studies conducted across the world [5,6]. In contrast to many major studies done across the world, the most prevalent adverse effect encountered was electrolyte imbalance and not gastrointestinal side effects. Hypokalemia was the most frequently encountered electrolyte imbalance in our study population. This might be because we were diligently looking for any contributing factors that can lead to the most apprehended side effect in concern to bedaquiline: QT prolongation. Hepatic derangements in the form of elevated transaminases were encountered in 17% of patients, which is fairly comparable to the findings of Guglielmetti *et al*. in a French cohort [7], and Borisov *et al.* in a multi-center study done across 15 countries [8]. Serum amylase/lipase elevation was not observed in any of the patients. This can be due to the difference in the design of the regimen and associated confounders like alcohol and comorbidities.

Despite pyridoxine prophylaxis, peripheral neuropathy was a very bothersome symptom encountered in 9 (15.78%) patients, although none was severe or life-threatening enough to warrant withdrawal. According to Mishra *et al*. [9], symptomatic management with or without dose reduction was done in all 9 patients without permanent withdrawal of any drugs. Because linezolid is the main offending agent as well as an integral factor in the success of the regimen, being able to manage the symptoms without progression or discontinuation of the drug was crucial to the study. Even though cycloserine was permanently discontinued in one patient due to seizures, levofloxacin was successfully re-introduced in reduced doses along with anti-convulsant therapy without any further episodes. QT prolongation was observed in 12.28% of patients, with one patient warranting discontinuation of the offending drug. Around 37.5% of patients experienced >60 ms fluctuation from baseline in QTc, which is slightly greater than many studies [10-12]. Even though these figures are higher than most of the previous studies, discontinuation of bedaquiline due to this was observed in one patient (1.75%) which is very optimistic. Given the fact that the QTc cut-off was kept at a lower value than in previous studies, prompt intervention with pro-active correction of electrolyte imbalances might have aided in this success. It was found that 83.4% of patients achieved culture conversion by 3 months and 93.1% achieved culture conversion by 6 months, with a median time to conversion of 90 days, which compares with the data provided by Diacon *et al*. in their phase 2 double-blinded randomized controlled clinical trial (83 days) [13]. In the *interim*

Table 4. Summary of interim outcomes by 90 and 120 days of treatment with a bedaquiline-containing regimen.

Interim outcome	At 3 months		At 6 months		At 9 months	
	Number	%	Number	%	Number	%
Bacteriologic conversion						
Attained	48+2 eptb	80.64	52+2 eptb	87.06	51+1 eptb	83.8
Not attained	8	12.9	0	0	2	3.2
Bacteriologic reversion	0	2				
Died	1	3	4			
Loss to follow-up	3	4	4			

eptb, extrapulmonary tuberculosis.

Table 5. Summary of the final outcome after 18 months of treatment with a bedaquiline-containing regimen.

Outcome variable	Number of patients	%
Favorable outcomes		
Cured	43	69.3
Treatment completed	9	14.51
Unfavorable outcomes		
Loss to follow-up	4	6.55
Died	4	6.55
Treatment failure	2	3.26

analysis reports published by Salhotra *et al*. in India [4], the culture conversion rate at 6 months was 83%, with a median time to culture conversion of 60 days.

At the end of treatment in our study, 83.81% had favorable outcomes (73% cured, 15% completed treatment), which are consistent with the study results of Guglielmetti *et al*. [7], and Borisov *et al*. [8], but slightly higher than those reported in some major clinical trials [8,13,14]. Our study cohort did not have any HIV-co-infected or extensively drug-resistant (XDR) patients, which would have improved the success rates. In the phase 2 clinical trial conducted by Pym *et al.* in 2014 [15], 72.2% of patients were cured, 8.6% of patients were lost to follow-up, and 6.9% of patients died, which is comparable with the final outcomes of our study. 3.2% of patients had treatment failure: one had culture reversion at the end of treatment, whereas in the other patient, bedaquiline had to be discontinued due to adverse effects. We had one patient who had negative cultures at the end of treatment but had symptomatic and clinical worsening. Despite ruling out other causes for the symptoms, the patient had to be categorized as cured according to recent WHO and PMDT guidelines. The failure rates reported by various authors were comparable to ours, like 2.2% by Guglielmetti *et al.* [7], 5.1% by Mbuagbaw *et al*. [16], 7.7% by Borisov *et al.* [8], and 4.5% by Ndjeka *et al*. [10] in their studies; 6.6% died during treatment, but the cause of death could not be traced to the treatment regimen or disease. Although the death rates were more favorable than most of the large-scale studies [8,10,16], it cannot be directly attributed to the regimen as the resistance patterns and other disease profiles were not comparable.

Conclusions

The promising results of bedaquiline from across the world, along with the phasing out of second-line injectable drugs and the introduction of a shorter oral regimen, have great hopes for achieving the WHO 2025 milestones of the End TB Strategy in India. Coupled with gradually increasing trends in success rates since 2012, lesser failure rates and fewer concerns regarding grave adverse effects are a silver lining along the cloud of increasing burden and widening resistance patterns. Notwithstanding the limitations of this study, sustained culture conversions and a lesser incidence of grave adverse effects are indicators that more efforts and budget must be put into ensuring adherence, increasing knowledge among patients, and empowering health services at the primary health level.

Limitations

This was a single-center study with a small sample size conducted over a short duration of 2 years. In this study, participants from some subgroups were not included, like HIV seropositive and XDR patients, which makes the generalizability of the findings rather difficult. We encountered some dilemmas where, in the absence of clinical and radiological improvement, the final outcome was determined to be cured due to the achievement of sputum conversion. The lack of definitions on these grounds makes the treatment incomplete, resulting in inadequate improvements in the quality of life of patients.

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